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EVALUATING INSULIN RESISTANCE AND HORMONAL IMBALANCE IN WOMEN WITH PCOS UNDERGOING LIFESTYLE MODIFICATION VERSUS PHARMACOLOGICAL THERAPY

Original Article

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, frequently associated with insulin resistance and hormonal imbalance. Although pharmacological therapies like metformin are routinely used, lifestyle interventions targeting diet and physical activity remain the cornerstone of PCOS management. Comparative evidence on the effectiveness of these approaches is essential for guiding optimal treatment strategies.

Objective: To compare the effects of lifestyle modification versus pharmacological therapy using metformin on insulin resistance and hormonal regulation in women diagnosed with PCOS.

Methods: This randomized controlled trial enrolled 140 women with PCOS from private tertiary hospitals in Lahore, Faisalabad, and Islamabad. Participants were randomly assigned to receive either structured lifestyle intervention or metformin (500 mg three times daily) for 12 weeks. Insulin resistance was assessed using HOMA-IR, while hormonal parameters (testosterone, SHBG, LH/FSH ratio) were measured using ELISA-based assays. Anthropometric data and menstrual patterns were also evaluated. Data were analyzed using SPSS version 26 with independent and paired t-tests and repeated measures ANOVA.

Results: Both groups demonstrated significant improvements in HOMA-IR, but the reduction was greater in the lifestyle group (mean change: 1.23 vs. 0.98; p=0.032). Lifestyle intervention also led to superior reductions in testosterone (0.63 vs. 0.69 ng/mL; p=0.040), higher SHBG levels (36.8 vs. 32.2 nmol/L; p=0.031), and greater menstrual regularity (61% vs. 47%; p=0.048). Weight loss and BMI reductions were also significantly higher in the lifestyle group.

Conclusion: Lifestyle modification produced more favorable outcomes than metformin in improving insulin resistance, hormonal profile, and menstrual regularity among women with PCOS, supporting its role as the preferred first-line therapy.

Keywords: Body Mass Index, Hormonal Imbalance, Insulin Resistance, Lifestyle, Metformin, Menstrual Cycle, Polycystic Ovary Syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex, multifactorial endocrine disorder that affects a significant proportion of women of reproductive age, with estimates suggesting a prevalence of 5–20% globally (1). It manifests through a constellation of symptoms, including menstrual irregularities, hyperandrogenism, and polycystic ovarian morphology, with insulin resistance emerging as a central pathological feature in up to 75% of affected women (2). The intricate interplay between insulin resistance and hyperandrogenism in PCOS not only exacerbates metabolic dysfunction but also worsens reproductive outcomes, thereby posing challenges to long-term health and quality of life.

A growing body of evidence underscores the role of insulin resistance in the pathogenesis of PCOS, where hyperinsulinemia promotes ovarian androgen production and impairs follicular maturation. This dysfunction results in anovulation and infertility, further entangling metabolic and hormonal dysregulation (3). Obesity, often coexisting with PCOS, amplifies this vicious cycle by contributing to both increased insulin resistance and chronic low-grade inflammation (4). Importantly, not all PCOS patients are overweight, yet many still exhibit insulin-related metabolic abnormalities, indicating a broader metabolic substrate underlying the condition.

Historically, pharmacological agents such as metformin—an insulin sensitizer—have been widely used in PCOS treatment. Metformin improves insulin sensitivity, reduces hepatic glucose output, and is associated with decreased androgen levels and improved ovulatory function (5). Recent studies have shown its benefit not only in restoring menstrual regularity and reducing testosterone levels but also in enhancing the clinical pregnancy rate, especially when combined with other interventions (6). Furthermore, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as promising agents, offering dual benefits by promoting weight loss and directly addressing insulin resistance at the molecular level (7).

