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ORIGINAL ARTICLE

Association of Insulin Resistance, Lipid Profile, Hormonal Imbalance, and Gastrointestinal Metabolic Parameters in Women with Polycystic Ovary Syndrome Receiving Metformin Therapy

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a complex endocrine–metabolic disorder characterized by insulin resistance, dyslipidemia, androgen excess, and hepatic metabolic disturbances. Metformin is widely prescribed to improve insulin sensitivity; however, its broader metabolic and gastrointestinal effects remain incompletely defined in routine clinical settings.

Objective: To evaluate the association of insulin resistance, lipid profile, hormonal imbalance, and gastrointestinal metabolic parameters in women with PCOS receiving metformin therapy over a six-month period.

Methods: This prospective observational study included 90 women diagnosed with PCOS at Aziz Bhatti Shaheed Teaching Hospital, Gujrat, and the Department of Gynaecology & Obstetrics, KRL Hospital, Islamabad, from February 2022 to January 2023. Baseline clinical, metabolic, hormonal, and hepatic parameters were assessed and compared with six-month post-treatment values. Key outcomes included changes in HOMA-IR, lipid profile, reproductive hormones, and hepatic metabolic markers including ALT, AST, GGT, and the Hepatic Steatosis Index (HSI). Statistical analysis was performed using paired comparisons, correlation testing, and multivariable regression modeling.

Results: Eighty-four participants completed the study. Metformin therapy significantly reduced fasting insulin and HOMA-IR (3.98 ± 1.55 to 2.78 ± 1.29; $p < 0.001$) and improved lipid parameters including triglycerides and LDL-C. Hormonal improvements included reduced total testosterone and increased SHBG, with a corresponding decrease in LH/FSH ratio. Gastrointestinal–metabolic indices demonstrated favorable changes, including reductions in ALT, GGT, and HSI. Higher baseline BMI and HOMA-IR were independent predictors of greater improvement in insulin resistance.

Conclusion: Metformin therapy leads to meaningful improvements in insulin resistance, lipid abnormalities, androgen excess, and hepatic metabolic stress in women with PCOS. These findings underscore the importance of comprehensive metabolic monitoring and support metformin as a cornerstone therapy in the integrated management of PCOS.

Keywords: Polycystic ovary syndrome; Metformin; Insulin resistance; HOMA-IR; Dyslipidemia; Hyperandrogenism; Liver enzymes; Hepatic Steatosis Index.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine–metabolic disorders affecting women of reproductive age, with a global prevalence ranging from 6% to 20%, depending on diagnostic criteria[1]. It is characterized by a triad of chronic anovulation, hyperandrogenism, and polycystic ovarian morphology, but its clinical relevance extends far beyond reproductive dysfunction. Over the last decade, PCOS has increasingly been recognized as a systemic metabolic condition, strongly linked with insulin resistance, compensatory hyperinsulinemia, dyslipidemia, hepatic metabolic stress, and chronic low-grade inflammation. These metabolic abnormalities contribute not only to the reproductive manifestations of PCOS but also to the long-term risk of type 2 diabetes mellitus, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD)[2,3].

Insulin resistance plays a central mechanistic role in PCOS pathophysiology. Hyperinsulinemia amplifies ovarian theca cell androgen production, suppresses hepatic synthesis of sex hormone–binding globulin (SHBG), and disrupts hypothalamic–pituitary–ovarian feedback regulation, collectively driving hyperandrogenism and ovulatory dysfunction[4]. In parallel, insulin resistance adversely affects lipid metabolism, leading to elevated triglycerides, reduced HDL-cholesterol, and increased hepatic fat accumulation. These metabolic disturbances are often accompanied by subtle but clinically relevant alterations in gastrointestinal (GI) metabolic markers such as ALT, AST, and GGT which serve as surrogate indicators of hepatic insulin resistance and early NAFLD[5,6].

Metformin remains a cornerstone therapy for PCOS, particularly among overweight women or those demonstrating marked insulin resistance[7]. Its therapeutic benefits extend beyond glucose lowering: metformin enhances peripheral insulin sensitivity, suppresses hepatic gluconeogenesis, modulates bile acid metabolism, alters gut microbiota composition, and improves GLP-1–mediated metabolic signaling. These gut–liver and endocrine–metabolic interactions collectively contribute to improvements in lipid profile, androgen levels, menstrual regularity, and hepatic metabolic stress[8].

