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ORIGINAL ARTICLE

Evaluation of the relationship between polycystic ovary syndrome and intestinal inflammation as measured by fecal calprotectin levels

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ABSTRACT

Objective: Factors such as chronic inflammation and oxidative stress are pivotal in the pathogenesis of polycystic ovary syndrome (PCOS). We aimed to evaluate the relationship between PCOS and fecal calprotectin levels—a proxy for intestinal inflammation.

Material and Methods: This research was carried out by including 54 women who applied to the obstetrics and gynecology clinic of our hospital. Twenty-seven of these women were diagnosed with PCOS, while 27 were healthy.

Results: Median fecal calprotectin in women with PCOS was significantly higher than in controls (p=0.040). Calprotectin had 37.0% sensitivity, 96.3% specificity, and 66.7% accuracy in predicting PCOS patients with a cut-off value of ≥60 (area under ROC curve: 0.667 (95% CI: 0.520–0.813), p=0.036). Multiple logistic regression showed that free androgen index was the only parameter independently associated with PCOS presence.

Conclusion: Fecal calprotectin level is increased in PCOS, and therefore, it appears that intestinal inflammation is increased in our PCOS group—despite similar levels of systemic inflammation. Fecal calprotectin may be valuable in the differential diagnosis of PCOS, and therapies targeting intestinal inflammation warrant research for their possible benefits in women with PCOS.

Keywords: Biomarkers, calprotectin, gastrointestinal tract, inflammation, leukocyte L1 antigen complex, polycystic ovary syndrome, predictive value of tests.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is characterized by ovarian dysfunctions that are associated with cystic tissue morphology, oligo/amenorrhea findings, and hyperandrogenism.[1] In women, it is the most prevalent endocrine disorder during reproductive age and is highly likely to cause anovulatory infertility.[2] PCOS frequency is reported between 5–21%, which differs based on ethnic differences, characteristics of study populations, and the use of different methods to assess key PCOS features.[3]

The factors involved in the etiology of PCOS have not been fully elucidated, but it has been associated with systemic inflammation, in addition to its strong (epi)genetic and environmental background.[4,5] Factors such as chronic inflammation and oxidative stress, which contribute to various disease states and endothelial dysfunction,[6,7] are reported to play causal roles in the pathogenesis of PCOS.[2]

According to the "Dysbiosis of Gut Microbiota" theory, infective disorders of the intestine cause an increase in intestinal mucosal permeability, resulting in transfer of lipopolysaccharides from colonic bacteria to the systemic circulation.[8] In the aftermath of this transfer, the immune system is activated, which elevates serum insulin levels by interfering with insulin receptor function and prevents normal follicle development by increasing androgen production.[9] Calprotectin, also known as MRP8/14 and S100A8/A9, is a calcium- and zinc-binding protein of the S-100 protein family that has been associated with the properties of the intestinal environment. The amount of fecal calprotectin is a non-invasive quantitative measure of neutrophil flow into the gut and has been associated with diseases such as Crohn's, ulcerative colitis, and irritable bowel syndrome.[10] It has also been reported to be involved in cell differentiation, tumorigenesis, and apoptosis, and is considered a positive acute phase protein.[11] Although previous studies have shown that PCOS patients have reduced diversity in their intestinal flora and higher calprotectin levels,[12,13] there are few studies evaluating potential relationships between intestinal inflammation and PCOS. If such a relationship exists, characterization of its effects may be crucial for the diagnosis, follow-up, and treatment of PCOS.

The aim of this study was to evaluate the relationship between PCOS and intestinal inflammation through investigation of fecal calprotectin.

MATERIAL AND METHODS

Study Design and Patients

This research was carried out at our hospital between 1 June 2022 and 30 August 2022. Ethics committee approval was obtained from the local ethics committee, and all processes were in accordance with the Helsinki Declaration.

