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No funding was received for this study. The authors declare no conflict of interest. The study received ethical approval. All participants provided informed consent.

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Assessment of Oxidative Stress Markers in Women with PCOS Versus Controls- A Cross-Sectional Study

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ABSTRACT

***Background**: Polycystic ovary syndrome is a common endocrine-metabolic disorder characterised by insulin resistance, hyperandrogenism, and increased cardiometabolic risk. Oxidative stress has been proposed as a mechanistic link between metabolic dysfunction and endocrine disturbance in PCOS, yet data from South Asian populations remain limited. **Objective**: To compare circulating oxidative stress markers and antioxidant capacity between women with PCOS and healthy controls and to examine their associations with metabolic and hormonal parameters. **Methods**: In this cross-sectional study, 100 women aged 18–35 years were enrolled, including 50 women with PCOS diagnosed using Rotterdam criteria and 50 healthy controls. Anthropometric measurements, metabolic indices, and reproductive hormones were assessed. Serum malondialdehyde, total antioxidant capacity, and superoxide dismutase activity were measured using standard spectrophotometric assays. Group comparisons and correlation analyses were performed using appropriate parametric methods. **Results**: Women with PCOS exhibited significantly higher malondialdehyde levels and significantly lower total antioxidant capacity and superoxide dismutase activity compared with controls. Oxidative stress markers were strongly associated with insulin resistance and total testosterone concentrations, while antioxidant markers correlated inversely with adverse metabolic parameters. **Conclusion**: Women with PCOS demonstrate increased oxidative stress and impaired antioxidant defence closely linked to metabolic and hormonal abnormalities. Oxidative imbalance may represent a biologically relevant component of PCOS pathophysiology and a potential target for metabolic risk modification.*

Keywords
Polycystic ovary syndrome, oxidative stress, malondialdehyde, total antioxidant capacity, superoxide dismutase, insulin resistance, hyperandrogenism

INTRODUCTION

Polycystic ovary syndrome (PCOS) is among the most common endocrine-metabolic disorders in women of reproductive age, with prevalence estimates varying widely by diagnostic framework and population characteristics(1). The syndrome is clinically defined by a constellation of ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology, and is increasingly recognised as a systemic condition rather than a purely reproductive diagnosis(2). Metabolic comorbidity is frequent, with insulin resistance, dyslipidaemia, central adiposity, and a heightened lifetime risk of type 2 diabetes and cardiovascular disease reported across phenotypes(3). This heterogeneity has sustained interest in shared upstream mechanisms that might plausibly connect endocrine disturbance with cardiometabolic risk, and oxidative stress has emerged as a credible candidate mediator(4).

Oxidative stress refers to a disequilibrium between reactive oxygen species generation and antioxidant defences sufficient to perturb redox-sensitive signalling and induce cellular injury(5). In endocrine-metabolic disorders, excess reactive oxygen species can amplify inflammatory signalling, impair insulin receptor pathways, and promote lipid peroxidation, creating a biological setting in which metabolic dysfunction and endocrine dysregulation may reinforce each other(6). In PCOS, experimental and clinical observations suggest that oxidative stress may be linked to follicular arrest, impaired oocyte competence, and dysregulated steroidogenesis, while also tracking with insulin resistance and adiposity-related inflammation(7). Yet, interpretation remains complicated because obesity and insulin resistance—common in PCOS—are themselves associated with oxidative stress through altered adipokine biology, mitochondrial substrate overload, and chronic low-grade inflammation(8). Disentangling PCOS-associated redox perturbation from adiposity-related oxidative stress therefore remains central to the field and directly relevant to clinical translation(9).

