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Assessing the Effects of Metformin on Lipid Metabolism in Women with PCOS

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a prevalent hormonal imbalance condition that is linked with insulin resistance and abnormal lipid metabolism. Metformin is a common drug given in the management of PCOS; the impact on the lipid profile and the role of adherence to therapy are not established. **Objectives:** To assess the therapeutic effects of Metformin on lipid profile, hormonal status, and insulin resistance in PCOS while exploring the influence of patient adherence on overall treatment response. **Methods:** One hundred and ten women with a diagnosis of PCOS in Health Net Hospital, Peshawar, were given Metformin (1500 mg/day) for six months. The assessments for the study included lipid profile, glucose, insulin level, HOMA-IR, and hormonal profiling both at baseline and after the treatment.Treatment adherence was evaluated with pill count and attendance to follow-up visits. Pre- and post-comparisons were done using paired t-tests, while group differences were examined using independent t-tests and chi-square tests. **Results:** Metformin significantly reduced total cholesterol (199.43 to 167.60 mg/dL, p<0.001), LDL-C (131.71 to 111.20 mg/dL, p<0.001), triglycerides (178.15 to 149.66 mg/dL, p<0.001), and VLDL-C (35.72 to 30.03 mg/dL, 'p<0.001'), while HDL-C increased (39.70 to 45.24, p<0.001)'. Insulin resistance and androgen levels also improved, with greater benefits observed in adherent participants. **Conclusions:** It was concluded that metformin positively impacts lipid metabolism, hormonal levels, and insulin responsiveness in patients with PCOS. Adherence significantly enhances therapeutic outcomes, emphasizing the need for strategies that promote consistent medication use.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in reproductive-aged women, with a global prevalence of 4% to 21% [1]. It disrupts hormonal balance, ovulation, and metabolism, leading to infertility, menstrual irregularities, and androgen excess, and is often associated with insulin resistance, dyslipidemia, and increased cardio-metabolic risk [2, 3]. PCOS is a common endocrine disorder in reproductive-aged women, affecting 4% to 21% globally. It disrupts hormonal balance, ovulation, and metabolism, leading to infertility, menstrual issues, androgen excess, and increased risk of insulin resistance, dyslipidemia, and type 2 diabetes. Dyslipidemia is of particular concern in PCOS because of the increased values of total cholesterol, LDL-C, triglycerides, and decreased HDL-C. These anomalies significantly increase the cardiovascular risk over a prolonged period [3]. The lipid abnormalities mentioned are strongly supported by insulin resistance, necessitating PCOS management to effectively address the metabolic control [4]. Metformin, originally used for type 2 diabetes, is now widely prescribed for PCOS. Though off-label, it is recommended by the 2013 Endocrine Society and 2023 global PCOS guidelines to

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improve ovulation and insulin sensitivity [2, 5]. Beyond glucose control, it also enhances lipid profiles by lowering LDL-C and triglycerides and raising HDL-C, reducing cardiovascular risk [6]. Even so, results regarding Metformin's impact on lipid metabolism differ across populations, probably because of genetics, lifestyle, and dietary habits. Additionally, adherence is vital to the success of treatment, but very few studies have explored how adherence affects the metabolic results of Metformin therapy [7]. These gaps concerning the lack of adherence analysis create obstacles in assessing the practical utility of Metformin in managing PCOS.

This study aims to investigate Metformin's impact on lipid parameters, hormonal regulation, and insulin sensitivity in women diagnosed with PCOS. It also compares adherent and non-adherent participants and investigates how treatment adherence influences these metabolic outcomes.By addressing both metabolic responses and the role of adherence in a South Asian population, this study contributes novel insights that may improve therapeutic strategies and long-term outcomes in women with PCOS.