At the time of the study, 54 women aged ≥18 years, who had applied to the obstetrics and gynecology clinic and agreed to participate in the study, were included in the study group. Among these, 27 women with a PCOS diagnosis formed the PCOS group, and 27 healthy women without any current or previous overt health problems were included in the control group. Inclusion criteria for the study were being 18 years or older, having a Body Mass Index (BMI)<30, and having normal liver and kidney functions. For those included in the control group, we excluded patients with irregular menstrual cycles. Exclusion criteria were hyperprolactinemia, hypothyroidism, hyperthyroidism, use of combined oral contraceptives, and receiving antiandrogen medications, ovulation induction agents, diabetic drugs, or steroids within the prior three months. Patients who had been prescribed antibiotic therapy within the prior three weeks and those diagnosed with any gastrointestinal disease or active infection were also excluded.

After giving detailed information about the purpose and scope of the study to the patients who met the inclusion criteria, written and verbal consent was obtained from those who agreed to participate in the study. Sociodemographic characteristics, medical histories, menarche characteristics, and fertility histories of the patients were recorded. During the examination, height (cm) and body weight (kg) were measured, and laboratory test results were recorded. Fecal calprotectin and hs-CRP levels were measured to assess intestinal inflammation. Laboratory examinations were performed on days 3–5 of spontaneous or progesterone-induced cycles. Sex hormones, thyroid function tests, liver function tests, lipid profiles, and other laboratory analyses were performed in the routine clinical chemistry units of our hospital.

Diagnosis and Data Collection

The women were diagnosed with PCOS according to the Rotterdam diagnostic criteria. Women who had at least two of the Rotterdam criteria (oligomenorrhea/amenorrhea, clinical/biochemical hyperandrogenism, polycystic ovary appearance on ultrasonography) were defined as having PCOS.[1]

Homeostatic Model Assessment Insulin Resistance (HOMA-IR) was used to detect insulin resistance, and it was calculated with the formula:

HOMA-IR=(Fasting insulin, μIU/mL)*(Fasting glucose, mg/dL)/405.[14]

The presence of hyperandrogenism was determined by evaluating the free androgen index (FAI). The formula used for the calculation of FAI was as follows:

FAI=(total testosterone (mmol/L))/(sex hormone-binding globulin [SHBG] (nmol/L))×100.

Women with a FAI score of ≥8 were considered to have hyperandrogenism.[15]

Fecal Sampling and Calprotectin Quantification

After explaining the optimal stool collection and transportation methods in detail, including information on how to avoid contamination of the stool sample, the women were given a written information brochure. For fecal calprotectin measurement, stool samples were taken into sterile containers by the women themselves after an overnight fast and were placed on ice. The specimens placed on ice brought by the women were immediately delivered to the laboratory and frozen at -20 °C.

Fecal calprotectin was measured using an enzyme-linked immunosorbent assay (ELISA; EUROIMMUN Medizinische Labordiagnostika AG; Lübeck, Germany) according to the manufacturer's instructions. The measuring range of the fecal calprotectin kit was between 19–1800 μg/g. The cut-off value for calprotectin was accepted as 60 μg/g.[10]

Statistical Analysis

All analyses, with a significance threshold of p≤0.05, were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The normality of distribution in continuous data was analyzed with the Shapiro-Wilk test. Data are given as mean±standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Normally distributed continuous variables were analyzed with the independent samples t-test. Non-normally distributed continuous variables were analyzed with the Mann-Whitney U test. Categorical variables were analyzed with chi-square tests or Fisher's exact test. Discrimination performance of calprotectin was evaluated with the Receiver Operating Characteristic (ROC) curve analysis. Multivariable logistic regression analysis (forward conditional method) was used to determine factors independently associated with PCOS.

RESULTS

The mean age of the 54 women in the study group was 31.02±5.04 years (range: 22–40). The mean age of the PCOS group was significantly lower compared to controls (p=0.020). Luteinizing hormone (LH, p<0.001), insulin (p<0.001), glucose (p=0.002), HOMA-IR (p<0.001), HbA1c (p=0.004), free testosterone (p<0.001), total testosterone (p<0.001), FAI (p<0.001), dehydroepiandrosterone sulfate (DHEA-S, p=0.011), low-density lipoprotein (LDL, p=0.004), total cholesterol (p=0.008), and vitamin B12 (p=0.033) levels were higher in the PCOS group. SHBG level was significantly lower in the PCOS group (p<0.001). Calprotectin was significantly higher in women with PCOS (p=0.040).