Despite extensive use of metformin in clinical practice, the majority of studies have focused on glycemic outcomes, while other important metabolic domains dyslipidemia, androgen excess, and GI metabolic markers have received comparatively less integrated evaluation. Understanding how metformin influences these inter-related pathways is critical for comprehensive PCOS management, especially in populations at high metabolic risk[9,10].

This study was therefore designed to assess the association between insulin resistance, lipid abnormalities, hormonal imbalance, and GI metabolic parameters in women with PCOS receiving metformin therapy. By evaluating these metabolic domains together, the study aims to generate clinically meaningful insights into the broader metabolic benefits of metformin and provide evidence to support holistic monitoring in PCOS care[11].

MATERIALS AND METHODS

Study Design and Setting: This prospective observational study was conducted to evaluate the metabolic, hormonal, and gastrointestinal effects of metformin therapy in women diagnosed with polycystic ovary syndrome (PCOS). The study was carried out at two tertiary-care centers in Pakistan: Aziz Bhatti Shaheed Teaching Hospital, Gujrat, and the Department of Gynaecology & Obstetrics, KRL Hospital, Islamabad. Both centers routinely

manage PCOS patients and follow standardized clinical and laboratory protocols. The total study duration extended from February 2022 to January 2023, allowing sufficient time for participant recruitment, baseline assessment, treatment follow-up, and final evaluation.

Sample Size and Sampling Technique: A total of **90 women** were enrolled using non-probability consecutive sampling. This sample size was considered adequate to detect meaningful clinical changes in insulin resistance and metabolic parameters over six months of metformin therapy. All eligible participants presenting to the collaborating departments during the recruitment period were screened for inclusion.

Eligibility Criteria: Women aged between 18 and 40 years who fulfilled the Rotterdam criteria for PCOS were included after ruling out secondary causes of hyperandrogenism and menstrual irregularities. Participants with established diabetes requiring medications other than metformin, chronic liver disease unrelated to metabolic dysfunction, chronic kidney disease, recent use of hormonal contraceptives or lipid-lowering medications, pregnancy, lactation, or significant comorbid conditions were excluded. Only women who agreed to participate and provided informed written consent were enrolled.

Baseline Assessment and Clinical Evaluation: All participants underwent a detailed clinical evaluation at enrollment. A structured proforma was used to record demographic characteristics, menstrual history, hyperandrogenic features such as hirsutism and acne, and physical findings including blood pressure, body mass index (BMI), and waist circumference. The presence of acanthosis nigricans was also documented as an indicator of insulin resistance. Baseline gastrointestinal symptoms were noted, including any prior intolerance to metformin. These assessments were repeated during follow-up visits to monitor progression and treatment tolerance.

Metformin Therapy Protocol: Metformin therapy was initiated according to routine clinical practice and titrated gradually to minimize gastrointestinal adverse effects. Participants were started on 500 mg once daily with meals during the first week. The dose was increased to 500 mg twice daily in the second week and further titrated to 1500–2000 mg per day based on tolerance. Women who developed gastrointestinal discomfort were advised on slow titration, dietary adjustments, or temporary dose modification. Treatment adherence was checked during each scheduled visit, and any side effects were recorded.

Laboratory Investigations: Blood samples were collected after an overnight fast of 8–12 hours at baseline and again after six months of therapy. All biochemical analyses were performed using standardized automated assays available at the respective hospital laboratories. Assessment of insulin resistance included fasting plasma glucose and fasting insulin levels, and HOMA-IR was calculated using the standard formula. The lipid profile consisted of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.

Hormonal evaluation included luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, and sex hormone-binding globulin (SHBG). These measurements allowed calculation of the LH/FSH ratio and provided insight into androgenic and reproductive abnormalities. Samples were ideally collected during the early follicular phase; however, in women with irregular cycles, samples were taken on a convenient day with appropriate documentation.

Gastrointestinal metabolic parameters were evaluated through hepatic enzyme levels including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT). The Hepatic Steatosis Index (HSI) was calculated to estimate hepatic metabolic stress and early non-alcoholic fatty liver changes, using BMI and enzyme ratios.

Outcome Measures: The primary outcome of the study was the change in insulin resistance, reflected by differences in HOMA-IR values from baseline to the six-month follow-up. Secondary outcomes included changes in fasting glucose, fasting insulin, lipid profile, hormonal imbalance parameters such as total testosterone and SHBG, alterations in LH/FSH ratio, and variations in gastrointestinal metabolic markers including ALT, AST, GGT, and HSI. Treatment response was analyzed in relation to baseline metabolic characteristics.

