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ORIGINAL ARTICLE

Study of Some Immunological Disorders Associated with Polycystic Ovary Syndrome

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ABSTRACT

Background: *Five to fifteen percent of females in reproductive age have polycystic ovarian syndrome, a hormonal disorder that may be linked to immune system problems.* ***Objective:*** *our study aim of Examine changes of certain immunological markers and their role in the progress in polycystic ovary syndrome in Iraqi women.* ***Methodology:*** *A total of 90 Iraqi women, ranging in age from 18 to 40 years, were included in the study. Of them, 46 had polycystic ovary syndrome (PCOS), while the other 44 served as a control group. blood samples were collected from all participants for the assessment of selected immunological markers. The serum levels of MCP-1, MIF, TNF, IL-6, IL-18, CRP, and 8-OHDG were measured using the Enzyme-Linked Immunosorbent Assay (ELISA) technique, following the manufacturer's instructions.* ***Results:*** *In PCOS, for women, all inflammatory markers, with the exception of 8-OHDG, are significantly higher in comparison to control women. These indicators include MCP-1, MIF, TNF, IL-6, IL-18, and CRP. BMI and age show positive association with the majority of inflammatory markers, this gives credibility to the idea that female with PCOS, who are older and overweight, are more likely to have elevated inflammatory levels. In comparison to the women with polycystic ovary syndrome and control group, exhibited considerably greater ranges of MCP-1 (67.21 ng/ml) than the control group (58.92 ng/ml). PCOS women exhibited significantly higher MIF levels (9.67 ng/ml) compared to control women (8.05 ng/ml). PCOS women had significantly higher TNF levels (27.52 pg/ml) compared to control women (21.03 pg/ml). PCOS women showed significantly higher IL-6 levels (6.2 ng/ml) compared to control women (4.14 ng/ml). PCOS women had significantly higher IL-18 levels (12.34 ng/ml) compared to control women (10.54 ng/ml). PCOS women had dramatically higher CRP levels (5.52 mg/dl) compared to control women (2.55 mg/dl). Interestingly. PCOS women had significantly lower 8-OHDG levels (176.41 pg/ml) compared to control women (216.5 pg/ml).* ***Conclusion:*** *The levels of inflammatory markers were significantly different between the control groups and the women who were diagnosed with polycystic ovarian syndrome (PCOS).*

INTRODUCTION

A prevalent endocrine condition that affects 5–18% of women of reproductive age is polycystic ovary syndrome[1]. Because PCOS is an exclusionary diagnosis, it requires the presence of two out of the three classic symptoms: Primarily, there has to be clinical and/or biochemical hyperandrogenism, polycystic ovarian morphology, and ovulatory dysfunction[2]. The clinical manifestations of polycystic ovary syndrome include infertility, irregular menstruation, hyperandrogenism, and metabolic disorders such as dyslipidemia, obesity, and insulin resistance[3]. Inflammatory reactions, which are important in the development of metabolic abnormalities and insulin resistance, as well as the higher chance of developing CHD (Coronary Heart Disease), have been shown to be the reason of the high incidence of obesity and overweight among women who have PCOS[4]. One common reason of irregular menstruation periods in women is low progesterone levels. Polycystic ovarian syndrome (PCOS) sufferers in females, it leads the immune system to become overstimulated, which in turn increases the production of estrogen. Additionally, it encourages the development of inflammatory cytokines, which in turn elevates the production of autoantibodies. Both of these pathways are responsible for the increased production of autoantibodies[5].