When dichotomization was performed according to the calprotectin positivity cut-off (>60 µg/mg), the frequency of patients exceeding this threshold was 37.0% in the PCOS group and 3.7% in the control group—again demonstrating a significant difference (p=0.007, Table 1).

Calprotectin had 37.0% sensitivity and 96.3% specificity in detecting the presence of PCOS based on the optimized cut-off value of >60 (higher values discriminatory for PCOS) (AUC=0.667; 95%CI: 0.520–0.813; p=0.036, Table 2).

Multivariable logistic regression revealed that high FAI (p=0.032) was independently associated with PCOS after adjusting for age. Other variables included in the analysis, LH (p=0.217), insulin (p=0.225), glucose (p=0.849), HOMA-IR (p=0.256), HbA1c (p=0.544), free testosterone (p=0.609), total testosterone (p=0.111), SHBG (p=0.085), DHEA-S (p=0.405), LDL (p=0.837), total cholesterol (p=0.095), vitamin B12 (p=0.232), and calprotectin (p=0.410), were found to be non-significant (Table 3).

DISCUSSION

It has been reported that inflammation and oxidative stress play a role in the pathophysiology of PCOS through both innate and adaptive immune cells.[2,16] IL-1β and IL-18 levels increase in the follicular fluid of women with PCOS, and the intracellular inflammatory process induces oxidative stress, damaging mitochondrial structures and functions. This affects cellular metabolism and impairs cell proliferation. The inflammation-favoring microenvironment in the follicular fluid of PCOS patients consequently leads to the arrest of oocyte maturation.[17]

Despite limited discriminatory results, our findings suggest that calprotectin levels may be associated with PCOS. Owing to the particularly high specificity and positive predictive value, fecal calprotectin may be utilized in differential diagnosis as a means to rule out PCOS. However, logistic regression showed that only FAI was independently associated with the presence of PCOS. Therefore, further studies are required to assess whether calprotectin levels are directly associated with PCOS.

In the study by Huang et al.,[12] it was reported that Trimethylamine N-oxide, a small organic compound produced by the gut microbiome, was significantly higher in PCOS patients than in non-PCOS women, thereby supporting the relationships between PCOS and systemic inflammation. We assessed intestinal inflammation with a proxy marker, calprotectin, and our results lend credibility to the aforementioned conclusions. With respect to the independent association described for FAI in the present study, the literature has reported that hyperandrogenism may be an important factor in shaping the gut microbiome, and changes in the microbiome may also affect the development of PCOS.[18]

In the case of intestinal inflammation, which occurs in pathological conditions increasing mucosal permeability, there is an increase in the migration of granulocytes and monocytes in the intestine.[19] Components derived from the intestinal lumen act as stimulators for the release of mediators such as calprotectin from granulocytes and monocytes, thereby releasing calprotectin into the lumen, which can be measured from fecal samples.[11,19] Based on this, it can be said that the elevation of calprotectin in stool is the result of migration of neutrophils to the gastrointestinal tissue due to infectious or inflammatory processes.[11] The quantitative fecal calprotectin test, which is a simple, non-invasive, and inexpensive test, is one of the most widely used markers to monitor intestinal inflammatory activity.[11] The amount of calprotectin in stool can therefore be utilized as a proxy marker for neutrophil influx into the gut, and there is a significant correlation between fecal calprotectin levels and other markers of acute inflammation in intestinal inflammatory diseases.[10]

Fecal calprotectin helps in the follow-up of clinical relapses and symptoms of disease by providing information that is usually complementary to endoscopy and has the advantage of occasionally revealing information that cannot be acquired from endoscopy in inflammatory bowel diseases.[10] Prior evidence establishes fecal calprotectin level as an indicator of disease activity, treatment outcome, and intestinal inflammation in many different diseases. These include research showing the potential role of fecal calprotectin in demonstrating mucosal activity in Crohn's patients,[20] the short-term outcome of steroid therapy in ulcerative colitis,[21] the diagnosis and prognosis of acute appendicitis,[22] Parkinson's disease and multiple system atrophy,[23] and hypoxic intestinal damage in COVID-19.[24]

