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ORIGINAL ARTICLE

Identification of Biomarker-Based Strategies for Managing Chronic Inflammation in Polycystic Ovarian Syndrome to Alleviate Population-Level Disease Burden

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ABSTRACT

Background: Polycystic Ovarian Syndrome (PCOS) is a common endocrine disorder of women of reproductive age with chronic inflammation, insulin resistance, and metabolic dysfunction. Although it is common in Pakistan, PCOS is underdiagnosed and contributes to the development of infertility, cardiovascular disease, and metabolic complications. As a result, the identification of biomarkers for early diagnosis and effective management of the disease requires strategies based on chronic inflammation.

Objectives: This study was designed to evaluate inflammatory biomarkers in PCOS patients to compare them with healthy controls and to evaluate the relationship with the metabolic parameters to establish potential diagnostic and therapeutic targets of PCOS.

Methods: A cross-sectional study was done at tertiary care hospitals in Lahore, Pakistan, among 120 PCOS patients and 60 age-matched healthy controls. Enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of C reactive protein (CRP), interleukin 6 (IL 6), and tumor necrosis factor-alpha (TNF alpha). Anthropometric and metabolic parameters, which included BMI, WHR, FBG, HOMA-IR, and lipid profile, were assessed. SPSS 25.0 was used to perform statistical analysis, and $p < 0.05$ was taken as statistically significant.

Results: The CRP, IL-6, and TNF-α levels were significantly elevated in PCOS patients compared to controls ($p < 0.001$). Chronic inflammation is also related to metabolic dysfunction as BMI, WHR, insulin resistance, and dyslipidemia are significantly higher.

Conclusion: PCOS is characterized by a pro-inflammatory state, which, together with metabolic and cardiovascular risks, contributes to the pathogenesis of PCOS. This could enable early detection and personalized treatment strategies via biomarker-based screening. Future research will be directed towards Anti-inflammatory interventions, Genetic markers, and Targeted therapies to enhance the management of PCOS in Pakistan.

Keywords: PCOS, Chronic Inflammation, Biomarkers, CRP, IL-6, TNF-α, Insulin Resistance, Metabolic Syndrome, Pakistan.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is a complex endocrine disorder in which a significant number of women of reproductive age present with hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology[1]. It is a major cause of infertility and metabolic disorders, including insulin resistance, type 2 diabetes, dyslipidemia, and cardiovascular complications. PCOS worldwide has a wide range of prevalence, and South Asian women, most of whom are Pakistani, are particularly prone to the disease because of genetic, environmental, and lifestyle factors[2].

Although PCOS is highly prevalent, it is underdiagnosed and mismanaged in Pakistan because of poor awareness, insufficient screening programs, and poor access to specialized medical care. Because many women do not get diagnosed until they develop severe reproductive or metabolic complications, this exacerbates the disease burden[3]. Although PCOS is related to reproductive problems, it has been closely associated with chronic low-grade inflammation, a major pathogenesis driver of insulin resistance, obesity, and cardiovascular diseases. In response to this endothelial damage, pro-inflammatory cytokines are thought to be elevated (C reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF–α), all of which are known to be involved in the pathogenesis of disease and which contribute to the severity of disease) [4].

Identification and application of inflammatory biomarkers in PCOS can be an important means for early diagnosis, targeted therapy, and effective management, as well as being a significant factor in determining the response to therapy and treatment, especially for oral contraceptives, which are used widely for treatment[5]. These biomarkers can be monitored by clinicians to personalize these interventions to prevent chronic inflammation and also prevent the associated metabolic and cardiovascular complications of PCOS. Such an approach is feasible for PCOS diagnosis and management using biomarkers in Pakistan, where health care resources are limited, resulting in the alleviation of long-term disease burden[6].

Furthermore, the interplay between genetics, lifestyle, and environmental factors in Pakistan necessitates a comprehensive approach to PCOS management. Obesity and metabolic dysfunction are ever-increasing in prevalence in the clinical landscape of PCO as a result of diet, physical inactivity, and socio-cultural factors. This rising heath concern necessitates interventions in the areas of high awareness and early screening, as well as lifestyle modifications, which are important public health initiatives[7].

