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Original Article

An evaluation of new and current inflammatory markers in patients with polycystic ovary syndrome

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Abstract

Aim: The aim of this study was to evaluate new and current inflammatory markers in women with polycystic ovary syndrome (PCOS) and to clarify the role of these markers in the etiopathogenesis of PCOS.

Material and Methods: This retrospective study included 97 women with PCOS and 124 body mass index-matched controls without PCOS. The parameters examined as new and current markers in both groups were the monocyte-to-high density lipoprotein cholesterol (HDL-C) ratio, high sensitivity C-reactive protein/ albumin ratio, systemic immune-inflammation index, inflammatory prognostic index, prognostic nutritional index, white blood cell count, mean platelet volume, platelet distribution width, plateletcrit, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, triglycerides to HDL-C ratio and the lipid accumulation product index.

Results: No significant difference was found between the PCOS and control group in respect of inflammatory markers. The age and follicle-stimulating hormone values of PCOS patients were found to be lower than those of the control group. Luteinizing hormone, free androgen index, insulin and the homeostasis model assessment of insulin resistance values of PCOS patients were significantly higher than those of the control group.

Conclusion: In terms of inflammatory parameters, no significant difference was determined between patients with PCOS and the control group. Chronic inflammation may be multifactorial in PCOS and there is a need for studies with larger sample sizes to be able to explain the exact role of inflammatory markers in PCOS etiology.

Keywords: Polycystic ovary syndrome; inflammation; inflammatory markers

INTRODUCTION

One of the most common endocrine disorders in females of reproductive age is polycystic ovary syndrome (PCOS), which affects 6-25 % of women in this period (1,2). The determination of polycystic ovaries together with oligo and/or anovulation, and clinical and/or biochemical hyperandrogenism are the 3 main features (1). Although the etiopathogenesis of PCOS has not been fully elucidated, several studies have shown PCOS to be associated with mild, chronic inflammation (3). An association has also been demonstrated between chronic low-grade inflammation in PCOS pathogenesis and hyperandrogenism, insulin resistance (IR) and long-term metabolic (type 2 diabetes, metabolic syndrome) and cardiovascular complications (endothelial dysfunction) of PCOS (4).

Some inflammatory markers derived from hematological parameters have recently been used for the prediction of the severity and prognosis of inflammatory diseases such as cerebrovascular events, cardiovascular diseases, and malignant diseases (5-19). It is well known that in response to systemic inflammation, changes in peripheral blood cells occur such as neutrophilia, lymphopenia, and thrombocytosis (5). Leukocytes play a basic role in mediating inflammation. Increased leukocyte count has been shown to be an independent risk and prognostic factor for the development of inflammation and atherosclerosis (6). Some studies have reported that increased total white blood cell count (WBC) and subtypes are associated with inflammation, cardiovascular disease, and the severity of malignancies (6). Platelet (PLT) indices are determinants of PLT functions assessed by mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) and complete blood count (CBC). PLT function has been shown to be altered in cerebrovascular, cardiovascular,

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and inflammatory diseases (7). As MPV demonstrates the platelet production rate, activation and function, it is used as an inflammatory marker (7). Neutrophil-to-lymphocyte ratio (NLR) is accepted as a marker of systemic inflammation (8) and the platelet-to-lymphocyte ratio (PLR) as a biological marker of the balance between thrombosis and inflammation and has been associated with cardiovascular diseases, malignancies, chronic diseases and infections (9).

While high sensitivity C-reactive protein (hs-CRP) is a positive acute phase protein, albumin is a negative acute phase protein. Recently, the ratio of hs-CRP / albumin (CAR) has been accepted as a new inflammatory index and has been shown to be a prognostic factor in diseases such as cancer and sepsis (10). The monocyte-to-high density lipoprotein cholesterol (HDL-C) ratio (MHR) is a new inflammatory marker identified by Kanbay et al (11). It is accepted that an increase in monocyte count is a marker of chronic inflammation. HDL-C inhibits the differentiation of monocytes from macrophages, suppresses the inflammatory response and breaks the inflammatory process. Hence, it has been proposed that MHR could be a good indicator of inflammatory conditions such as cardiovascular events (12). The triglycerides to HDL-C ratio (TG/HDL-CR) is used as an inflammatory index in screening metabolic syndrome, IR and coronary artery disease (13). The lipid accumulation product (LAP) index is based on the evaluation of waist circumference and serum triglycerides. For both general and PCOS populations, LAP index has been suggested as an inflammatory predictor of metabolic syndrome and IR (14,15).