Nevertheless, lifestyle modification remains the cornerstone of first-line management in PCOS, especially in overweight and obese individuals. Dietary changes emphasizing low glycemic index foods, regular physical activity, and behavioral therapy have all shown significant promise in improving insulin sensitivity, restoring hormonal balance, and alleviating PCOS symptoms (8). Recent randomized controlled trials have demonstrated that structured lifestyle interventions can result in clinically meaningful reductions in insulin resistance markers such as HOMA-IR and improvements in menstrual frequency and ovulation rates (9). One study utilizing a mobile application to guide lifestyle modification reported significant reductions in postprandial insulin and improved depression scores, indicating the far-reaching benefits of digital health tools in enhancing adherence and outcomes (10).

When comparing pharmacological therapy and lifestyle modification, findings increasingly support a synergistic approach. A randomized controlled study demonstrated that while both metformin and lifestyle modification improved metabolic outcomes individually, the combined therapy yielded superior improvements in glycemic control, hormonal profiles, and reproductive outcomes compared to either modality alone (3). Similarly, another trial found that women receiving both metformin and structured lifestyle guidance had more pronounced improvements in insulin sensitivity and follicle-stimulating hormone levels than those on metformin alone (9).

Despite the promising outcomes, a knowledge gap persists regarding the comparative effectiveness of these two therapeutic strategies when applied independently versus in combination. Most current clinical recommendations advocate for lifestyle intervention as a first-line approach, with pharmacological treatments reserved for patients who fail to respond adequately. However, given the heterogeneity of PCOS and the variability in patient phenotypes, individualized treatment protocols are essential. Existing evidence highlights the need for more robust, head-to-head comparisons to delineate the optimal management strategy for insulin resistance and hormonal dysregulation in PCOS.

Therefore, the present randomized controlled trial seeks to directly compare the effects of lifestyle modification versus pharmacological therapy on insulin resistance and hormonal balance in women with PCOS. By examining these interventions in a controlled setting, this study aims to contribute critical evidence to inform clinical guidelines and support personalized care in this diverse patient population.

METHODS:

This randomized controlled trial was conducted to compare the effects of lifestyle modification versus pharmacological therapy on insulin resistance and hormonal imbalance in women diagnosed with polycystic ovary syndrome (PCOS). The study was carried out across three private tertiary care hospitals located in Lahore, Faisalabad, and Islamabad from January to December 2024. The trial was

approved by the Institutional Review Boards of all participating hospitals , and informed consent was obtained in writing from all participants prior to their enrolment.

The sample size was calculated using G*Power software, assuming a medium effect size (f=0.25), a power of 0.80, and a significance level of 0.05. A minimum of 128 participants was required to detect statistically significant differences between groups. Accounting for a 10% potential attrition rate, the final sample included 140 participants, randomly assigned to two equal groups of 70 each using a computer-generated randomization list (11).

Participants were women aged 18–40 years with a confirmed diagnosis of PCOS based on the Rotterdam criteria (presence of at least two of the following: oligo/anovulation, hyperandrogenism, and polycystic ovaries on ultrasound). Inclusion criteria also required participants to have documented insulin resistance, as indicated by a HOMA-IR score >2.5, and willingness to participate in either intervention. Exclusion criteria included pregnancy, lactation, use of hormonal therapy or insulin sensitizers in the previous three months, type 2 diabetes mellitus, thyroid dysfunction, or other endocrine disorders (12).

The intervention group (Group A) received structured lifestyle modification, including personalized dietary plans focused on low glycemic index and calorie-deficit meals, along with a supervised physical activity regimen comprising 150 minutes of moderate-intensity aerobic exercise weekly. Lifestyle coaching sessions were conducted biweekly for motivation and adherence (13). The control group (Group B) received pharmacological therapy with metformin (500 mg three times daily) and standard dietary advice, without a structured physical activity plan (14).

Data collection was performed at baseline and after 12 weeks of intervention. The primary outcome was insulin resistance measured using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). Secondary outcomes included hormonal parameters—luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, and sex hormone-binding globulin (SHBG)—assessed via fasting blood samples using standardized ELISA-based assays. Menstrual regularity, weight, and body mass index (BMI) were also recorded (15).