METHODS

This was a prospective quasi-experimental study conducted at Health Net Hospital, Peshawar, from May 15, 2023, to June 15, 2024. The study aimed to investigate the impact of Metformin on lipid parameters, hormonal balance, and insulin sensitivity in women with a confirmed diagnosis of PCOS. Ethical approval was obtained from the hospital's Ethics Review Committee (Ref No: 3057/HNH/HR). Consent to participate was secured from each subject after explaining the study protocol. The sample size for this study was determined using the formula appropriate for continuous outcome variables, as the primary endpoints included measures like lipid levels and insulin resistance. The calculation was based on the following parameters: Confidence level: 95% (Z=1.96), Power: 80% (Z=0.84), Assumed standard deviation (σ): 25 mg/dL for LDL-C, derived from prior studies evaluating lipid profiles in women with PCOS [8].Minimum detectable difference (Δ): 10 mg/dL, considered clinically meaningful. Using the standard formula for comparing two means: $n=2\times(Z\alpha/2+Z\beta)2\times\sigma2/\Delta2$.Plugging in the values: $n=2\times(1.96+0.84)2\times252/100=2\times(2.8)2\times625/100=2\times7.84\times625/100=9800/100=98$.Thus, the estimated sample size was approximately 98 participants.To enhance the study's statistical power and compensate for potential dropout or missing data, a 10% increase was applied: Adjusted sample size= 98/1-0.10=109.This adjustment led to a final sample size of 110 participants.This sample size was consistent with that used in previous studies. Trolle *et al.*, conducted a randomized, double-blinded, placebo-controlled cross-over trial involving 56 women with PCOS who completed both treatment phases, effectively utilizing 112 participant-periods.Their study assessed similar outcomes, including lipid profiles and insulin resistance, thereby supporting the adequacy of our sample size [9].And Calculations in Clinical Research by Chow *et al.*, [10] and aligns with guidelines provided by the World Health Organization in Sample Size Determination in Health Studies by Lwanga and Lemeshow [11].Inclusion criteria: Women aged 18–35 years with a diagnosis of PCOS utilizing Rotterdam criteria, as specified in 2003 [12] when either 2 of the following three indicators are provoke: (1) Disrupted or absent menstrual periods (2) higher-than-normal androgen values detected either clinically or through laboratory evaluation, and (3) the presence of multiple cysts on the ovaries observed via ultrasound imaging.Exclusion criteria: Prior Metformin use within 6 months, current use of lipid-lowering drugs, pregnancy or lactation, thyroid disorders, diabetes, Cushing's syndrome, and significant liver or kidney dysfunction.All participants received Metformin 1500 mg/day in divided doses of 500 mg three times daily, following published PCOS management guidelines [13]. Participants were also counselled about lifestyle modifications, including diet and physical activity. No other pharmacological treatments were allowed during the study period.This study involved a standard therapeutic intervention, not a clinical trial, so it did not require DRAP registration, as per Bio-Study Rules 2017 and DRAP Act 2012 guidelines.Data were collected in three phases: baseline (pre-treatment), treatment phase (with monthly follow-up), and post-treatment (at six months).The clinical data gathered consisted of the following: age, body mass index (BMI), duration of PCOS, menstrual irregularities, a family history of PCOS or diabetes, and lifestyle factors, including the level of physical activity and smoking habits. Venous blood samples were taken and analyzed for the lipid profile (total cholesterol (TC), LDL-C, HDL-C, triglycerides (TG), VLDL-C), fasting glucose, insulin, glycated hemoglobin (HbA1c), and insulin resistance calculated via HOMA-IR after an 8-10 hour overnight fast. Additionally, the reproductive and androgenic hormones assessed included 'luteinizing hormone (LH), follicle-stimulating hormone (FSH), the LH/FSH ratio, total testosterone, sex hormone-binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEA-S)' were assessed.Lipid parameters were measured using enzymatic colourimetric methods; fasting glucose was evaluated by the hexokinase method, insulin by electro-chem-iluminescence immunoassay (ECLIA), and HbA1c via high-performance liquid chromatography (HPLC). Hormonal assays were performed using automated chemiluminescence immunoassay (CLIA) on platforms such as the Abbott Architect i2000.Manufacturer-provided reference ranges were used: Reference ranges used in this study were based on manufacturer specifications. For lipid parameters, total cholesterol was considered normal at values below 200 mg/dL, LDL-C under 100 mg/dL, HDL-C above 40 mg/dL, triglycerides under 150 mg/dL, and VLDL-C ranging between 5 and 40 mg/dL. Regarding reproductive and androgenic hormones, the expected ranges included luteinizing hormone (LH) from 1.9 to 12.5 mIU/mL, 'Follicle-