This study attempts to explore the role of inflammatory biomarkers as a means of managing PCOS in the Pakistani population to guide early detection and intervention strategies. Healthcare providers can improve treatment efficacy, improve patient outcomes, and reduce PCOS-related burden on individuals and the healthcare system by using biomarker-based screening and personalizing the therapeutic approaches[8, 9].

MATERIALS AND METHODS

Study Design and Setting: This was a cross-sectional study conducted at different tertiary care hospitals in Lahore, Pakistan, for 12 months from January 2022 to January 2023. The study was conducted by the International Review Board (IRB), and all participants gave written informed consent before their enrollment. The objective of the study was to assess the role of inflammatory biomarkers in Pakistani women diagnosed with polycystic ovarian syndrome (PCOS) and to determine their significance in disease management.

Study Population: In the study, 120 women with PCOS, according to the Rotterdam criteria, were recruited. For comparison, a control group of 60 age-matched healthy women without PCOS was also included. Specific inclusion and exclusion criteria were used to select participants so that there is uniformity in data collection and confounding variables. Participants had to be women aged 18–40 years old with a confirmed diagnosis of PCOS according to at least two of the three Rotterdam criteria, i.e., hyperandrogenism (clinical or biochemical), ovarian dysfunction (irregular or absent menstrual cycle) and polycystic ovarian morphology on ultrasound. The study also included women who had not been treated hormonally in the past three months. Participants who were pregnant, lactating, with a history of other endocrine disorders like Cushing's syndrome or thyroid disease, chronic inflammatory diseases such as rheumatoid arthritis or lupus, or used anti-inflammatory medications or hormonal therapy in the past 3 months.

Biomarker Assessment: All participants had blood samples drawn after an overnight fast for measurement of serum inflammatory biomarkers. C reactive protein (CRP), interleukin 6 (IL6), and tumor necrosis factor-alpha (TNFα) were the biomarkers examined. The sensitivity of CRP as a marker of systemic inflammation was analyzed by a high-sensitivity ELISA. IL-6, which is a pro-inflammatory cytokine involved in metabolic dysfunction, and TNF-α, which is a cytokine involved in immune regulation, were also measured using ELISA kits. Blood samples were processed immediately, and measurements were all performed in a standard laboratory setting, with all measurements being taken in a standard laboratory setting to ensure accuracy and reliability.

Anthropometric and Metabolic Assessments: Anthropometric and metabolic assessments were performed on the participants to evaluate their metabolic profiles. Body mass index (BMI) was used as a weight in kilograms divided by height in meters squared (kg/m²) to assess overall obesity. Central obesity was assessed by measurements of waist-to-hip ratio (WHR). The glucose oxidase method was used to evaluate fasting blood glucose (FBG) fasting insulin levels, and the HOMA-IR was calculated from ELISA. A lipid profile analysis, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, was carried out to find out about cardiovascular risk factors connected with PCOS by utilizing an automated biochemistry analyzer.

Lifestyle and Dietary Analysis: A structured questionnaire was completed by participants to ascertain lifestyle factors, dietary habits, and physical activity levels. The International Physical Activity Questionnaire (IPAQ) was used to evaluate the physical activity status of individuals as sedentary, moderately active, or highly active. A food frequency questionnaire to assess dietary habits was used to record the intake of high-fat, high-sugar, and fiber foods. Additionally, smoking status and other lifestyle factors that might influence inflammation and metabolic parameters were noted.

Statistical Analysis: SPSS version 25.0 software was used to analyze all collected data. Demographic and clinical characteristics were given descriptive statistics and mean values with standard deviations. Student's t-test and Mann Whitney U test were conducted on normally and non normally distributed variables, respectively, for PCOS and control groups. Pearson's correlation coefficient was used to analyze the correlations of inflammatory biomarkers with metabolic parameters to determine the strength and direction of associations. All the analyses were deemed statistically significant if a p-value was less than 0.05, and thus, the reliability and validity of the findings were ensured.