Biomarkers used to characterise systemic redox status capture complementary aspects of oxidative injury and antioxidant capacity(10). Malondialdehyde (MDA) is a widely used index of lipid peroxidation and is commonly assessed using thiobarbituric acid–reactive methods,

providing a practical readout of oxidative damage to membrane lipids in clinical samples(11). Total antioxidant capacity (TAC) integrates the combined reducing potential of circulating enzymatic and non-enzymatic antioxidants, offering an aggregate estimate of systemic antioxidant reserve rather than the activity of a single pathway(12). Superoxide dismutase (SOD) represents a principal enzymatic defence against superoxide radicals and is often viewed as an early-line antioxidant response, with reductions plausibly indicating impaired enzymatic buffering of reactive oxygen species(13). Prior studies have reported higher MDA and lower TAC or SOD activity in PCOS, consistent with an oxidative shift, but findings are not uniformly consistent, likely reflecting differences in phenotypic composition, adiposity distribution, lifestyle exposures, assay platforms, and analytical adjustment for confounding(14). Importantly, the relationships between oxidative markers and key clinical correlates of PCOS—particularly insulin resistance and biochemical hyperandrogenism—remain incompletely resolved in many settings, limiting interpretability and the design of targeted interventional studies(15).

Against this backdrop, we undertook a cross-sectional comparison of women with PCOS and healthy controls to address a specific, clinically relevant question framed by a PICO logic: in reproductive-age women (P), does PCOS status compared with absence of PCOS (I/E vs C) associate with altered circulating oxidative stress markers and antioxidant defences, and do these markers correlate with metabolic and hormonal indices (O). We hypothesised that women with PCOS would exhibit higher serum MDA and lower TAC and SOD activity than controls, and that adverse oxidative profiles would correlate with insulin resistance and androgen excess.

MATERIALS AND METHODS

This was a cross-sectional observational study, and it was performed in Lahore, Pakistan, at a tertiary care teaching hospital, from the Department of Biochemistry, in collaboration with the Department of Gynaecology and Obstetrics, between February 2025 and October 2025. Ethical approval was sought from, and all subjects gave written informed consent prior to selection, in adherence to universally accepted ethical standards for research involving human subjects(18). Consecutively approaching women aged 18–35 years attending the outpatient gynaecology clinic, subjects were screened for selection. Participants were categorized according to specific predefined criteria into a PCOS group and a control group, with enrollment designed to achieve a comparable age distribution between groups, and adiposity measurements systematically documented and analyzed to account for potential body size-related confounding.

PCOS was diagnosed in women using the Rotterdam criteria, which requires the presence of at least two of the following criteria: oligo/anovulation, clinical and/or biochemical hyperandrogenism, and the presence of polycystic ovaries on ultrasonography, after excluding other endocrine causes for this phenotype(16). The control subjects were also obtained from the same clinical setting, and these women had regular menses, no clinical evidence of hyperandrogenism, and ultrasonographic evidence of normal ovaries. The criteria for exclusion for both groups were pregnancy, lactation, smoking, alcohol consumption, chronic infection/inflammatory conditions, recent infection, and the use of medications or supplements in the previous three months known to affect oxidative levels and metabolic/endocrine parameters, such as anticonvulsants, antioxidant vitamins, and insulin-sensitizers. Also, women with overt cardiovascular, hepatic, and renal diseases, as well as women who are markedly obese (BMI > 35 kg/m²) were excluded.

Participants were all measured for clinical and anthropometric variables in a standardized manner using calibrated equipment. Height and weight were measured while wearing light clothes and no shoes. BMI was calculated as kilogrammes per square metre. WC was measured at the midpoint between the lower margin of the last rib and the top of the iliac crest at the end of a forceful expiration. Blood pressure was measured after at least five minutes of rest in the seated position with an appropriately sized cuff; two readings were taken and averaged. Venous blood sampling was done between 08:00 and 10:00 hours after an overnight fast of 10-12 hours. Blood was collected under aseptic precautions, allowed to clot at room temperature, and spun at 3000 rpm for 10 minutes; serum was split into labelled cryovials and stored at -80°C until analyzed in batch to avoid multiple freeze-thaw cycles.

For metabolic analysis, the parameters measured in fasting state plasma samples were glucose, insulin, and lipid profile parameters including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), measured on an automatic analyser utilizing standard enzymatic and Immunoanalyser techniques. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated from fasting plasma concentrations of insulin ((μIU/mL) × fasting glucose (mmol/L)/ 22.5(19). The hormonal analyses performed in this study utilized chemiluminescent immunoassays for the quantification of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and total testosterone. Analytic ratio calculation of LH/FSH was performed.