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stimulating hormone was within the range of 2.5–10.2 mIU/mL',testosterone between 15 and 70 ng/dL, sex hormone-binding globulin(SHBG)from 18 to 114 nmol/L, and dehydroepiandrosterone sulfate (DHEA-S) between 65 and 380 µg/dL.Insulin resistance was evaluated using the HOMA-IR index, derived by taking the product of fasting insulin and glucose levels, then dividing that value by 405. A value exceeding 2.5 was considered reflective of insulin resistance.All laboratory testing was carried out in a centralized, ISO 15189-certified diagnostic facility adhering to international standards for medical laboratory quality and competence.Quality control was maintained by processing internal control samples at low, normal, and high levels with every batch, while external validation was ensured through participation in recognized quality assurance schemes.To ensure reproducibility, 10% of randomly selected samples were re-tested.The same equipment, protocols, and calibrators were used throughout the study to maintain consistency and reliability.Adherence was assessed through pill counts, follow-up attendance, and a structured adherence questionnaire adapted from previously validated tools [14]. Adherent group: Took ≥80% of prescribed doses and missed no more than 1 follow-up. Non-adherent group: Took <80% of doses or missed ≥2 consecutive follow-ups. To monitor adverse drug reactions (ADRs), a checklist-based ADR tool was used to record common side effects (nausea, diarrhea, abdominal discomfort) at each follow-up. ADRs were documented but not formally categorized using scales like Naranjo, as the study focused on treatment efficacy rather than pharmacovigilance.Safety was assessed based on the absence of severe ADRs and overall tolerability.The distribution of continuous variables was examined using the Shapiro-Wilk test.The analysis of the information was carried out using the SPSS program, version 26.0.Continuous data were summarized using mean values along with standard deviations, whereas categorical data were presented as counts and corresponding percentages.The assessment of the normality of continuous variables was performed by the Shapiro-Wilk's test revealed that the variables with normal distribution included.The Paired sample t-test was used to compare baseline and post-treatment values within the same group.The comparison of these variables for adherent and non-adherent groups was conducted through an independent sample t-test.Non-parametric methods were employed for data that did not exhibit normal distribution patterns, the Mann-Whitney U test was employed as an alternative to parametric analysis, including triglycerides, VLDL-C, HOMA-IR, DHEA-S, and the LH/FSH ratio.Categorical data, such as physical activity, family history, and reported side effects, were assessed using the 'Chi-square test'.Results were deemed significant when the p-value was equal to or below 0.05 (Figure 1).