Follow-Up and Data Management: Participants were evaluated at baseline, at three months, and at six months. At each visit, adherence to metformin therapy, development of gastrointestinal side effects, and any intercurrent illnesses were recorded. Biochemical tests were repeated at the six-month visit using the same laboratory facilities to ensure consistency. Data were entered into a secured database with full confidentiality, and only anonymized data were used for analysis.

Statistical Analysis: All data were analyzed using SPSS version 25. Continuous variables were expressed as mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. Pre- and post-treatment values were compared using paired t-tests or non-parametric equivalents when required. Correlations between changes in insulin resistance and metabolic/hormonal parameters were explored using Pearson or Spearman correlation coefficients. A multivariable linear regression model was used to identify independent predictors of improvement in HOMA-IR, incorporating baseline BMI, initial HOMA-IR, triglyceride levels, and hepatic enzyme values. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations: The study protocol was reviewed and approved by the ethical review committees of both participating institutions. Written informed consent was obtained from all participants prior to enrollment. Confidentiality, anonymity, and the ethical principles of the Declaration of Helsinki were strictly maintained throughout the study.

RESULTS

Participant Characteristics: A total of 90 women with confirmed PCOS were enrolled at baseline. Out of these, 84 participants completed the full six-month follow-up period, while six were lost to follow-up due to relocation or poor treatment adherence. The analysis presented below includes all 84 participants with complete paired biochemical and hormonal data. The mean age of the cohort was 27.4 ± 4.6 years, and the majority were overweight or obese, with a baseline mean BMI of 29.8 ± 4.9 kg/m². Oligomenorrhea and clinical hyperandrogenism were highly prevalent at enrollment. Baseline anthropometric and metabolic profiles of the participants are presented in Table 1.

Changes in Insulin Resistance After Six Months of Metformin Therapy: Metformin therapy produced a statistically significant improvement in insulin resistance. Fasting insulin levels declined from 17.1 ± 6.1 µIU/mL at baseline to 12.7 ± 5.3 µIU/mL after six months, while fasting glucose demonstrated a modest decline. Consequently, mean HOMA-IR decreased from 3.98 ± 1.55 to 2.78 ± 1.29, representing a clinically meaningful enhancement in insulin sensitivity. These changes are detailed in Table 2.

Changes in Lipid Profile: Significant improvements were noted in lipid parameters following metformin therapy. Total cholesterol and LDL-C showed modest but statistically significant reductions, whereas triglycerides declined substantially from 167.2 ± 50.9 mg/dL to 141.5 ± 46.1 mg/dL. HDL-C increased slightly, consistent with improved metabolic function. These findings are presented in Table 3.

Changes in Hormonal Profile: Metformin therapy led to favorable hormonal modulation. Total testosterone levels declined significantly from 55.1 ± 18.4 ng/dL to 47.2 ± 17.1 ng/dL after six months. SHBG levels increased from a mean of 27.1 ± 10.8 nmol/L at baseline to 33.2 ± 11.6 nmol/L, reducing overall androgen exposure. The LH/FSH ratio also demonstrated a downward trend, indicating partial normalization of gonadotropin dynamics. These findings are shown in Table 4.

Changes in Gastrointestinal and Hepatic Metabolic Parameters: Metformin was associated with improvement in gastrointestinal metabolic markers, particularly hepatic enzymes.

ALT levels declined from 35.1 ± 14.4 U/L to 30.4 ± 12.8 U/L, while GGT decreased significantly. AST showed a mild reduction that did not reach statistical significance. The Hepatic Steatosis Index (HSI) exhibited a significant decline, indicating improvement in hepatic metabolic stress. These results are presented in Table 5.

Table 1. Baseline Characteristics of Women with PCOS (n = 84)

Variable	Mean ± SD / n (%)
Age (years)	27.4 ± 4.6
BMI (kg/m²)	29.8 ± 4.9
Waist circumference (cm)	90.1 ± 9.4
Oligomenorrhea	68 (81.0%)
Clinical hyperandrogenism	57 (67.8%)
Acanthosis nigricans	49 (58.3%)
Fasting glucose (mg/dL)	94.8 ± 10.4
Fasting insulin (µIU/mL)	17.1 ± 6.1
HOMA-IR	3.98 ± 1.55
Total cholesterol (mg/dL)	195.6 ± 38.1
LDL-C (mg/dL)	125.8 ± 33.4
HDL-C (mg/dL)	41.3 ± 7.7
Triglycerides (mg/dL)	167.2 ± 50.9
ALT (U/L)	35.1 ± 14.4
AST (U/L)	27.9 ± 10.1
GGT (U/L)	30.4 ± 13.2
LH/FSH ratio	2.10 ± 0.86
Total testosterone (ng/dL)	55.1 ± 18.4
SHBG (nmol/L)	27.1 ± 10.8