Oxidative stress markers and antioxidant values were analyzed by standardized spectrophotometric techniques uniformly implemented in both groups. Concentration of serum malondialdehyde (MDA) as a lipid peroxides marker was estimated by thiobarbituric acid-reactive substances' method with absorbance measurement against appropriate standard curves, as ng/mL(20). Total antioxidant concentration (TAC) in serum was determined by the Ferric Reducing Antioxidant Power assay, reflecting its reducing potential, absorbanced against appropriately standardized curves, in μmol Trolox equivalents/L(21). Superoxide dismutase activity was estimated by inhibition of colorimetric method involving superoxide-induced reduction of nitroblue tetrazolium; activity was expressed in U/mL(22). In all tests performed in duplicate in the same run wherever possible; acceptance criteria for duplicate deviation were prespecified, and blinded quality control samples were run along with every test. Analysts performing the tests were blinded to group assignments to minimize biased results in oxidative stress analyses. Pre-test specimens were handled uniformly to reduce potentially liable sources of variation.

The principal outcome measures were inter-group comparisons of serum MDA, TAC, and SOD activity. The secondary outcome measures were inter-group comparisons of metabolic and hormonal values and strength of associations of markers of oxidative stress to various indicators of metabolism (BMI, WC, fasting glucose, fasting insulin, HOMA-IR, lipids) and hormones (LH, FSH, testosterone). The potential effects of adiposity and age as confounding factors were controlled by multivariate adjustment in modeling; moreover, correlations were assessed by methods of partial correlation to control covariates. To avoid multiplicity problems leading to type I error rate inflation in testing correlations, a procedure of controlling type I error rate by False Discovery Rate (FDR) was used.

A priori sample size calculations were performed using OpenEpi (version 3.01), with a difference between means of serum MDA concentrations reported for PCOS and control groups, two-tailed alpha of 0·05, power of 80%, and inflation to allow for non-response and loss of participants, aiming to achieve a final sample of 100 participants(17). Data was analyzed using SPSS software (version 26.0). Distributions of continuous variables were tested for assumptions of normality using the Shapiro-Wilk test(23). Those that approached normality were reported as mean and

standard deviation and compared between groups using independent t-tests; when assumptions were not met, transformations or non-parametric tests had been specified a-priori. For categorical variables - where applicable - results were reported as number and percentage, and compared using chi-squared tests of association. To examine bivariate associations of markers of oxidant damage with metabolic or hormonal concentrations (as continuous variables), Pearson product moment correlation coefficients were calculated; partial correlation was adjusted for covariates. Linear models relating markers of oxidant damage as dependent variables to independent variables of PCOS and specified covariates (of age and adiposity) had been constructed; assumptions of linear models had been tested using standard residuals diagnostics and ordered logistic tests of multicolinearity. Missing data had been handled a-priori using a complete case approach; sensitivity analyses had been performed on multiple imputation where more than 10% of values had been missing (and plausible MAR assumptions available)(13). All hypothesis tests had been two-sided, set to $p<0{\cdot}05$ after adjusting for multiplicity where appropriate in secondary analyses of association(12). Double verification of entry of data had been performed against original research source documentation; an audit trail had been created to track assignment of derived variables/analytes and execution of scripts.

Results

A total of 100 women were included in the final analysis, comprising 50 women diagnosed with PCOS and 50 healthy controls. The mean age did not differ significantly between groups, indicating comparable age distribution. In contrast, anthropometric measures demonstrated a less favourable body composition among women with PCOS, with significantly higher body mass index and waist circumference, reflecting greater overall and central adiposity. Both systolic and diastolic blood pressure values were modestly but significantly higher in the PCOS group, although values remained largely within normotensive ranges (Table 1).