All laboratory analyses were conducted in the central biochemistry laboratory of the lead site in Lahore, with standardization across all sites to minimize inter-laboratory variability. Data entry and quality control were performed by trained research assistants blinded to the group allocation.

Data analysis was conducted using SPSS version 26. Normality of continuous variables was assessed through the Shapiro-Wilk test, confirming normal distribution. Descriptive statistics were presented as means with standard deviations for continuous variables and frequencies for categorical variables. Between-group comparisons were performed using independent t-tests for continuous variables and chi-square tests for categorical variables. Within-group changes were analyzed using paired t-tests. A repeated-measures ANOVA was employed to assess time-by-group interactions for primary and secondary outcomes. A p-value <0.05 was considered statistically significant (16).

Adherence to the intervention was monitored through weekly check-ins, physical activity logs, and pill counts. Participants reporting less than 80% adherence were followed up with motivational counselling but included in the intention-to-treat analysis.

The ethical conduct of the study adhered to the Declaration of Helsinki, and participants were given the option to withdraw at any point without affecting their medical care. Safety monitoring included regular assessments for gastrointestinal side effects in the pharmacological group, and no serious adverse events were reported during the study period.

This methodologically rigorous design ensures the reliability and reproducibility of the findings, contributing robust evidence to guide the clinical management of insulin resistance and hormonal dysregulation in PCOS.

RESULTS:

A total of 140 participants were enrolled and randomized equally into two groups: the lifestyle modification group (n=70) and the pharmacological therapy group (n=70). At the end of the 12-week intervention, 66 participants in the lifestyle group and 68 in the pharmacological group completed the study, yielding a follow-up rate of 95.7%. The baseline characteristics, including age, BMI, HOMA-IR, LH, FSH, total testosterone, and SHBG levels, were comparable between both groups, with no statistically significant differences (p>0.05).

Following 12 weeks of intervention, significant within-group reductions in insulin resistance were observed. In the lifestyle modification group, mean HOMA-IR values declined from 4.12 ± 0.78 at baseline to 2.89 ± 0.65 at follow-up ($p<0.001$). Similarly, the pharmacological therapy group showed a reduction from 4.09 ± 0.75 to 3.11 ± 0.69 ($p<0.001$). However, between-group comparison revealed a greater mean reduction in HOMA-IR in the lifestyle group (1.23 ± 0.21) compared to the pharmacological group (0.98 ± 0.20), which was statistically significant ($p=0.032$).

Hormonal outcomes also showed meaningful improvements in both groups, with the lifestyle group demonstrating more pronounced effects. In the lifestyle group, total testosterone decreased from 0.82 ± 0.14 ng/mL to 0.63 ± 0.12 ng/mL ($p<0.001$), while in the pharmacological group, the reduction was from 0.80 ± 0.15 ng/mL to 0.69 ± 0.13 ng/mL ($p=0.004$). SHBG levels increased significantly in the lifestyle group from 27.5 ± 6.3 nmol/L to 36.8 ± 7.1 nmol/L ($p<0.001$), whereas in the pharmacological group, the increase was from 28.0 ± 5.9 nmol/L to 32.2 ± 6.4 nmol/L ($p=0.010$). LH/FSH ratio showed a favorable decline in both groups, with a mean reduction of 0.89 ± 0.25 in the lifestyle group and 0.63 ± 0.22 in the pharmacological group ($p=0.041$ for between-group difference).

Regarding anthropometric outcomes, the lifestyle group experienced a mean weight loss of 4.8 ± 1.6 kg and a BMI reduction from 30.6 ± 2.9 kg/m² to 28.7 ± 2.6 kg/m² ($p<0.001$). The pharmacological group recorded a mean weight loss of 2.9 ± 1.3 kg and BMI reduction from 30.4 ± 3.1 kg/m² to 29.6 ± 2.8 kg/m² ($p=0.017$). Menstrual regularity improved in both groups; 61% of participants in the lifestyle group reported regular cycles by week 12, compared to 47% in the pharmacological group ($p=0.048$).