Table 2. Changes in Glycemic and Insulin Resistance Parameters (n = 84)

Parameter	Baseline	6 Months	Mean Change	p-value
Fasting glucose (mg/dL)	94.8 ± 10.4	91.2 ± 9.3	−3.6	<0.001
Fasting insulin (µIU/mL)	17.1 ± 6.1	12.7 ± 5.3	−4.4	<0.001
HOMA-IR	3.98 ± 1.55	2.78 ± 1.29	−1.20	<0.001

Significant improvement in insulin resistance is shown in Table 2.

Table 3. Changes in Lipid Profile After Metformin Therapy (n = 84)

Parameter (mg/dL)	Baseline	6 Months	Mean Change	p-value
Total cholesterol	195.6 ± 38.1	184.7 ± 35.4	−10.9	0.002
LDL-C	125.8 ± 33.4	115.9 ± 31.0	−9.9	0.003
HDL-C	41.3 ± 7.7	43.4 ± 7.9	+2.1	0.015
Triglycerides	167.2 ± 50.9	141.5 ± 46.1	−25.7	<0.001

Lipid profile improvements are detailed in Table 3.

Table 4. Changes in Hormonal Parameters After Six Months (n = 84)

Parameter	Baseline	6 Months	Mean Change	p-value
LH (IU/L)	9.7 ± 4.2	8.5 ± 4.0	−1.2	0.018
FSH (IU/L)	5.1 ± 1.8	5.2 ± 1.9	+0.1	0.61
LH/FSH ratio	2.10 ± 0.86	1.84 ± 0.79	−0.26	0.011
Total testosterone (ng/dL)	55.1 ± 18.4	47.2 ± 17.1	−7.9	<0.001
SHBG (nmol/L)	27.1 ± 10.8	33.2 ± 11.6	+6.1	<0.001

Hormonal modulation associated with metformin therapy is summarized in Table 4.

Table 5. Changes in Gastrointestinal–Metabolic Parameters (n = 84)

Parameter	Baseline	6 Months	Mean Change	p-value
ALT (U/L)	35.1 ± 14.4	30.4 ± 12.8	−4.7	0.001
AST (U/L)	27.9 ± 10.1	25.8 ± 9.6	−2.1	0.07
GGT (U/L)	30.4 ± 13.2	26.9 ± 12.3	−3.5	0.010
HSI (units)	42.3 ± 5.3	40.7 ± 5.1	−1.6	<0.001

Metformin-associated improvement in hepatic metabolic status is shown in Table 5.

Correlation and Predictive Analysis: A moderate positive correlation was observed between the reduction in HOMA-IR and the reduction in triglycerides ($r = 0.41$, $p < 0.01$), suggesting that metabolic and lipid improvements are closely linked. Regression analysis demonstrated that higher baseline HOMA-IR and higher BMI were independent predictors of greater insulin resistance improvement, indicating that individuals with more pronounced baseline metabolic dysfunction benefitted most.

DISCUSSION

The present study demonstrates that metformin therapy over a six-month period is associated with significant improvements in insulin resistance, lipid abnormalities, hormonal imbalance, and gastrointestinal–metabolic parameters in women with polycystic ovary syndrome (PCOS)[10]. These findings reinforce metformin's central therapeutic role not only as an insulin-sensitizing agent but also as a broad metabolic modulator with systemic benefits[11].

A key observation in this study was the substantial decline in fasting insulin levels and the marked reduction in HOMA-IR, indicating improved insulin sensitivity. Since insulin resistance is considered the fundamental pathophysiological abnormality in PCOS, its improvement is clinically meaningful[12]. Hyperinsulinemia drives ovarian androgen production, suppresses hepatic SHBG synthesis, and impairs menstrual regularity. Therefore, the observed enhancement in insulin sensitivity likely contributed to the accompanying hormonal improvements. The magnitude of HOMA-IR reduction observed in this cohort is consistent with international literature, highlighting metformin's effectiveness among South Asian populations where metabolic risk is inherently high[13].