Hyperandrogenism is a key component in the onset of immunological problems in PCOS, and there have been a lot of recent studies on the effects of low-grade and chronic inflammation on immunity. Several inflammatory factors, including mcp-1, IL-6, MIF, IL18, and inflammasomes, have been shown to have a

significant relationship with the frequency of polycystic ovarian syndrome[6]. Individuals diagnosed with polycystic ovary syndrome experience a persistent low-grade inflammatory condition resulting from the buildup of inflammatory cells and cytokines[7]. It has also been suggested that autoimmune illnesses and PCOS are related to each other. Since autoimmune diseases strike women earlier than in men, a correlational research has revealed that 78% of people with autoimmune disorders are female. This finding may be related to estrogen levels[8]. Furthermore, immunological dysregulation in PCOS is becoming more widely known. There is growing evidence that the regulation of PCOS involves immune processes. Notably, human preovulatory follicles include significant numbers of competent immune cells (such as macrophages, B cells and T cells)[9]. The proinflammatory cytokine interleukin-18 (IL-18) triggers the cascade of events that culminates in TNF-α, which in turn triggers interleukin-6, which regulates CRP synthesis in the liver[10]. Plasma IL-18 levels were greater in PCOS women, obese women, and types 2 diabetic patients[11]. Polycystic ovary syndrome is distinguished by low-grade chronic inflammation; symptoms include an increased leucocyte count, elevated C-reactive protein levels, and inflammatory cytokines including IL-6 and IL-18[12]. CRP is a biomarker of inflammation that is exceedingly accurate. Additionally, it is one of the most sensitive indicators of cardiovascular morbidity[13].

METHODOLOGY

Experimental design

Blood samples were collected from the Fertility Center in Najaf Governorate. The data collection process spanned a specific period, from November 2024 to January 2025, allowing us to collect a sufficient number of samples. Ninety women, of the ages 18 to 45, were a part of the research. In the first set, forty-six women met the criteria for diagnosis of polycystic ovarian syndrome. The second group consisted of forty-four women who were healthy and did not have any hormonal issues or PCOS. In addition serum samples from each participant, demographic and clinical data, such as BMI (Weight (kilogram)/Height (in m^2)), were also collected . The serum samples were used to measure the amounts of TNF, IL-18, CRP, MIF, IL-6, MCP-1, and 8-OHDG using commercially available ELISA assay from (Bio Tek, U.S.A) and following the manufacturer's instructions.

Diagnosis of PCOS

All participants were diagnosed clinically by a gynecologist. using various tests, such as ultrasound, hormone tests, and general immunological tests, e.g. measuring inflammatory cytokine levels.

Collection of blood samples

5 ml of blood samples were collected using a sterile syringe. The sample remain at room temperature for thirty to sixty minutes to facilitate the normal clotting of the blood. The sample is then centrifuged at a speed of 3,000 RPM for ten to fifteen minutes to separate the cells from the serum.

Serum samples were frozen at -20°C or -80°C until used for analysis. It is preferable to divide the serum into several small samples to avoid repeated freezing and thawing.

Methods

The blood samples were obtained in the morning after an overnight fast and during the early follicular phase of a menstrual cycle (days 3–5). Samples were collected in clot activator tubes, and the serum was separated after centrifugation and divided in to five Eppindroff tubes to avoid multiple freezing and thawing and kept frozen until time of analysis. Blood samples were collected from all participants for the assessment of selected immunological markers. The serum levels of MCP-1, MIF, TNF, IL-6, IL-18, CRP, and 8-OHDG were measured using the Enzyme-Linked Immunosorbent Assay (ELISA) technique, following the manufacturer's instructions.

Statistical analysis

For all of the statistical studies, the usage of SPSS version 28.0 (SPSS Inc., Chicago, Illinois, United States) was used. For the purpose of comparing clinical data in the form of continuous variables, analysis of covariance was used. The median and IQR were provided for skewed data, whereas the mean plus or minus the SD was reported for data that was regularly distributed. Both of these variables were reported. The comparison of categorical variables, which are shown as percentages, was carried out with the use of Chi-square tests. An investigation of the links that exist between inflammatory markers and demographic parameters such as body mass index (BMI) was carried out with the assistance of Pearson's correlation analysis. Statistical significance was determined to be present in each and every one of the tests that were carried out utilizing a two-sided design if the p-value was less than 0.05[14].