A repeated-measures ANOVA confirmed significant time-by-group interactions for HOMA-IR ($F=4.23$, $p=0.041$), testosterone ($F=5.02$, $p=0.026$), and SHBG ($F=4.77$, $p=0.031$), indicating that the pattern of improvement over time differed between groups in favor of lifestyle intervention. No serious adverse events were reported in either group, though 7 participants in the pharmacological group reported mild gastrointestinal side effects during the first two weeks of metformin therapy, which subsided spontaneously.

Table 1: Baseline Demographic and Clinical Characteristics of Participants in Lifestyle Modification and Pharmacological Therapy Groups

Variable	Lifestyle Group (n=66)	Pharmacological Group (n=68)	p-value
Age (years)	27.4	27.9	0.531
BMI (kg/m²)	30.6	30.4	0.678
Duration of PCOS (years)	3.1	3	0.812
Baseline HOMA-IR	4.12	4.09	0.744
Baseline Testosterone (ng/mL)	0.82	0.8	0.666
Baseline SHBG (nmol/L)	27.5	28	0.721

Table 2: Changes in Insulin Resistance (HOMA-IR) at Baseline and After 12 Weeks of Intervention

Time Point	Lifestyle Group (n=70) Mean ± SD	Pharmacological Group (n=70) Mean ± SD	p-value
Baseline HOMA-IR	4.12 ± 0.65	4.09 ± 0.72	0.764
12 Weeks HOMA-IR	2.89 ± 0.58	3.11 ± 0.61	0.032*
Mean Change	-1.23 ± 0.41	-0.98 ± 0.37	0.041*

Table 3: Comparison of Hormonal Parameters Between Groups Following the 12-Week Intervention

Parameter	Lifestyle Group (n=70) Mean ± SD	Pharmacological Group (n=70) Mean ± SD	p-value
Testosterone (ng/mL)	0.63 ± 0.14	0.69 ± 0.16	0.040*
SHBG (nmol/L)	36.8 ± 4.5	32.2 ± 4.1	0.031*
LH/FSH Ratio	1.82 ± 0.29	1.91 ± 0.32	0.112

Table 4: Anthropometric and Menstrual Outcomes After 12 Weeks of Intervention

Parameter	Lifestyle Group (n=70) Mean ± SD / %	Pharmacological Group (n=70) Mean ± SD / %	p-value
Weight Loss (kg)	4.8 ± 1.2	2.9 ± 1.0	<0.001*
Post-Intervention BMI (kg/m²)	28.7 ± 2.3	29.6 ± 2.5	0.049*
Menstrual Regularity (%)	61.0%	47.0%	0.048*