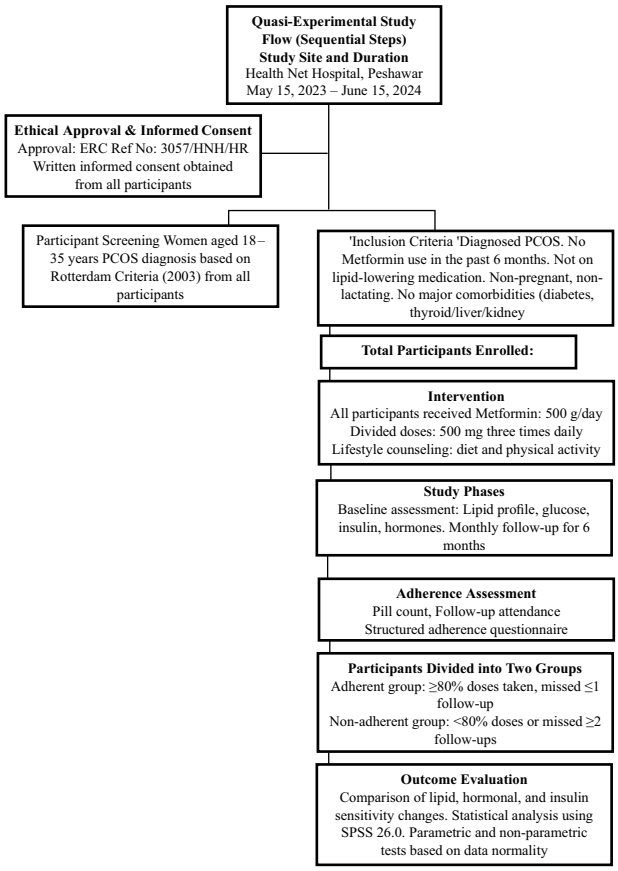

Figure 1: Methods Used for This Research

RESULTS

The study included 110 women diagnosed with PCOS.The mean age was 25.15 ± 3.61 years, and the average BMI was 29.51 ± 4.97 kg/m^2.The average duration of PCOS is approximately four years.More than half of the participants (55.5%) were single, and a majority (81.8%) reported menstrual irregularities.A family history of PCOS and diabetes, or dyslipidemia was present in about 49% of participants.Only 6.4% of women reported smoking, while 39.1% engaged in regular physical activity (Table 1).

Table 1: Demographic and Clinical Characteristics (n=110)

Study Indicators		n (%)
Age	Years	25.15 ± 3.61
BMI	kg/m^2	29.51 ± 4.97
Duration of PCOS	Years	4.12 ± 2.02
Marital Status	Single	61 (55.5%)
	Married	49 (44.5%)
Menstrual Irregularities	Yes	90 (81.8%)
	No	20 (18.2%)
Reported Family Occurrence of PCOS	Yes	54 (49.1%)
	No	56 (50.9%)
Family Incidence of Diabetes	Yes	54 (49.1%)
	No	56 (50.9%)
Smoking Status	Yes	7 (6.4%)
	No	103 (93.6%)

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Regular Physical Activity	Yes	43 (39.1%)
	No	67 (60.9%)

Following six months of Metformin therapy, there were significant improvements in lipid profile, hormonal balance, and insulin sensitivity. Total cholesterol decreased from 199.43 to 167.60, LDL-C from 131.71 to 111.20, and triglycerides from 178.15 to 149.66 mg/dL ($p<0.001$ for all comparisons). HDL-C levels significantly increased. Androgen levels, including testosterone and DHEA-S, showed marked reductions, while SHBG levels increased, indicating improved hormonal regulation. Fasting insulin, HOMA-IR, and HbA1c also improved significantly, reflecting enhanced insulin sensitivity (Table 2).

Table 2: Comparison of Key Metabolic and Endocrine Variables Before and After Metformin Administration

Measured Parameters	Before Treatment (Mean ± SD)	After Treatment (Mean ± SD)	p-value
Cholesterol – Total (mg/dL)	199.43 ± 26.84	167.60 ± 29.38	<0.001 *
LDL-C (mg/dL)	131.71 ± 24.24	111.20 ± 26.52	<0.001 *
HDL-C (mg/dL)	39.70 ± 7.60	45.24 ± 8.77	<0.001 *
Triglycerides (mg/dL)	178.15 ± 47.26	149.66 ± 42.82	<0.001 *
VLDL-C (mg/dL)	35.72 ± 8.51	30.03 ± 8.04	<0.001 *
LH (mIU/mL)	9.67 ± 3.20	8.11 ± 2.78	<0.001 *
Serum FSH Concentration	5.73 ± 1.24	5.52 ± 1.19	0.040 *
LH-to-FSH Proportion	1.59 ± 0.51	1.34 ± 0.47	<0.001 *
Serum Testosterone Level	66.78 ± 17.80	55.93 ± 16.05	<0.001 *
SHBG (nmol/L)	34.91 ± 7.80	42.16 ± 9.70	<0.001 *
DHEA-S (µg/dL)	208.12 ± 45.61	175.08 ± 45.01	<0.001 *
Fasting Glucose (mg/dL)	95.21 ± 12.86	80.09 ± 14.68	<0.001 *
Fasting Insulin (µU/mL)	18.65 ± 5.93	13.66 ± 4.85	<0.001 *
HOMA-IR	4.25 ± 1.65	3.15 ± 1.49	<0.001 *
HbA1c (%)	5.90 ± 0.86	4.97 ± 0.99	<0.001 *