Although limited, there exist recent studies of calprotectin in patients diagnosed with PCOS. In a study by Li et al.,[25] it was reported that the S100-A9 (calprotectin) protein contained in follicular fluid exosomes in PCOS patients significantly increased inflammation and impaired steroidogenesis through the activation of nuclear factor kappa B (NF-κB) signaling. Furthermore, serum calprotectin concentrations have been reported to be significantly higher in women with PCOS compared to healthy women. The authors determined

Table 1: Summary of patient characteristics and laboratory measurements with regard to groups

	Groups		p
	PCOS (n=27)	Control (n=27)	
Age	29.44±5.16	32.59±4.47	**0.020**
Body mass index	24.10±3.52	23.16±2.62	0.271
FSH	6.5 (4.4–7.8)	5.0 (4.3–6.12)	0.095
LH	7.63 (6.62–11.40)	5.30 (4.21–6.80)	**<0.001**
E2	41 (35.79–43)	38 (32–41)	0.056
TSH	1.25 (0.78–1.78)	0.88 (0.69–1.52)	0.143
T4	1.05 (0.99–1.10)	1.02 (0.90–1.08)	0.336
Prolactin	21.03±7.74	18.98±5.33	0.263
Insulin	13.0 (10.03–29.5)	5.1 (4.2–7.7)	**<0.001**
Glucose	87.78±8.61	81.67±4.61	**0.002**
HOMA-IR	2.88 (2.35–6.63)	1.05 (0.85–1.51)	**<0.001**
Insulin resistance (>2.4)	20 (74.1%)	2 (7.4%)	**<0.001**
HbA1c	5.3 (4.9–5.6)	5.1 (4.8–5.2)	**0.004**
Free testosterone	1.69±0.62	0.94±0.28	**<0.001**
Total testosterone	77.15 (34.16–88.37)	17.90 (12.15–22.40)	**<0.001**
SHBG	35.3 (31.1–43.7)	78.9 (65.3–93.1)	**<0.001**
Free androgen index	6.44±3.36	0.83±0.34	**<0.001**
Hyperandrogenism (≥8)	9 (33.3%)	0 (0.0%)	**0.002**
DHEA-S	261.59±117.05	193.94±61.74	**0.011**
Albumin	44.37±3.25	43.11±2.15	0.099
HDL	50.00±11.34	54.96±8.77	0.078
LDL	117 (104–164)	103 (88–123)	**0.004**
Total cholesterol	181 (167–222)	167 (150–187)	**0.008**
Triglycerides	69 (62–84)	66 (55–84)	0.345
GGT	13 (11–16)	13 (11–16)	0.924
Ferritin	22.8 (15–31)	24 (20–32)	0.350
Hemoglobin	12.93±1.12	12.36±1.14	0.068
Vitamin B12	374 (286–421)	298 (256–341)	**0.033**
AST	17 (15–19)	19 (16–22)	0.085
ALT	13 (11–17)	14 (11–18)	0.543
BUN	10.94±2.85	11.78±4.22	0.397
Creatinine	0.68 (0.66–0.72)	0.67 (0.66–0.75)	0.656
hs-CRP	0.82 (0.45–2.57)	0.73 (0.43–0.93)	0.283
Calprotectin	18 (18–237)	18 (18–23)	**0.040**
>60	10 (37.0%)	1 (3.7%)	**0.007**

Data are given as mean±standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. PCOS: Polycystic ovary syndrome; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; TSH: Thyroid-stimulating hormone; T4: Thyroxine; HOMA-IR: Homeostatic model assessment insulin resistance; HbA1c: Hemoglobin A1C; SHBG: Sex hormone binding globulin; DHEA-S: Dehydroepiandrosterone sulfate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; GGT: Gamma-glutamyl transferase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; BUN: Blood urea nitrogen; hs-CRP: High-sensitivity C-reactive protein.

Table 2: Performance of calprotectin to discriminate patients with PCOS and healthy controls

Cut-off	>60
Sensitivity	37.0%
Specificity	96.3%
Accuracy	66.7%
PPV	90.9%
NPV	60.5%
AUC (95.0% CI)	0.667 (0.520–0.813)
p	**0.036**

PCOS: Polycystic ovary syndrome; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under ROC curve; CI: Confidence intervals; ROC: Receiver operating characteristic.

a serum calprotectin threshold value of 2.4 μg/mL, which yielded a specificity of 85.2% and a sensitivity of 75.6%.[26] In a study by Şener and colleagues, serum calprotectin levels were again found to be significantly higher in women with PCOS than in healthy women, and a serum calprotectin cut-off value of >204.54 pg/mL was reported to have a sensitivity of 66.7% and a specificity of 54.7%.[27] Lindheim et al.,[13] in a study with a similar design to ours, concluded that fecal calprotectin was associated with gut microbiome parameters, but they noted that fecal calprotectin levels were similar among healthy women and those with PCOS.

