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Comparison of Metformin and Metformin Plus Liraglutide for Treating Metabolic Syndrome in Patients with Polycystic Ovarian Syndrome (PCOS)

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ABSTRACT

Background: This study compares the effectiveness of metformin (MET) monotherapy versus a combination of MET and liraglutide (LIRA) in managing metabolic syndrome in overweight women with polycystic ovary syndrome (PCOS), focusing on weight reduction and body mass index (BMI). **Methods:** A prospective cohort was conducted at Lady Dufferin Hospital, Karachi from April 2024 to Oct 2024, involving 70 women aged 18–40 years, diagnosed with PCOS based on Rotterdam criteria, and having a BMI ≥ 27.5 kg/m². Participants were randomly assigned into two groups: Group A received MET (1500 mg/day), and Group B received MET (1500 mg/day) plus LIRA (1.2 mg/day) for 12 weeks. Baseline and post-treatment outcomes, including weight, BMI, waist circumference, and lipid profiles, were analyzed. **Results:** Both treatment regimens significantly improved metabolic parameters. Group B demonstrated superior results with an average weight loss of 10.30 ± 1.30 kg and BMI reduction of 3.72 ± 0.67, compared to Group A's weight loss of 5.99 ± 2.87 kg and BMI reduction of 2.24 ± 1.07 ($p < 0.001$). Improvements in triglyceride levels, HDL cholesterol, and waist circumference were more pronounced in Group B. However, no significant changes in hypertension parameters were observed in either group. **Conclusion:** The combination of MET and LIRA is more effective than MET monotherapy in managing metabolic syndrome in overweight PCOS patients. This dual therapy offers enhanced metabolic benefits, potentially improving both reproductive and overall health. Further long-term, multicenter studies are warranted to explore its broader impacts and sustainability.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a widespread endocrine disorder affecting 8–13% of women of reproductive age worldwide, with prevalence varying based on diagnostic criteria (1). In South Asia, particularly Pakistan, the prevalence is notably high, reaching up to 52%, highlighting the condition's significant impact in the region (2). PCOS is a complex condition marked by hyper-androgenism, irregular ovulation, and polycystic ovarian morphology, often linked with metabolic issues such as obesity, insulin resistance, dyslipidemia, and an elevated risk of cardiovascular diseases (3).

Obesity, especially central adiposity, is a key factor in the development of PCOS (4). Approximately 25.6% of individuals with PCOS are overweight or obese, with visceral fat significantly contributing to insulin resistance and elevated androgen levels (5, 6). Insulin resistance, a hallmark of PCOS, affects more than 70% of women with the condition and worsens metabolic syndrome and its related risks (6). Therefore, strategies focused on weight loss and metabolic control are essential for managing PCOS and enhancing both metabolic health and reproductive outcomes (5).

Metformin, a widely used insulin-sensitizing agent, is effective in managing PCOS by improving insulin resistance, lowering blood sugar levels, and aiding in weight loss (7). Recently, the use of glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide, has gained attention as a promising treatment option (8, 9). Liraglutide, a long-acting GLP-1 analog, improves glycemic control while promoting substantial weight loss by suppressing appetite and slowing gastric

emptying (10). Studies suggest that combining metformin with GLP-1 receptor agonists produces synergistic effects, achieving better outcomes in weight reduction, BMI improvement, and metabolic regulation than either treatment alone (9, 11).

Although evidence supporting the use of GLP-1 receptor agonists in managing PCOS is expanding, most research has concentrated on Western populations (9, 11). There is a lack of data on their efficacy in South Asian populations, who often present unique metabolic characteristics, such as elevated insulin resistance and central obesity. Additionally, while the advantages of metformin-liraglutide combination therapy are well-documented, there is limited research comparing its effectiveness specifically in PCOS patients with metabolic syndrome (11). The main objective of this study to provide robust evidence on the relative efficacy of treatment with metformin mono therapy or with a combination of metformin and liraglutide in managing metabolic syndrome associated with PCOS, with a particular focus on weight reduction, BMI, and metabolic parameters. The findings are expected to inform clinical decision-making and optimize therapeutic approaches for PCOS patients, particularly those with significant metabolic derangements.