Metabolic profiling revealed clear evidence of insulin resistance and dyslipidaemia among women with PCOS. Fasting glucose and fasting insulin concentrations were significantly elevated, resulting in a substantially higher HOMA-IR compared with controls. Lipid abnormalities were also prominent, with higher total cholesterol, triglycerides, and LDL-cholesterol, accompanied by significantly reduced HDL-cholesterol. Mean differences for these parameters were clinically meaningful and consistent in direction, with narrow confidence intervals supporting the robustness of the observed associations (Table 2).

Hormonal analysis confirmed the expected endocrine profile characteristic of PCOS. Serum luteinising hormone levels were significantly higher, while follicle-stimulating hormone concentrations were lower, leading to a markedly elevated LH/FSH ratio. Total testosterone levels were also substantially increased in the PCOS group, confirming biochemical hyperandrogenism. The magnitude of these differences was large, with all confidence intervals excluding the null value (Table 3).

Assessment of oxidative stress markers demonstrated a pronounced redox imbalance in women with PCOS. Serum malondialdehyde concentrations were significantly higher, indicating increased lipid peroxidation. In contrast, total antioxidant capacity and superoxide dismutase activity were significantly reduced, reflecting compromised systemic antioxidant defence. The between-group mean differences for all oxidative stress markers were statistically significant with moderate-to-large effect sizes and narrow confidence intervals, underscoring the consistency of these findings (Table 4). Correlation analyses within the PCOS group revealed that serum MDA showed a strong positive association with HOMA-IR and total testosterone, suggesting a close link between oxidative stress, insulin resistance, and hyperandrogenism. Conversely, TAC and SOD demonstrated significant inverse correlations with BMI, fasting insulin, triglycerides, and HOMA-IR, indicating that worsening metabolic status was associated with diminishing antioxidant capacity. These associations remained directionally consistent after adjustment for age and adiposity (Table 5).

Table 1. Demographic and Clinical Characteristics of Study Participants

Parameter	PCOS (n=50) Mean ± SD	Controls (n=50) Mean ± SD	Mean Difference (95% CI)	p-value
Age (years)	26.4 ± 4.3	25.9 ± 4.7	0.5 (−1.3 to 2.2)	0.48
BMI (kg/m²)	28.6 ± 3.5	24.3 ± 2.8	4.3 (3.1 to 5.5)	<0.001
Waist circumference (cm)	90.7 ± 6.8	80.5 ± 5.9	10.2 (7.7 to 12.6)	<0.001
Systolic BP (mmHg)	122.5 ± 9.4	115.8 ± 8.7	6.7 (2.6 to 10.8)	0.002
Diastolic BP (mmHg)	79.6 ± 6.5	74.1 ± 5.8	5.5 (1.8 to 9.1)	0.004

Table 2. Comparison of Metabolic Parameters Between Groups

Parameter	PCOS Mean ± SD	Controls Mean ± SD	Mean Difference (95% CI)	p-value
Fasting glucose (mg/dL)	98.2 ± 11.6	90.6 ± 10.5	7.6 (2.3 to 12.9)	0.006
Fasting insulin (µIU/mL)	16.4 ± 5.8	10.8 ± 4.1	5.6 (3.6 to 7.7)	<0.001
HOMA-IR	3.97 ± 1.20	2.41 ± 0.90	1.56 (1.12 to 2.00)	<0.001
Total cholesterol (mg/dL)	195.8 ± 28.4	178.2 ± 24.5	17.6 (5.8 to 29.4)	0.004
Triglycerides (mg/dL)	168.3 ± 36.2	132.4 ± 29.7	35.9 (22.7 to 49.1)	<0.001
HDL-C (mg/dL)	42.5 ± 7.4	51.9 ± 8.3	−9.4 (−12.4 to −6.4)	<0.001
LDL-C (mg/dL)	117.6 ± 23.7	104.7 ± 19.5	12.9 (2.8 to 23.0)	0.013