Metformin therapy also produced favorable changes in lipid metabolism. Significant reductions in total cholesterol, LDL-C, and triglycerides were accompanied by a modest rise in HDL-C. These lipid changes reflect reduced hepatic VLDL production, increased peripheral lipid clearance, and improved insulin-regulated lipolytic control[14]. Dyslipidemia is prevalent among women with PCOS and significantly increases long-term cardiometabolic risk. Therefore, the lipid-lowering effects of metformin may provide additional cardiovascular protection beyond its glycemic benefits. The strong correlation observed between reductions in HOMA-IR and triglycerides further supports the interdependence of insulin and lipid metabolic pathways in PCOS[15].

Similarly, improvements in the hormonal profile underscore metformin's endocrine regulatory potential. Significant reductions in total testosterone and improvements in SHBG levels were accompanied by a decrease in the LH/FSH ratio[16]. Hyperinsulinemia enhances ovarian androgen secretion and reduces SHBG production, thereby increasing free androgen levels. By lowering insulin resistance, metformin indirectly modulates androgen excess. The normalization trend in gonadotropin ratios observed in this study suggests partial restoration of hypothalamic–pituitary–ovarian axis dynamics, which may translate into better ovulatory patterns, although ovulation monitoring was beyond the scope of this study[17].

An important strength of this study is the inclusion of gastrointestinal–metabolic parameters, particularly hepatic enzymes and the Hepatic Steatosis Index (HSI). ALT, GGT, and HSI showed significant improvement after treatment, reflecting a reduction in hepatic metabolic stress and a likely decrease in early non-alcoholic fatty liver disease (NAFLD) tendencies[18]. NAFLD is highly prevalent among women with PCOS, often occurring at younger ages. Metformin exerts beneficial hepatic effects through mechanisms including AMPK activation, reduced de novo lipogenesis, improved insulin signaling, and modulation of gut–liver bile acid pathways. The consistent improvement in hepatic markers in this study supports monitoring liver-related metabolic status as part of routine PCOS management[19].

Predictive analysis showed that women with higher baseline HOMA-IR and BMI demonstrated greater metabolic improvement. This finding is clinically relevant because it suggests that women with more severe metabolic dysfunction at baseline may derive the most benefit from metformin therapy. Identifying such responders

may help clinicians personalize treatment strategies, optimize metabolic control, and set realistic treatment expectations[20].

The study has several strengths, including a well-defined sample, standardized biochemical assessment, and comprehensive evaluation of metabolic, hormonal, and hepatic indicators. However, certain limitations must be acknowledged. The observational design without a control group limits causal inference[14]. Dietary patterns and physical activity were not strictly controlled, which may have influenced outcomes. Additionally, direct measures of visceral fat, insulin clamp studies, or advanced hepatic imaging were not performed. Despite these limitations, the consistency and magnitude of improvements observed strongly support metformin's integrated metabolic benefits in PCOS[17,19].

Overall, the findings of this study reinforce current clinical guidance that PCOS should be managed not only as a reproductive disorder but as a complex metabolic condition requiring broad and continuous evaluation. Metformin remains a cornerstone therapy with multidimensional benefits, and its use should be accompanied by structured metabolic monitoring including insulin resistance indices, lipid parameters, and hepatic markers[15-20].

CONCLUSION

Metformin therapy produced significant improvements in insulin resistance, lipid profile, hormonal imbalance, and gastrointestinal–metabolic parameters in women with PCOS over a six-month period. These findings highlight the multidimensional metabolic benefits of metformin, extending beyond glycemic control to include lipid modulation, androgen reduction, and improvement in hepatic metabolic stress. Women with higher baseline metabolic dysfunction experienced the greatest therapeutic response, suggesting that early identification and targeted treatment of high-risk PCOS phenotypes may offer greater clinical benefit. Incorporating comprehensive metabolic monitoring including HOMA-IR, lipid profile, and hepatic indices into routine PCOS care may improve long-term metabolic and reproductive outcomes. The results of this study support the continued use of metformin as a key therapeutic option in the integrated management of PCOS.

Availability of Data and Materials: The datasets generated and analyzed during the current study are available from the corresponding author (RA[1]) upon reasonable request.

Competing Interests: The authors declare that they have no competing interests or financial conflicts relevant to this manuscript.

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Authors' Contributions: RA[1] conceived the study, supervised data collection, and contributed to manuscript drafting. RB[2] and FS[3] were responsible for patient recruitment, clinical evaluation, and coordination of follow-up visits. YK[4] and NA[5] performed biochemical data acquisition and supported data interpretation. SK[6] contributed to analysis of metabolic and gastrointestinal parameters and critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript.

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