RESULTS

The findings of the study show the difference in the inflammatory biomarkers, metabolic parameters, and anthropometric indices of the PCOS group compared to the control group (Table 1).

Inflammatory Biomarkers: Inflammatory biomarkers were significantly increased in PCOS patients compared to the control group. The levels of mean CRP were 5.8 ± 1.3 mg/L in the PCOS group, which was significantly higher than in the control group, 2.1 ± 0.7 mg/L ($p < 0.001$, Table 1). Likewise, IL-6 and TNF-α levels were elevated in PCOS patients (12.4 ± 2.1 pg/mL; 8.9 ± 1.7 pg/mL) compared to controls (5.6 ± 1.4 pg/mL; 3.5 ± 0.9 pg/mL; $p < 0.001$; Table 1), indicating very strong statistical significance.

Anthropometric Measurements: Table 1. BMI (kg/m²) of PCOS patients (29.6 ± 4.1) was significantly higher than that of controls (23.4 ± 3.5, $p < 0.001$). In PCOS individuals, waist-to-hip ratio (WHR) increased significantly to the point of 0.89 ± 0.04 compared to controls (0.79 ± 0.03, $p < 0.001$, Table 1), indicating greater central adiposity in affected women.

Metabolic Parameters: Fasting blood glucose (FBG) was significantly increased in the PCOS subjects (108.5 ± 15.2 mg/dL) compared to controls (90.2 ± 12.7 mg/dL) ($p < 0.001$, Table 1). The HOMA-IR value was also increased markedly in PCOS patients ($p < 0.001$, Table 1), which confirmed the strong association between PCOS and metabolic dysfunction compared with controls (3.2 ± 0.6 vs 1.9 ± 0.4).

Lipid Profile: The lipid profile analysis indicated that total cholesterol and LDL levels were significantly higher in the PCOS patients (198.6 ± 22.4 mg/dL and 134.2 ± 18.6 mg/dL, respectively) versus the controls (176.3 ± 18.5 mg/dL and 112.4 ± 16.2 mg/dL respectively) ($p < 0.001$, Table 1). PCOS patients had lower HDL levels compared to controls (45.6 ± 6.3 mg/dL vs. 53.8 ± 7.1 mg/dL, $p = 0.002$, Table 1). PCOS patients (156.8 ± 19.2 mg/dL) had also higher levels of triglycerides than controls (128.4 ± 15.8 mg/dL) ($p < 0.001$, Table 1).

Interpretation: These results emphasize a significant proinflammatory state, central obesity, insulin resistance, and dyslipidemia, which are all related to long-term cardiovascular risks and are associated with PCOS.

CRP, IL-6, and TNF α levels are significantly higher in PCOS patients, leading to the possibility of the use of targeted anti-inflammatory interventions for controlling disease severity (Table 1). These findings highlight the importance of early screening and lifestyle modifications to prevent the metabolic and cardiovascular complications of PCOS.

Table 1: Comparison of Inflammatory, Metabolic, and Anthropometric Parameters Between PCOS and Control Groups

Parameter	PCOS Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
CRP (mg/L)	5.8 ± 1.3	2.1 ± 0.7	<0.001
IL-6 (pg/mL)	12.4 ± 2.1	5.6 ± 1.4	<0.001
TNF-α (pg/mL)	8.9 ± 1.7	3.5 ± 0.9	<0.001
BMI (kg/m²)	29.6 ± 4.1	23.4 ± 3.5	<0.001
WHR	0.89 ± 0.04	0.79 ± 0.03	<0.001
FBG (mg/dL)	108.5 ± 15.2	90.2 ± 12.7	<0.001
HOMA-IR	3.2 ± 0.6	1.9 ± 0.4	<0.001
Total Cholesterol (mg/dL)	198.6 ± 22.4	176.3 ± 18.5	<0.001
LDL (mg/dL)	134.2 ± 18.6	112.4 ± 16.2	<0.001
HDL (mg/dL)	45.6 ± 6.3	53.8 ± 7.1	0.002
Triglycerides (mg/dL)	156.8 ± 19.2	128.4 ± 15.8	<0.001