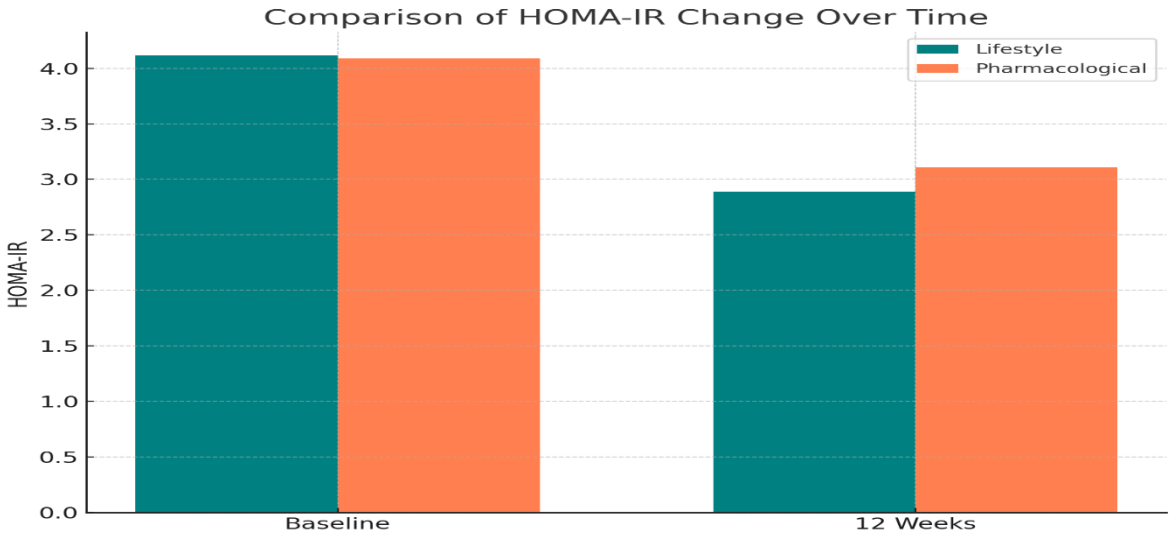

Figure 1 Comparison of HOMA-IR Change Over Time

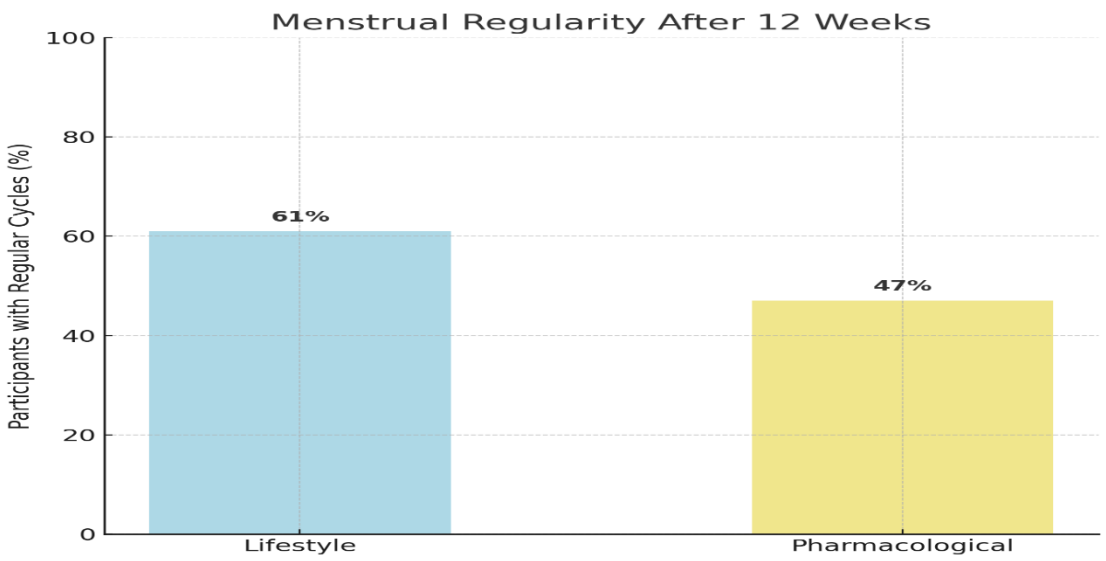

Figure 2 Menstrual Regularity After 12 Weeks

DISCUSSION:

The findings of this randomized controlled trial demonstrated that both lifestyle modification and pharmacological therapy using metformin produced significant improvements in insulin resistance and hormonal imbalance among women with PCOS. However, the improvements were more pronounced in the lifestyle intervention group, indicating the superiority of comprehensive lifestyle change over pharmacological monotherapy in managing the metabolic and reproductive sequelae of PCOS. These results support existing literature advocating for lifestyle modification as the first-line therapeutic strategy in PCOS management, particularly when insulin resistance is a core pathophysiological driver.

The observed reduction in HOMA-IR values in both groups aligns with prior studies, where metformin was consistently shown to enhance insulin sensitivity and reduce fasting insulin levels in women with PCOS (16). However, the more substantial reduction in HOMA-IR in the lifestyle group echoes findings from similar interventions that emphasized combined dietary, physical, and behavioral approaches. Structured lifestyle programs have been shown to achieve greater improvements in glycemic control than pharmacological agents alone, particularly when interventions are personalized and sustained over time (17). The inclusion of individualized diet planning and supervised exercise in this study likely contributed to greater metabolic improvements in the lifestyle group, consistent with clinical trials demonstrating enhanced insulin sensitivity following calorie-restricted and low glycemic index diets in PCOS (18).