Serum albumin concentration and absolute lymphocyte count (ALC) have been shown to be strongly influenced by inflammatory conditions. The prognostic nutritional index (PNI) proposed by Onodera et al. (16), combines these two markers. The inflammatory state of PNI has been shown to predict general survival and perioperative complications in various malignancies (17). A new index was developed by Hu et al. (18) as a systemic immune-inflammation index (SII) on the basis of lymphocyte, neutrophil and platelet counts. The SII value has been shown to reflect the inflammatory state better than indexes such as NLR and PLR (18). The inflammatory prognostic index (IPI) is a new inflammatory marker proposed by Dirican et al (19).

From a review of literature, it can be seen that many inflammatory markers have been studied in PCOS patients. However, there appear to be no previous studies in literature that have investigated MHR, CAR, SII, IPI and PNI in PCOS. The aim of this study was to compare, for the first time, current and new inflammatory markers such as MHR, CAR, SII, IPI and PNI in women with and without PCOS and to clarify the role of these markers in the etiopathogenesis of PCOS.

MATERIAL and METHODS

This retrospective study was conducted in the Department of Obstetrics and Gynecology, Kafkas University Faculty of Medicine Hospital. Approval for the study was granted by the Local Ethics Board (decision date: June 26, 2018; issue number: 80576354-050-99/111). From a screening of the archives, data were evaluated of patients who presented for routine gynaecological check-ups between November 2017 and June 2018 and who fulfilled the inclusion criteria.

The patients included in the study were those for whom tests were requested for any reason such as for a routine gynaecological check-up or for evaluation of ovarian reserve, had normal kidney and liver function test results, were in the early follicular phase with spontaneous or progesterone withdrawal bleeding, had fasted for 12 hours, and had a sufficient amount of patient data recorded. Patients without data for the tests planned to be investigated were excluded.

Patients were also excluded from the study if they were smokers, were taking antiandrogen, antidiabetic, insulin sensitising or lipid lowering drugs, glucocorticoids or other hormonal drugs, if they were pregnant or lactating, if they had hyperprolactemia, Cushing syndrome, congenital adrenal hyperplasia, thyroid disease, impaired glucose tolerance, type 1 or type 2 diabetes mellitus or if they had a history of ovarian surgery.

From a retrospective screening of the archives, a total of 221 patients were identified who met the study criteria in the defined period. The PCOS group included 97 women and the control group comprised 124 body mass index (BMI)-matched non-PCOS women. The patients determined with PCOS and those in the control group were coincidentally able to be statistically matched in terms of BMI, but age-matching was not possible.

Control group subjects were those with no polycystic findings on ultrasonographic examination, a regular menstrual cycle (25-32 days), and normal biochemical and hormone profiles. The PCOS diagnosis was made in accordance with the revised Rotterdam criteria, of the determination of two of the following three findings: 1) oligo and / or anovulation, 2) clinical and / or biochemical hyperandrogenism and 3) polycystic ovaries determined on ultrasonography (1). The determination of ≥12 follicles with a diameter of 2-9 mm. and / or increased ovarian volume (> 10 mL) was used as ultrasonographic criteria for the determination of polycystic ovary. Biochemical hyperandrogenism was defined as total testosterone level above the normal accepted range (normal range: 0.34-2.60 nmol/L). Clinical hyperandrogenism was defined as a patient score of at least 8 points according to the Ferriman-Gallwey hyperandrogenic scoring system (20). Oligomenorrhea was defined as the absence of menstruation for 45 days or more and amenorrhea as the absence of bleeding for 3 months or more.

Venous blood samples for hormone analysis, lipid profile, fasting blood glucose (FBG) and insulin analysis were taken following a 12-hour fast during the early follicular phase of spontaneous or progesterone withdrawal bleeding. A detailed history and anthropometric data

(age, weight, height, and waist circumference) of all patients were recorded. The BMI was calculated using the following fomula: weight [kg]/ height squared [m^2]. The waist circumference [cm] was also measured.