RESULTS

Table 1 summarizes the concentrations of several inflammatory cytokines (IL-6, MCP-1, MIF, TNF, IL-18, and CRP) and the oxidative stress marker 8-OHDG in control women and women diagnosed with polycystic ovarian syndrome (PCOS). Data are presented as median (interquartile range) and mean ± standard deviation. Statistical significance was determined at a p-value < 0.05.

Compared to controls, women with PCOS exhibited significantly higher serum levels of MCP-1 (ng/ml), MIF (ng/ml), TNF (ng/ml), IL-6 (ng/ml), and IL-18 (ng/ml) ($p < 0.05$ for all). CRP levels (mg/dl) were also significantly elevated in the PCOS group compared to controls. Conversely, 8-OHDG levels were significantly lower in women with PCOS relative to the control group.

Table (1): Assessment of Inflammatory Markers in PCOS compared to Healthy Women

Parameter	Group	Mean ± SD	Median (IQR)	P-value
Mcp-1 (ng/ml)	PCOS Women	67.21 ± 19.22	67.51 (51.7-81.49)	**0.020***
	Controls Women	58.92 ± 13.59	55.58 (48-71.89)	
MIF (ng/ml)	PCOS Women	9.67 ± 3.3	9.82 (7.48-12.36)	**0.017***
	Controls Women	8.05 ± 3.01	7.54 (6.3-10.73)	
TNF (pg/ml)	PCOS Women	27.52 ± 10.23	28.18 (18.28-36.86)	**0.001***
	Controls Women	21.03 ± 8.2	22.99 (14.01-27.07)	
IL-6 (ng/ml)	PCOS Women	6.2 ± 2.36	5.84 (4.28-8.24)	**0.0001***
	Controls Women	4.14 ± 1.99	4.02 (2.43-5.09)	
IL-18 (ng/ml)	PCOS Women	12.34 ± 4.93	11.5 (9.09-13.74)	**0.029***
	Controls Women	10.54 ± 2.32	11 (8-12.37)	
CRP (mg/dl)	PCOS Women	5.52 ± 1.49	5.61 (4.55-6.46)	**0.0001***
	Controls Women	2.55 ± 1.68	2.54 (0.69-3.58)	
8-OHDG (pg/ml)	PCOS Women	176.41 ± 45.35	165.21 (142.32-210.95)	**0.002***
	Controls Women	216.5 ± 70.57	197.29 (178.12-229.62)	

** Significant differences at p-value≤ 0.05. Median (IQR) inter quartile range. Independent t-test or Mann Whitney test. NS: non-significant.*

Table (2) analyzes the results of relationship between weight as BMI (normal weight vs. overweight/obese) and inflammatory/oxidative stress markers in both PCOS women and control women.

BMI and Mcp-1 levels

With a p-value less than or equal to 0.05, the Mcp-1 level is significantly higher in the group of PCOS women who are overweight or obese than it is in the group of women who have normal weight of the same weight. When the levels of Mcp-1 in women who act as controls are examined, it is shown that there is no statistically significant difference ($p < 0.05$) in comparison to the other categories of body mass index (BMI).

BMI and MIF levels

Among women who were diagnosed with polycystic ovarian syndrome (PCOS), the group that was overweight or obese had a tendency to have a higher mean intraperitoneal fluid (MIF) concentration (ng/ml) , this difference does not meet the criteria for statistical significance ($p < 0.05$). Furthermore, it is important to highlight that there is no statistically significant difference ($p < 0.05$) in MIF levels among the control women, irrespective of the different BMI categories.

BMI and TNF levels

In the overweight/obese category, the analysis reveals no statistically significant difference ($p < 0.05$) in TNF levels (pg/ml) when comparing the first and second groups. The findings indicated a significant reduction in TNF levels among overweight or obese women compared to the control group ($p < 0.05$). On the contrary, the disagreement does not attain statistical significance when the p-value is below 0.05.