METHODS

This study was a six-month, prospective cohort at the Department of Obstetrics and Gynecology, Lady Dufferin Hospital, Karachi from April 2024 to Oct 2024. The hospital, a tertiary care institution, is well-equipped for managing diverse patient populations, including women with complex endocrine and metabolic disorders. Ethical approval for the study was obtained from the hospital's ethical review committee, and Collage of physicians and Surgeons Pakistan. A total of 70 women aged 18–40 years, diagnosed with polycystic ovary syndrome (PCOS) based on the Rotterdam criteria, were recruited. Participants were required to have a body mass index (BMI) of ≥27.5 kg/m² and evidence of metabolic syndrome. Exclusion criteria encompassed pregnancy, breastfeeding, unwillingness to use contraception, significant comorbid conditions, recent use of medications affecting glucose metabolism, or known contraindications to the study drugs. Participants were randomly assigned to one of two treatment groups using a computer-generated randomization code. Group A received metformin monotherapy (1500 mg/day), while Group B was treated with a combination of metformin (1500 mg/day) and liraglutide (1.2 mg/day). The intervention lasted for 12 weeks. Throughout the study, participants were advised to maintain consistent dietary habits, physical activity levels, and contraceptive measures to ensure comparability across groups. Baseline data, including demographic characteristics (age, marital status, and lifestyle), clinical parameters, and disease duration, were recorded. Outcome measures included weight (kg), BMI (kg/m²), waist circumference (cm), triglycerides (mg/dL), high-density lipoprotein (HDL) levels (mg/dL), fasting blood glucose (mg/dL), and mean arterial pressure (MAP). These parameters were assessed at baseline and after 12 weeks of treatment. Data were analyzed using SPSS software. Normality was tested with the Shapiro-Wilk test. Paired t-tests were employed for parametric data, and the Wilcoxon signed-rank test was used for non-parametric data. Between-group differences were assessed using independent t-tests and the Mann-Whitney U test, depending on the data distribution. Effect sizes were calculated using Cohen's d and rank biserial correlation (r). A p-value of <0.05 was considered statistically significant. Ethical considerations included obtaining written informed consent from all participants, ensuring voluntary participation, and maintaining confidentiality. Participants were regularly monitored for adverse events and adherence to the treatment protocol throughout the study duration.

RESULTS

Total number of 70 patients with PCOS was included in the study, 35 participants in each group, with the mean age of 28 ± 6.83 and the mean duration of disease was 19.36 ± 9.044 months. About 62.9% women were unmarried. (Table 1)

Table 1
Demographic Data

Variable	Mean/frequency
Age	28 ± 6.83
Duration of disease	19.36 ± 9.04
Marital Status	
Married	26 (37.1%)
Un married	44 (62.9%)

For Generalized metabolic Syndrome analysis, the data was divided into pre and post treatment effect and further classified into parametric and non-parametric categories which are calculated via Shapiro walik test. For weight and BMI paired Sample T test was performed and it was found to be significant. For the non-parametric data Wilcoxon Signed rank test was performed, and for those in which one variable was normally distributed and other is not normally distributed, the non-parametric test is applied because of more robust and doesn't rely on specific distributional assumptions. The data found to be significant (P -0.001); it shows both drugs even single or combined could lead to better results in metabolic syndrome associated with PCOS. (Table 2)

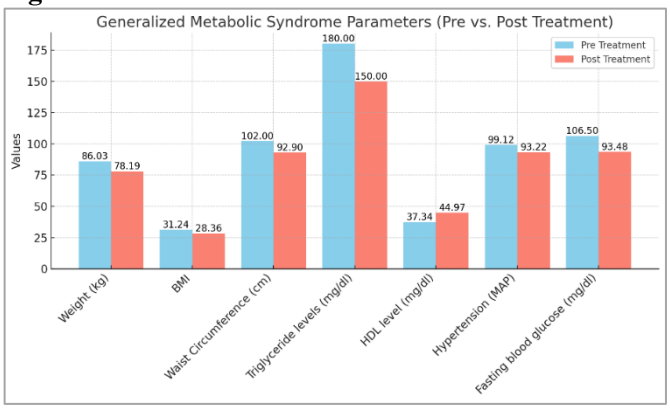
Table 2
Generalized Metabolic Syndrome parameters

Parameters	Pre treatment	Post treatment
Weight (kg)	86.03 ± 11.02*	78.19 ± 11.37*
BMI	31.24 ± 2.11*	28.36 ± 2.30*

Waist Circumference (cm)	102 ± 4.39^{+}	92.9 ± 3.79^{+}
Triglyceride levels (mg/dl)	180 ± 16.72^{+}	150 ± 13.70*
HDL level (mg/dl)	37.34 ± 2.80^{+}	44.97 ± 3.26^{+}
Hypertension (MAP)	99.12 ± 5.43^{+}	93.22 ± 4.41*
Fasting blood glucose (mg/dl)	106.5 ± 9.1^{+}	3.48 ± 6.13^{+}

*Parametric Data, + Non parametric Data

Figure 1



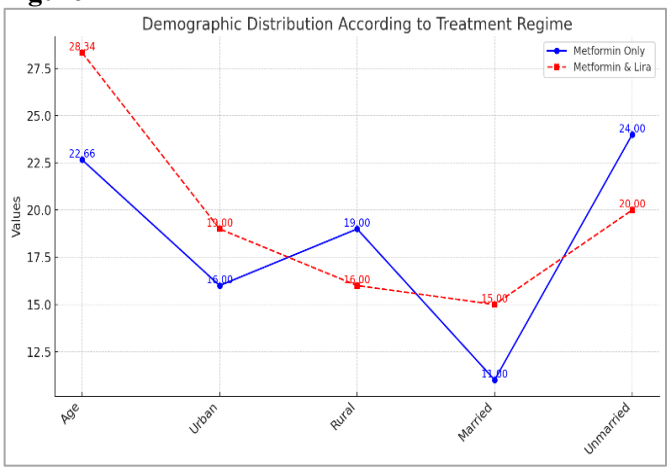
Now the distribution of Data according to treatment group, first the Demographic data is distributed and it showed the age of combined treatment was more as compare to single regime group with more unmarried patients in both groups. (Table 3)