Hormonal and inflammatory index analysis was applied as follows:

1. Measurements were taken of serum FBG, serum insulin, HDL-C, low density lipoprotein cholesterol (LDL-C), triglycerides, total cholesterol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), thyroid-stimulating hormone (TSH), total testosterone, dehydroepiandrosterone sulfate (DHEA-S), sex hormone-binding globulin (SHBG), hs-CRP, albumin levels and CBC. The FBG, hs-CRP, total cholesterol, HDL-C, LDL-C and triglycerides levels were measured using an automated analyzer (Abbott Architect C 16000, IL, USA) with the relevant kits (AbbottDiagnostics, Wiesbaden, Germany). Serum insulin levels were measured with an automated analyzer (Abbott Architect I2000, IL, USA) using a chemiluminescent microparticle immunoanalysis (CMIA) with the associated kit (Abbott Diagnostics, Wiesbaden, Germany). The serum FSH, LH, E_2, total testosterone, TSH, SHBG and DHEA-S levels were measured using CMIA (BeckmanCoulter Inc., Brea, CA, USA). A blood analyzer (ABX Pentra DX120, ABX-Horiba, Montpellier, France) was used to determine CBC.

2. IR was calculated using the homoeostasis model assessment of insulin resistance (HOMA-IR) according to the following formula: HOMA-IR = Fasting serum insulin (μIU/ mL) X FBG (mg/ dL) / 405. Most studies in literature have used a cut-off value of 2.5 for IR positivity (21). Therefore, a HOMA-IR score >2.5 was considered positive for IR in this study.

3. The free androgen index (FAI) was obtained as the quotient 100 testosterone/SHBG.

4. Inflammatory markers were defined as: NLR [absolute neutrophil count (× 10^9/ L) divided by ALC (× 10^9/ L)], PLR [absolute platelet count (× 10^9/ L) divided by ALC (× 10^9/ L)], CAR [serum albumin (g/ dL) cleavage of hs-CRP (mg/ L)], TG/HDL-CR [triglycerides (mg/ dL) divided by HDL-C (mg/ dL)], MHR [Monocyte (×10^9/ L) divided by HDL-C (mg/ dL)], SII [absolute platelet count (×10^9/ L) × NLR], IPI [hs- CRP (mg/ L) × NLR/ serum albumin (g/ dL)], and LAP index [(waist circumference (cm)- 58) × triglycerides (mmol/ L)] was calculated as PNI [serum albumin (g/ L)+ (5 × ALC (×10^9/ L))].

Data were analyzed using the Statistical Package for Social Science version 25.0 program (SPSS, Inc., Chicago, IL, USA). The conformity of continuous variables to normal distribution was examined using the Kolmogorov-Smirnov test. Quantitative data were expressed as mean ± SD values. As variables did not show normal distribution, the Spearman Correlation test and Mann Whitney U-test were applied. The Kolmogorov-Smirnov test results were taken into account when the patient sample was >30 in the normal distribution test. In all analyses a value of p<0.05 was accepted as statistically significant.

RESULTS

A total of 221 patients were included in the study. The PCOS group consisted of 97 women diagnosed according to the revised Rotterdam criteria and the control group comprised 124 BMI-matched, non-PCOS women. The age and FSH values of the PCOS patients were found to be lower than those of the control group (p = 0.01, p = 0.006 respectively). The LH, FAI, insulin and HOMA-IR values of the PCOS patients were significantly higher than those of the control group (p = <0.0001, p = 0.014, p = 0.008, p = 0.01, respectively). No significant difference was found between the PCOS and control group in terms of other variables. The demographic characteristics, and serum hormonal and biochemical parameters of the groups are shown in Table 1.

No statistically significant difference was determined between the PCOS and control group in respect of inflammatory markers (Table 2).

Table 1. Demographic features, serum hormonal and biochemical parameters of PCOS and healthy control groups