*Statistically significant ($p\leq0.05$) Shapiro-Wilk test was used to assess data normality. Paired Sample t-test was applied to normally distributed variables (Total Cholesterol, LDL-C, HDL-C, Serum FSH, Serum Testosterone, SHBG, Fasting Glucose, Fasting Insulin, HbA1c). Mann-Whitney U test was applied to non-normally distributed variables (Triglycerides, VLDL-C, LH, LH/FSH Ratio, DHEA-S, HOMA-IR).

Comparison between adherent and non-adherent participants revealed significantly better metabolic and hormonal outcomes in the adherent group. Fasting insulin was significantly reduced in the adherent group (11.48 vs. 16.27 µU/mL, $p<0.001$), LDL-C values were also lower (95.76 vs. 129.72, $p<0.001$), and SHBG levels were elevated (44.71 vs. 39.09 nmol/L, $p=0.002$)(Table 3).

Table 3: Comparison of Adherent vs. Non-Adherent Participants

Parameter	Adherent Participants	Non-Adherent Participants	p-value
LH (mIU/mL)	7.40 ± 2.53	8.96 ± 2.85	0.003 *
LH-to-FSH Proportion	1.18 ± 0.37	1.54 ± 0.49	<0.001 *
Serum FSH Concentration	51.67 ± 11.76	61.04 ± 18.91	0.002 *
SHBG (nmol/L)	44.71 ± 9.18	39.09 ± 9.50	0.002 *
Cholesterol (mg/dL)	150.27 ± 21.39	188.38 ± 23.67	<0.001 *
LDL-C (mg/dL)	95.76 ± 17.28	129.72 ± 23.74	<0.001 *
HDL-C (mg/dL)	46.83 ± 8.67	43.34 ± 8.59	0.037 *
Triglycerides (mg/dL)	134.69 ± 37.13	167.62 ± 42.60	<0.001 *
Fasting Glucose (mg/dL)	71.25 ± 9.28	90.69 ± 12.86	<0.001 *
Fasting Insulin (µU/mL)	11.48 ± 3.94	16.27 ± 4.58	<0.001 *
HbA1c (%)	4.35 ± 0.69	5.71 ± 0.75	<0.001 *

*Statistically significant ($p\leq0.05$). Normality was assessed using the Shapiro-Wilk test. Independent Sample t-test was used for normally distributed variables (e.g., LDL-C, HDL-C, SHBG, Fasting Glucose, Fasting Insulin, HbA1c). The Mann-Whitney U test was used for non-normally distributed variables (LH, Serum FSH, LH/FSH Ratio).

Categorical comparisons further revealed that a family history of PCOS was significantly associated with better adherence ($p=0.012$). No significant associations were found for physical activity or family history of diabetes. Adverse effects were reported with similar frequency in both groups and were not statistically significant.Most participants (66.7% adherent vs. 62.0% non-adherent) reported no side effects(Table 4).

Table 4: Categorical Variables and Adverse Effects by Adherence Status

Variable / Adverse Effects	Adherent n (%)	Non-Adherent n (%)	p-value
Physical Activity (Regular)	23 (38.3%)	20 (40.0%)	0.858
Physical Activity (No)	37 (61.7%)	30 (60.0%)	
Family History of PCOS (Yes)	36 (60.0%)	18 (36.0%)	0.012 *
Family History of PCOS (No)	24 (40.0%)	32 (64.0%)	
Family History of Diabetes (Yes)	33 (55.0%)	21 (42.0%)	0.174
Family History of Diabetes (No)	27 (45.0%)	29 (58.0%)	
Abdominal Discomfort	5 (8.3%)	5 (10.0%)	0.961
Diarrhea	6 (10.0%)	6 (12.0%)	
Nausea	9 (15.0%)	8 (16.0%)	
No Adverse Effects	40 (66.7%)	31 (62.0%)	

*Statistically significant ($p\leq0.05$). Chi-square test was used for comparisons of categorical variables (physical activity, family history, adverse effects).