In the current study, while the groups were similar in terms of hs-CRP, fecal calprotectin was significantly higher in the PCOS group, suggesting that intestinal inflammation had a more pronounced relationship with PCOS presence, regardless of systemic inflammatory status. Although the sensitivity value for fecal calprotectin was not very high, it was found that calprotectin successfully detected women without PCOS from women with PCOS with high specificity (96.3%). There are limited studies on fecal calprotectin in women with PCOS. In addition to having a discriminatory role, it can also be said that fecal calprotectin can be used in the evaluation of intestinal inflammation in women with PCOS due to its low cost compared to endoscopy[10] and ease of administration.

Studies investigating the relationship between serum calprotectin level and PCOS are highly heterogeneous, particularly in terms of sampling and outcomes. However, with respect to our results, it may be feasible to suggest that reducing intestinal inflammation may be an approach that can benefit patients with PCOS. Much research is needed before it can be speculated whether these benefits can translate into better quality of life and/or fertility. This information is crucial because there is a need for new treatment options for patients with PCOS.[17] For instance, in the study of Yang et al.,[28] it was reported that inhibition of UCA1 prevented inflammatory cell proliferation in PCOS patients, and as a result, granulocyte cell proliferation was increased and progression was limited.

It is also crucial to note that treatment of PCOS with oral contraceptive drugs may decrease fecal calprotectin levels. Therefore, longitudinal and prospective studies are needed to reveal the direction and chronology of the relationship between intestinal inflammation and PCOS with stronger evidence.

Limitations

Our study has some limitations. Generalizability is limited by the fact that the research was carried out in a single center. The cross-sectional design provides a 'snapshot' in terms of variables, and therefore, the causality of the association between fecal calprotectin and PCOS cannot be fully explained. A longitudinal analysis can potentially address this problem.

Another limitation is that the PCOS group was younger; however, both groups were well within reproductive age, and logistic regression was performed with adjustment for age. Individuals with any gastrointestinal disease were excluded from the study group; however, there may exist variables associated with bowel function that we could not control.

The performance of fecal calprotectin measurement kits, the application of the test, and the fact that a standard for threshold values has not yet been developed may have affected our results. Nonetheless, this is one of the few studies evaluating the relationship between PCOS and fecal calprotectin, and the results are important as they can be clinically instructive.

CONCLUSION

In light of the analyses, it can be said that the level of fecal calprotectin increases in PCOS, possibly as a direct result of intestinal inflammation. Fecal calprotectin was elevated despite similar systemic inflammation levels and had very high specificity to rule out PCOS. These findings suggest that fecal calprotectin concentration can be used to successfully distinguish healthy women from those with PCOS, regardless of systemic inflammation. Population-based prospective longitudinal studies may be beneficial to reveal the relationship between fecal calprotectin and PCOS, creating stronger evidence.

Table 3: Significant factors independently associated with PCOS, multiple logistic regression analysis

	β coefficient	Standard error	p	Exp(β)	95.0% CI for Exp(β)	
Age	-0.520	0.260	0.046	0.595	0.357	0.991
Free androgen index	2.465	1.153	0.032	11.762	1.229	112.603
Constant	10.409	6.754	0.123			

PCOS: Polycystic ovary syndrome; CI: Confidence interval; Nagelkerke R^2=0.895.

Statement

Ethics Committee Approval: The Izmir Bakircay University Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 17.05.2022, number: 600).

Author Contributions: Concept – BSF, ZA; Design – BSF, ZA; Supervision – BSF, ZA; Resource – BSF, ZA; Materials – BSF; Data Collection and/or Processing – BSF, ZA; Analysis and/or Interpretation – BSF, ZA; Literature Search – BSF, ZA; Writing – BSF, ZA; Critical Reviews – BSF.

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