Variables	Control (n=124)	PCOS (n=97)	pa
Age [years]	29.29 ± 8.33	26.04 ± 6.98	0.001*
BMI [kg/m^2]	24.32 ± 4.5	24.7 ± 5.13	0.901
Waist circumference [cm]	78.31 ± 9.79	77.57 ± 11.35	0.531
FBG [mg/dL]	92.67 ± 17.62	93.84 ± 11.61	0.098
Insulin [μIU/mL]	11.89 ± 11.68	16.78 ± 33.46	0.008*
HOMA-IR	2.97 ± 3.61	4.21± 9.14	0.010*
FSH [mIU/mL]	8.71 ± 5.12	7.16 ± 2.6	0.006*
LH [mIU/mL]	5.91 ± 3.63	8.06 ± 4.46	<0.0001*
Estradiol [pg/mL]	59.91 ± 43.54	63.99 ± 46.13	0.325
TSH [mIU/mL]	1.97 ± 1.04	2.25 ± 1.37	0.191
Triglycerides [mg/dL]	112.75 ± 61.64	120.26 ± 71.61	0.633
HDL-C [mg/dL]	57.56 ± 13.15	56.04 ± 13.39	0.387
LDL-C [mg/dL]	94.29 ± 31.48	91.39 ± 27.68	0.642
Total cholesterol [mg/dL]	173.45 ± 37.21	171.99 ± 30.95	0.952
DHEA-S [μg/dL]	196.02 ± 86.91	214.09 ± 99.18	0.276
Total testosterone [nmol/L]	1.55 ± 0.78	1.67 ± 0.93	0.519
SHBG [nmol/L]	62.76 ± 27.42	59.49 ± 37.38	0.059
FAI [%]	2.85 ± 1.86	3.83 ± 3.08	0.014*
Albumin [g/dL]	4.59± 0.33	4.61± 0.37	0.823
Neutrophil [×109/L]	4.23± 1.63	4.36± 1.37	0.149
Lymphocyte [×109/L]	1.87± 0.53	1.98± 0.47	0.083

Results are given as mean ± SD . [a] Mann-Whitney U test was used. A value of p < 0.05 was considered significant*. PCOS – polycystic ovary syndrome; BMI – body mass index; FBG – fasting blood glucose; HOMA-IR – homeostasis model assessment of insulin resistance; FSH – follicle-stimulating hormone; LH – luteinizing hormone; TSH – thyroid-stimulating hormone; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; DHEA-S – dehydroepiandrosterone sulfate; SHBG – sex hormone-binding globulin; FAI – free androgen index

Table 2. Comparisons of inflammatory markers between the patients with PCOS and the healthy control group

Variables	Control (n=124)	PCOS (n=97)	pa
WBC [×109/L]	6.82 ± 1.86	6.94 ± 1.69	0.494
Platelet [×109/L]	287.65 ± 64.86	288.46 ± 65.38	0.682
PCT [%]	0.25 ± 0.06	0.25 ± 0.06	0.410
PDW [%]	15.23 ± 2.35	14.78 ± 2.07	0.145
MPV [fl]	8.67 ± 0.89	8.69 ± 0.82	0.879
NLR	2.46 ± 1.56	2.29 ± 0.84	0.766
PLR	164.89 ± 58.86	153.23 ± 47.87	0.247
CAR	0.07 ± 0.18	0.06 ± 0.13	0.799
MHR	0.01 ± 0	0.01 ± 0.00	0.562
TG/HDL-CR	2.15 ± 1.53	2.44 ± 2.14	0.502
LAP index	35.35 ± 79.44	29.1 ± 27.25	0.586
PNI	97.94 ± 475.05	55.49 ± 6.84	0.423
SII	712.98 ± 500.46	657.48 ± 264.66	0.668
IPI	0.18 ± 0.59	0.14 ± 0.26	0.746
hs-CRP [mg/L]	0.31 ± 0.73	0.28 ± 0.52	0.791

Results are given as mean ± SD . [a] Mann-Whitney U test was used. A value of p < 0.05 was considered significant*. PCOS — polycystic ovary syndrome; hs-CRP — high sensitivity C-reactive protein; WBC — white blood cell count; PCT — plateletcrit; PDW — platelet distribution width; MPV — mean platelet volume; NLR — neutrophil-to-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio; CAR — hs-CRP-to- albumin ratio; MHR — Monocyte-to-HDL-C ratio; TG/HDL-CR — triglycerides to HDL-C ratio; LAP index — lipid accumulation product index; PNI — prognostic nutritional index; SII — systemic immune-inflammation index; IPI — inflammatory prognostic index; hs-CRP — high sensitivity C-reactive protein

DISCUSSION

The aim of the current study was to examine current and new inflammatory markers and to determine their role in the etiopathogenesis of PCOS. In accordance with the Rotterdam criteria, the prevalence of PCOS in Turkey has been reported as 19.9% (22). The high number of PCOS patients in our study can be attributed to the fact that our hospital is a reference hospital so a greater number of PCOS patients are referred for tests at an appropriate time in the menstrual cycle after an appropriate fasting period. Whether chronic low-grade inflammation depends on PCOS itself or obesity has not yet been clarified (23). Since BMI and waist circumference did not differ between the current study patients, obesity effects were excluded. Low-grade chronic inflammation has been shown to be associated with hyperlipidemia, IR and androgen secretion in PCOS (3). In the current study, no difference was determined in the lipid profile of patients with PCOS. Although PCOS patients had significantly higher IR and FAI than the control group, no significant difference was detected between the groups in terms of inflammatory markers.