BMI and IL-6 levels

The levels of IL-6 (ng/ml) in the PCOS were substantially higher in overweight or obese, with a p-value that was less than or equal to 0.05. This was demonstrated by the fact that the p-value was less than but equal to 0.05. The levels of interleukin-6 (IL-6) in women who were in the control group were not significantly affected by the various categories of BMI ($p < 0.05$).

BMI and IL-18 levels

IL-18 (ng/ml) levels are significantly higher ($p < 0.05$) in the overweight/obese cohort of women who have PCOS. The levels of IL-18 in the control group of women do not exhibit any statistically significant fluctuation ($p < 0.05$) across the different categories of body mass index (BMI).

BMI and CRP levels

There is a tendency for the CRP (mg/dl) to be raised in the overweight/obese group among women who have PCOS. However, it is important to note that this difference does not meet the criteria for statistical significance ($p < 0.05$). There is not a discernible difference in CRP levels across the different BMI categories among the women who make up the control group.

BMI and 8-OHDG levels

The result shows 8-OHDG (pg/ml) in PCOS women is significantly at $p>0.05$ lower in the overweight/obese group. In control women, there is no significant difference in 8-OHDG levels between BMI categories.

Table 2: Relationship between Inflammatory Markers with BMI in PCOS

Parameters	BMI Status	PCOS Women		Controls Women	
		Mean ± SD	P-value	Mean ± SD	P-value
Mcp-1 (ng/ml)	Normal weight	48.71±9.23	**0.002***	59.15±14.23	**0.877**
	Overweight/ Obesity	71.11±18.54		58.47±12.74	
MIF (ng/ml)	Normal weight	8.02±2.53	**0.122 NS**	8.54±2.94	**0.136**
	Overweight/ Obesity	10.01±3.37		7.1±3.02	
TNF (pg/ml)	Normal weight	23.68±11.38	**0.248 NS**	22.65±7.24	**0.067**
	Overweight/ Obesity	28.32±9.95		17.89±9.26	
IL-6 (ng/ml)	Normal weight	4.72±1.49	**0.015***	4.03±2.04	**0.623**
	Overweight/ Obesity	6.51±2.41		4.34±1.93	
IL-18 (ng/ml)	Normal weight	8.7±2.39	**0.020***	10.36±2.45	**0.484**
	Overweight/ Obesity	13.11±5.01		10.88±2.08	
CRP (mg/dl)	Normal weight	4.62±1.44	**0.059 NS**	2.5±1.7	**0.796**
	Overweight/ Obesity	5.71±1.45		2.64±1.7	
8-OHDG (pg/ml)	Normal weight	227.09±42.86	**0.004***	214.85±72.85	**0.832**
	Overweight/ Obesity	165.75±38.49		219.68±68.29	

** Significant differences at p-value≤ 0.05. Median (IQR) inter quartile range. Independent t-test or Mann Whitney test. NS: non-significant.*

DISCUSSION

According to the results of our research, it was shown that all inflammatory indicators, e.g TNF, CRP, IL-18, MIF, IL-6 and MCP-1, are considerably greater in women who have PCOS in comparison to women who acted as controls, with the exception of 8-OHDG. Low-grade chronic inflammation is a persistent immunological inflammation that is defined by a lower degree of inflammatory microenvironment. This kind of inflammation is seen in people who have polycystic ovarian syndrome (PCOS). The opposite of chronic inflammation is acute inflammation, which is brought on by an infection caused by bacteria or viruses. Inflammatory markers and chronic low-grade inflammation states are now acknowledged to have a significant part in the pathogenesis of polycystic ovary syndrome, which is a condition that the disease is named after. Additionally, the development of PCOS symptoms is connected to the intrinsic relationship that exists between inflammatory response (IR) and persistent low-grade inflammation. This association is responsible for the development of PCOS symptoms. Patients diagnosed with PCOS had elevated amounts of inflammatory indicators, involving TNF, monocyte chemoattractant protein-1, IL-6, white blood cell count, and IL-18. When compared to healthy women of the BMI and same biological age, this was the result[15].