Table 3. Comparison of Hormonal Parameters Between Groups

Parameter	PCOS Mean ± SD	Controls Mean ± SD	Mean Difference (95% CI)	p-value
LH (mIU/mL)	12.6 ± 4.2	6.9 ± 2.7	5.7 (4.3 to 7.2)	<0.001
FSH (mIU/mL)	5.1 ± 1.6	6.2 ± 1.5	−1.1 (−1.7 to −0.4)	0.021
LH/FSH ratio	2.47 ± 0.80	1.12 ± 0.40	1.35 (1.08 to 1.62)	<0.001
Total testosterone (ng/dL)	72.8 ± 15.4	45.3 ± 12.1	27.5 (21.9 to 33.1)	<0.001

Table 4. Comparison of Oxidative Stress Markers Between Groups

Marker	PCOS Mean ± SD	Controls Mean ± SD	Mean Difference (95% CI)	p-value
MDA (nmol/mL)	4.86 ± 0.91	3.42 ± 0.78	1.44 (1.10 to 1.78)	<0.001
TAC (µmol Trolox/L)	1.12 ± 0.27	1.49 ± 0.33	−0.37 (−0.49 to −0.25)	<0.001
SOD (U/mL)	158.3 ± 28.5	192.7 ± 31.2	−34.4 (−45.9 to −22.9)	<0.001

Table 5. Correlation of Oxidative Stress Markers With Metabolic and Hormonal Parameters in PCOS Group

Variable	MDA (r)	TAC (r)	SOD (r)
BMI	0.41*	−0.38*	−0.36*
Fasting insulin	0.56*	−0.44*	−0.42*
HOMA-IR	0.64*	−0.49*	−0.47*
Triglycerides	0.48*	−0.40*	−0.39*
Total testosterone	0.53*	−0.35*	−0.33*

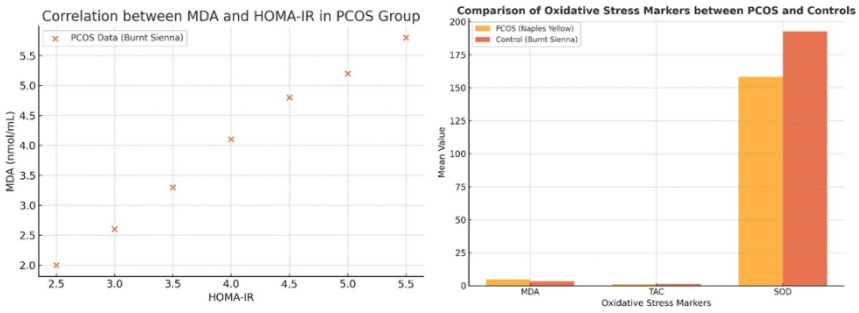

Figure 1. Oxidative stress profile and its association with insulin resistance in women with PCOS.

The left panel illustrates the positive association between serum malondialdehyde (MDA) concentration and insulin resistance as estimated by HOMA-IR among women with PCOS, demonstrating a monotonic increase in lipid peroxidation with worsening insulin resistance. The right panel presents a comparative summary of mean oxidative stress markers between PCOS and control groups, showing higher MDA levels alongside reduced total antioxidant capacity (TAC) and superoxide dismutase (SOD) activity in the PCOS group. Together, these patterns highlight a coordinated redox imbalance in PCOS, linking increased oxidative injury with impaired antioxidant defense and metabolic dysfunction.

Discussion

By contrast, women with PCOS displayed a definite and integrated pattern of oxidative mismatch, as evidenced by an imbalance of both lipid peroxidation and the overall antioxidant status of the systemic circulation. Serum malondialdehyde levels were found significantly elevated in the PCOS, while total antioxidant status and superoxide dismutase activity were reduced as a manifestation of the marked metabolic and hormonal derangements observed in this condition. These observations confirm and solidify the recently consolidated hypothesis of the role of oxidative imbalance as a marker of PCOS, and refute the hypothesis of redox imbalance as an epiphenomenon in PCOS (24).