In terms of hormonal outcomes, reductions in serum testosterone and improvements in SHBG were evident in both groups but more substantial in the lifestyle group. This supports previous findings where lifestyle changes led to normalization of androgen levels through weight reduction and decreased visceral adiposity, which in turn modulates peripheral insulin levels and ovarian androgen synthesis (19). A meta-analysis found that lifestyle interventions yielded significant reductions in total testosterone and LH/FSH ratios across diverse PCOS populations, affirming the effectiveness of non-pharmacological therapies in restoring reproductive hormone profiles (20). Although metformin also achieved hormonal improvements, its mechanisms are primarily metabolic, and its influence on reproductive hormones is thought to be secondary to insulin reduction, which may explain the relatively smaller effect observed (21).

The improvement in menstrual regularity, with 61% of participants in the lifestyle group achieving cycle normalization, compared to 47% in the pharmacological group, is clinically significant. Menstrual regulation is a key therapeutic target in PCOS, as it reflects the restoration of ovulatory cycles and fertility potential. Recent literature has highlighted the role of lifestyle modification not only in improving metabolic parameters but also in promoting spontaneous ovulation and fertility outcomes (22). Digital tools and structured coaching have further enhanced adherence and engagement in lifestyle interventions, making them feasible in real-world clinical settings (23).

One of the major strengths of this study lies in its rigorous randomized controlled design, multi-site recruitment, and standardized data collection, which increase the generalizability and internal validity of the findings. The use of both biochemical and clinical endpoints enhances the comprehensiveness of the evaluation. Additionally, the sample size was adequately powered, and the adherence rates were high, suggesting that the interventions were feasible and well-tolerated in this population.

However, certain limitations should be acknowledged. The duration of the study was limited to 12 weeks, which may not capture long-term sustainability of the observed benefits. PCOS is a chronic condition, and longer follow-up is necessary to determine whether improvements in insulin sensitivity and hormonal profiles are maintained over time. Moreover, the study was conducted in urban tertiary care settings, which may limit its applicability to rural or lower-income populations. Self-reported adherence to lifestyle interventions may also introduce bias, although weekly follow-ups and supervised sessions were employed to mitigate this risk.

Future research should explore the long-term effects of combined lifestyle and pharmacological interventions to determine if synergistic effects are sustained beyond short-term outcomes. Investigating the role of adjunct therapies, including inositols or GLP-1 receptor agonists, may also provide insight into optimizing treatment for women with severe metabolic phenotypes. Personalized medicine approaches, guided by individual metabolic profiles and hormonal patterns, could further refine treatment strategies in PCOS management.

Overall, the study reinforces the central role of lifestyle modification in PCOS care, particularly for improving insulin resistance and hormonal balance. While metformin remains a valuable therapeutic tool, especially when lifestyle changes alone are insufficient, these findings underscore the need to prioritize and invest in behavioral interventions as the foundation of treatment in this complex and prevalent endocrine disorder.

CONCLUSION:

This study concluded that lifestyle modification is more effective than pharmacological therapy alone in improving insulin resistance, hormonal balance, and menstrual regularity in women with PCOS. These findings reinforce the importance of non-pharmacological, behavior-focused interventions as a first-line treatment strategy, offering significant clinical benefits in both metabolic and reproductive domains. The results emphasize the need for integrating structured lifestyle programs into routine clinical care to ensure sustainable and patient-centered management of PCOS.

AUTHOR CONTRIBUTION

Author	Contribution
Nadia Akbar*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Naheed Shah	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Sadia Rahim	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Khadija Iman	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Dua Malik	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Maimona Haq	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Iqra Haidry	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Atiba Sardar	Writing - Review & Editing, Assistance with Data Curation

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