In addition to studies reporting WBC increases in PCOS (24), there are studies reporting normal WBC in PCOS (25). In a previous study, while non-obese PCOS subjects had normal WBC, obese PCOS women showed increased WBC (26). In the current study, no difference was determined between the groups in respect of BMI or WBC.

It has been reported that NLR is increased in PCOS and it can be used as a marker of inflammation (24,25). In contrast to these findings in literature, NLR was similar between the groups in the current study.

When the literature was reviewed, MPV levels in PCOS are not clear. In the current study, similar MPV levels were determined in both groups.

There are only two studies in the literature on the levels of PLR in PCOS (25,26). Both studies reported increased PLR in PCOS. In contrast, no difference was observed between the groups in terms of PLR in the current study.

Some studies have indicated that there are no differences in PLT in patients with PCOS (26). Isık et al. (27) reported high PLT and PCT values in PCOS. No difference was determined between the groups in terms of PLT and PCT in the current study.

Current data on hs-CRP and albumin levels in patients with PCOS are contradictory. In the literature, no study could be found evaluating CAR in PCOS patients. In the current study, no difference was observed between the PCOS and control groups in terms of both hs-CRP and albumin and CAR.

The relationship between stress hyperglycemia and inflammation is well known. It has been shown that the number of mononuclear cells increases in response to hyperglycemia in PCOS (28). In addition, hyperglycemia causes more reactive oxygen species (ROS) release than mononuclear cells (29). An increase in ROS production and oxidative stress creates an environment conducive to inflammation (30). In accordance with this theoretical knowledge, it has been shown that the rate of monocyte count and MHR is higher in cases with hyperglycemia (31). However, from current information it can be said that the most common metabolic deviation in PCOS is dyslipidemia. Hypertriglyceridemia, a decrease in HDL-C levels and mildly elevated LDL-C levels are second most frequently seen (32). However, it has been reported that the decline in expected HDL-C cholesterol concentrations in PCOS starts from the third decade of life, and the increase in triglycerides starts from the second decade of life (33).

No study could be found in literature in which the rate of MHR was evaluated in PCOS patients. No difference was found between the current study groups in terms of MHR ratio. Similarly, no study was found in literature related to the evaluation of SII, IPI and PNI, and no difference was observed between the current study groups in respect of these markers.

Some studies have reported high TG/HDL-CR in patients with PCOS (27,32). Consistent with the current study results, Macut et al. (34) reported no difference in PCOS

patients in respect of TG/HDL-CR. They showed that the rate of TG/HDL-CR did not differ in cases with PCOS aged <30 years, independent of BMI, and increased above 30 years of age. No difference was found between the current study groups despite waiting for an increase in the rate of TG/HDL-CR.

Some studies have found a high LAP index in PCOS patients (14). However, Hosseinpanah et al. (15) determined no difference in LAP index in PCOS cases, and similarly in the current study, no difference was observed between the groups in respect of LAP index.

The lack of difference in MHR, TG/HDL-CR, LAP index related to lipid levels could be attributed to the young age of PCOS patients in the current study, who had not reached the age of dyslipidemia.

Study limitations

This study has a retrospective design and a small sample size. The PCOS patient group had not reached the age at which dyslipidemia and chronic low-grade inflammation markers would become evident. Therefore, there is a need for more extensive and multicenter studies.

CONCLUSION

To the best of our knowledge, this is the first study to have evaluated PNI, SII, IPI, MHR, CAR levels in PCOS patients. In terms of both these and other inflammatory parameters, no significant difference was determined between patients with PCOS and the control group. One possible explanation of this may be that the PCOS patient group had not reached the age at which dyslipidemia and chronic low-grade inflammation markers would become evident. In conclusion, it would appear that chronic inflammation may be multifactorial in PCOS and therefore, there is a need for more extensive studies to be able to explain the exact role of new and current inflammatory markers in PCOS etiology.

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