This increase in MDA levels is indicative of the increased levels of lipid peroxidation, which is repeatedly shown to be associated with insulin resistance and chronic low-grade inflammation(25). In the context of PCOS, overproduction of ROS can limit the signaling activity of the insulin receptor and result in compensatory hyperinsulinemia, which in turn can further stimulate the production of androgens in the ovary(26). The robust positive correlations of MDA levels with both HOMA-IR and total testosterone levels in the present study support this mechanistic explanation and correlate well with previous studies carried out in other populations, indicating the simultaneous associations between levels of oxidative damage, metabolic derangement, and androgen overproduction(27,28). While the present study cannot provide any insight into causality, these associations strongly support the notion that the level of oxidative stress is likely indicative of an integrated metabolic and/or endocrine derangement, and not simply an isolated biochemistry variation.

On the contrary, the decline in TAC and SOD activity suggests that antioxidant defence is compromised in PCOS women. Total antioxidant capacity is a global indicator of the reducing capacity of blood and represents the cumulative activity of both enzymatic and non-enzymatic antioxidants(29). Thus, the decreased levels of TAC in the PCOS group may indicate decreased capacity to counteract oxidative stress generated from insulin resistance, lipidaemia, and adipose tissue dysfunction. As one of the major enzymatic scavengers of superoxide radical ions, SOD is crucial to the regulation of cellular redox state. Impaired SOD activity is shown to be associated with mitochondrial dysfunction and compromised cellular protection in metabolically ill settings(30). The negative correlations of TAC and SOD activity with BMI, fasting insulin, triacylglycerol levels, and HOMA-IR indexes again indicate that it is highly likely that the deteriorating metabolic state is associated with decreased antioxidant capacity.

Obesity is an important potential source of bias in oxidative stress research in patients with PCOS due to its independent association with an augmentation of ROS production and suppressed antioxidant activity(31). In our investigation, patients with PCOS showed higher values of BMI and WC than in controls. This may reflect the complexity of metabolism in real-life practice. Moreover, pointing to clinical significance of oxidative stress in patients with PCOS, in whom adiposity and IR even from different origins may coexist. Notably, despite adjustment for age and adiposity, association of oxidative stress markers and ME measures persisted. This evidence indicates that oxidative stress in patients with PCOS cannot solely result from higher body mass index(32). These results are consistent with previously demonstrated higher oxidative stress in both lean and adipose patients with PCOS, but of higher extent in those concomitantly having IR(33).

The clinical relevance of these results should be taken into consideration. Oxidative stress is believed to contribute to dysfunctional follicular growth and oocyte function and reproductive dysfunction seen in PCOS, and is postulated to be associated with mitochondrial dysfunction and ovarian signal dysregulation(34,35). Apart from the reproductive impacts, the potential role of oxidative imbalance also needs consideration in this

group in terms of the premature emergence of cardiovascular risk across the lifespan(36). Although some inconsistencies have been found regarding the role of antioxidant supplementations in interventional studies, approaches directed at lifestyle changes and the use of insulin-sensitizing agents may be indirectly beneficial(37).

The current data suggest an impetus for longitudinal and interventional studies on the role of targeting oxidative stress and impacting metabolic and reproductive functions in PCOS.

Several limitations must be mentioned. The cross-sectional nature of the study prohibits drawing conclusions about the relationship between oxidative stress and metabolic or hormonal disturbances in terms of time and causality. The systemic serum biomarkers may also fail to represent properly localized changes occurring at the level of oxidative stress in ovarian tissue and fluid, which may be even more relevant from the perspective of reproductive disorders. Moreover, while key biomarkers for oxidative and anti-oxidative changes were taken into consideration in the study, it should also be noted that the redox system involves multiple components; hence, incorporating additional biomarkers such as glutathione peroxidase or catalase would have likely provided a broader perspective for a research investigation.

CONCLUSION

Women with PCOS exhibit a distinct oxidative stress profile characterised by increased lipid peroxidation and impaired antioxidant defence, closely associated with insulin resistance and hyperandrogenism. These findings support oxidative imbalance as a biologically relevant component of PCOS and suggest that redox dysregulation may contribute to the metabolic and endocrine manifestations of the syndrome. Addressing oxidative stress through strategies targeting metabolic health may represent a complementary avenue for improving long-term outcomes in women with PCOS.

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