Infertility may arise from PCOS, a common reproductive condition that significantly impacts individuals' health, relationships, and economic well-being. A considerable amount of research has been conducted to date, examining the amounts of circulating MCP-1 in women with conditions related to PCOS. The research findings indicate that individuals with PCOS exhibit significantly elevated levels of circulating MCP-1 compared to those without the condition[16].

The findings of our research are in agreement with the observations which made by Koce *et al*.,[17] and Dawood *et al*.,[18] showed an increase in blood IL-18 levels among the group of individuals with PCOS. Al-Musawy *et al*.,[19] revealed data that were similar to those seen in the Iraqi population, which suggests that IL-18 plays a role in the genesis of insulin resistance. It is possible that, this is the cause of the higher levels of IL-18 found in females who were diagnosed with PCOS[20]. The higher levels of IL-18 associated with PCOS may be connected to a genetic variation that is responsible for IL-18, according to the hypothesis put out by Kretowski *et al*.,[21]. This genetic variation may also be known to correlate with obesity and insulin resistance. The findings of our research indicated that interleukin-18 (IL-18) may have a role as an adipogenic cytokine, which is linked to the rise in the prevalence of obesity. In addition, as compared to those who have a lean physique, the adipocytes that are found in obese persons create much higher quantities of the cytokine IL-18. Additionally, those who were classed as obese, demonstrated greater levels of circulating IL-18. This was also the case for individuals who had a high body mass index (BMI)[22].

Our findings indicated that females with polycystic ovary syndrome also likely to have elevated amounts of IL-6. It is well recognized that immune and nonimmune cells, particularly endocrine cells, release the cytokine IL-6, which has pathophysiologic roles in humans[23].

Furthermore, we reported that women, who had polycystic ovary syndrome (PCOS), had an 8-OHdG blood level that was statistically significantly lower than that of healthy controls. This suggests that, rather than low ROS generation in PCOS tissue, the low levels may

be due to either enhanced antioxidant capacity or impaired repair of oxidative DNA damage[24].

MIF plays a role in the pathophysiology of autoimmune disorders, and severe sepsis because of its pro-inflammatory and immunomodulatory characteristics. Disease severity and a poor prognosis are linked to elevated MIF expression[25]. Numerous investigations have demonstrated a connection between MIF and the etiology of PCOS[26]. It has recently been shown by González *et al*.,[27]. polycystic ovary syndrome patients exhibit elevated levels of circulating MIF. These results imply a connection between MIF and the pathophysiology and genesis of PCOS.

CONCLUSION

A strong association between polycystic ovarian syndrome (PCOS) and autoimmune illnesses was shown to exist, according to the results of the particular investigations. The levels of inflammatory markers were significantly different between the control groups and cases with polycystic ovarian syndrome (PCOS). Among the indications that were used: the IL-18, TNF-beta, IL-6, MIF, and MCP-1. The fact that this raises that occurred, shows that those women are enduring low-grade chronic inflammation. The levels of 8-OHdG, which is a measure of oxidative stress, were lower in women who had polycystic ovarian syndrome.

Recommendations

Improving knowledge of the connection between immunity and PCOS given that women with polycystic ovarian syndrome had higher levels of inflammatory markers like CRP, MCP-1, MIF, IL-18, TNF and IL-6 than the control group, more research on the correlation between these markers' levels and the length of the syndrome is advised in order to better understand how inflammation changes over time. Investigate strategies to reduce chronic inflammation correlated with elevated BMI. Given the significant role of therapeutic strategies aimed at reducing inflammation. This could include lifestyle modifications (e.g., weight loss, exercise), dietary interventions (e.g., anti-inflammatory diets).

Ethical approval

Official permission to conduct this study was granted by the Faculty of Science at the University of Kufa, as per the letter addressed to the Fertility Center at Al-Sadr Teaching Hospital. The procedures followed the ethical principles of the Declaration of Helsinki. Sample collection was conducted during the period 2024–2025, and written informed consent was obtained from all participants. The approval was granted on December 9, 2024.

Declarations:

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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