The chart illustrates significant lipid profile improvements after Metformin therapy, with reductions in total cholesterol, LDL-C, triglycerides, and VLDL-C, and an increase in HDL-C, indicating reduced cardiovascular risk (Figure 2).

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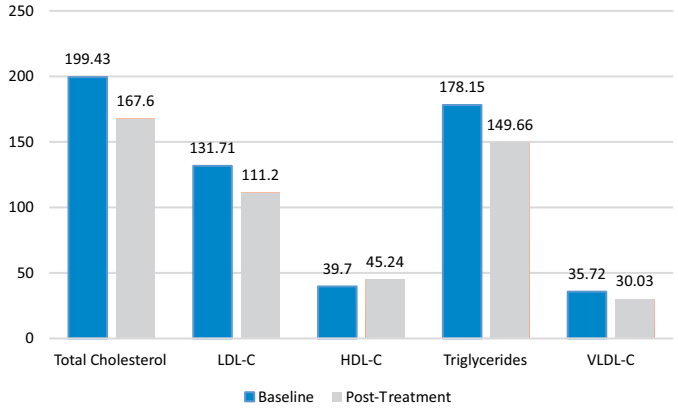

Figure 1: Comparison of Lipid Profile Before and After Metformin Treatment

DISCUSSION

This study reinforces the role of Metformin as a first-line therapy in managing both metabolic and reproductive features of PCOS. Significant improvements in lipid profile were observed, with reductions in total cholesterol, LDL-C, triglycerides, and VLDL-C, along with increased HDL-C levels. These findings were consistent with previous studies demonstrating Metformin's lipid-lowering effects, which may reduce cardiovascular risk in women with PCOS [8, 15]. Notably, these changes occurred independent of significant weight loss, supporting the hypothesis that Metformin directly influences lipid metabolism [16]. Metformin improved hormonal markers by lowering LH, LH/FSH ratio, and testosterone, while increasing SHBG, indicating better control of hyperandrogenism [17]. These changes support enhanced menstrual regularity and ovulation, with reduced symptoms like acne, hirsutism, and infertility [18]. Testosterone, thus further alleviating symptoms like acne, hirsutism, and infertility. Metformin improved glycemic control by reducing fasting glucose, insulin, HOMA-IR, and HbA1c, reflecting enhanced insulin sensitivity [19]. By targeting insulin resistance, a core feature of PCO, it offers dual benefits for metabolic and endocrine regulation. Adherence significantly influenced outcomes, with adherent women showing greater improvements in hormonal, lipid, and insulin parameters. This aligns with previous research linking long-term Metformin use to sustained metabolic and reproductive benefits, emphasizing the need for ongoing patient education and support [20]. Although mild gastrointestinal side effects such as nausea and diarrhoea were reported, the frequency of these events showed no meaningful statistical difference was observed between the adherent and non-adherent groups. This suggests that such side effects were not a major deterrent to treatment. Similar studies report that these symptoms usually subside with continued use [21, 22], reinforcing Metformin's favourable safety profile. Being a single-centre study, generalizability is limited, particularly to rural settings. Reliance on self-reported adherence and a short follow-up may affect accuracy and overlook long-term outcomes.

CONCLUSIONS

It was concluded that Metformin improves lipid regulation, enhances hormonal activity, and promotes better glucose-insulin balance in females diagnosed with PCOS. Patients who adhered to medication experienced optimal results, demonstrating the need for greater focus on compliance towards treatment plans. These results further confirm Metformin's prescription validity regarding the patient's PCOS metabolic and reproductive complexities. Additional measures to improve patient education and support are necessary to increase treatment adherence and maximize prolonged therapeutic outcomes.

Authors Contribution

Conceptualization: SA[2]
Methodology: SS, SFF, FN, SA[1], AS
Formal analysis: SFF, FN, SA[1]
Writing review and editing: SA[1], SS, SFF, FN, SA[2], AS
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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