All values are presented as mean ± standard deviation. A p-value ≤ 0.05 is considered statistically significant

DISCUSSION

This study's findings strongly indicate that chronic low-grade inflammation is an important factor in the pathophysiology of polycystic ovarian syndrome (PCOS) and contributes largely to insulin resistance, obesity, and metabolic dysfunction [10]. This study is in line with previous studies, significantly higher levels of CRP, IL6, and TNFα in the PCOS group compared to healthy controls (Table 1) were found. Previous Studies have shown that chronic inflammation in PCOS is mostly due to increased visceral adiposity and hyperinsulinemia, which induce the production of pro-inflammatory cytokines. Previous studies also show that inflammatory pathways in PCOS patients play a role in increasing oxidative stress and endothelial dysfunction, and vice versa. Our study findings further validate these observations in the Pakistani

population, underscoring the need for early intervention strategies for this demographic[11, 12].

In PCOS patients, anthropometric and metabolic parameters such as BMI, WHR, fasting glucose, and HOMA-IR were also significantly higher, which confirms the established close correlation between PCOS and metabolic syndrome. According to Sidra et al. (2019), previous reports have stated that obesity and insulin resistance in PCOS are both independent and interrelated risk factors that worsen inflammation and hormonal imbalances[13]. Our study results of lipid profile abnormalities such as increased total cholesterol, LDL, triglycerides, and decreased HDL levels are in agreement with the findings of Akram et al. (2020), who reported similar dyslipidemic patterns in PCOS patients, implying increased cardiovascular risk. If not appropriately addressed, these metabolic alterations can predispose PCOS patients to type 2 diabetes, atherosclerosis, and hypertension, and thus, metabolic screening is warranted at the clinic[14, 15].

However these results offer important information about inflammatory and metabolic disturbances in PCOS, but limitations[16]. First, this study adopted a cross-sectional design that does not allow to set up causal relationships between inflammation and disease progression. Second, the sample size of 120 PCOS patients and 60 controls is adequate but may not completely represent the genetic and environmental influences on PCOS in Pakistan. Third, the use of self-reported questionnaires for assessment of such lifestyle factors as dietary habits, stress levels, and physical activity, which are known to affect inflammation and metabolic parameters, may introduce bias[17, 18]. Fourth, inflammatory markers such as CRP, IL-6, and TNF-α and their potential contributors to inflammation in PCOS, such as oxidative stress markers and adipokines (e.g., leptin, adiponectin, resistin), were not examined in this study. Additional studies that include a wider range of biomarkers will be required to gain a better picture of how inflammatory mechanisms may be involved in PCOS[19, 20].

CONCLUSION

This study demonstrates that chronic inflammation is a key factor in the pathophysiology of PCOS and significantly contributes to both insulin resistance and obesity associated with PCOS and dyslipidemia. Biomarker-based screening for early diagnosis and risk stratification is suggested by the elevated levels of CRP, IL-6, and TNF-α observed in PCOS patients. The very strong metabolic and cardiovascular implications of PCOS should lead to the routine incorporation of inflammatory biomarker assessment in clinical practice, especially in resource-limited settings such as Pakistan, where such tests will be affordable. Future research should study the long-term effect of chronic inflammation on metabolic health in PCOS patients and interventional trials to determine if anti-inflammatory therapies, lifestyle modifications, and pharmacological agents can decrease disease severity. Furthermore, genetic and molecular studies related to the underlying mechanisms between inflammation and PCOS progression should be conducted to develop personalized treatment strategies. Biomarker-based screening programs could be expanded to the population level to mitigate the burden of disease and improve health outcomes amongst women with PCOS.

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