Table 3

Demographic Distribution according to treatment regime

Variables	Treatment with metformin	Treatment with metformin & Lira
Age	22.66 ± 6.91	28.34 ± 6.82
Lifestyle (N)		
Urban	16 (45.7 %)	19 (54.2%)
Rural	19 (54.2%)	16 (45.7%)
Marital Status (N)		
Married	11 (31.42%)	15 (42.85%)
Un-married	24 (68.5%)	20 (57.1%)

Figure 2



The comparison of pre and post treatment effect on metabolic parameters were analyzed, there is significant improvement with group was found, it shows both treatment regimen is significantly effective in treating the metabolic syndrome but the combined regime is more robust than single therapy. (Table 4)

Table 4

Comparison of Treatment effect on Metabolic parameters

Parameters	Treatment with metformin		Treatment with metformin & Lira	
	Pretreatment	Post-treatment	Pretreatment	Post-treatment
Weight (kg)	84.25 ± 11.41	78.19 ± 11.93	87.81 ± 10.86	78.20 ± 10.96
BMI	30.74 ± 2.0	28.50 ± 2.41	31.71 ± 2.12	28.23 ± 2.22
Waist Circumference	101.3 ± 3.69	94.51 ± 2.68	101.8 ± 5.04	91.40 ± 4.12
Triglycerides levels	176.4 ± 14.3	156.4 ± 13.1	184.2 ± 18.2	145.2 ± 12.03
HDL levels	36.68 ± 2.68	43.17 ± 2.95	38 ± 2.80	46.8 ± 2.49
Hypertension	99.7 ± 5.43	94.6 ± 3.77	98.5 ± 5.45	91.8 ± 4.60
Fasting blood glucose	103.7 ± 8.2	94.05 ± 6.87	109 ± 9.32	92.9 ± 5.34

The effect of treatment on metabolic syndrome highlights the greater effect was seen with metformin with liraglutide more on Body mass index. The Hypertension is not significantly improved across the group. The change in each variable was identified and calculated separately and label as changed variable and mean of each change variable was calculated and the significance of combined change simple T test for parametric data and Wilcoxon signed rank test for non-parametric data. For the significances across the groups independent T test for parametric data and Mann whitney U test for non-parametric data was applied. For the generalized effect of the treatment Cohen's d for parametric and Rank Bi-serial correlation (r) for non-parametric data was applied. (Table-5)

Table 5

The combined effect of Treatment on Metabolic Syndrome

	Combined change	Metformin Group	Metformin with liraglutide	d/r value
Weight	7.84 ± 3.16^{b}	2.24 ± 1.09^{ab}	3.51 ± 0.90^{b}	0.57
BMI	2.87 ± 1.18^{ab}	6.06 ± 2.97^{ab}	9.62 ± 2.21^{ab}	0.9
Waist Circumference	8.61 ± 2.98^{b}	6.82 ± 2.41^{b}	10.40 ± 2.39^{b}	0.6
Triglycerides levels	29.51 ± 13.08^{b}	20.02 ± 7.04^{ab}	39.0 ± 10.61^{b}	0.7
HDL levels	7.62 ± 2.3^{b}	6.48 ± 1.46^{b}	8.77 ± 2.59^{ab}	0.4
Hypertension	5.89 ± 3.48^{b}	5.06 ± 4.28^{c}	6.73 ± 2.19^{c}	0.1
Fasting blood glucose	13.07 ± 6.15^{b}	9.62 ± 4.31^{b}	16.51 ± 5.81^{b}	0.6

a; parametric data, b; significant, c; Not significant

The Disease duration was converted into two groups, one group with disease duration greater than 12 months and other vice versa. The treatment with metformin with liraglutide is more effective as compare to metformin only. The significant change in BMI, Weight reduction, waist Circumference reduction, reduction in

Triglycerides levels, improvement of HDL levels and reduction of fasting blood glucose but the disease duration greater than 12 months are more effective in producing better outcomes suggestion prolong use is more effective and more in group with combined treatment. (Figure 1) The P-value of all except BMI was calculated via kruskal wallis test and BMI values was calculated via ANOVA.

DISCUSSION

The results of this study underscore the superior efficacy of metformin combined with liraglutide (MET + LIRA) compared to metformin monotherapy in managing metabolic syndrome in PCOS patients. Both therapies demonstrated significant weight loss and BMI reduction, with Group B achieving greater results (mean weight loss: 10.30 ± 1.30 kg; BMI reduction: 3.72 ± 0.67) compared to Group A (mean weight loss: 5.99 ± 2.87 kg; BMI reduction: 2.24 ± 1.07; $p < 0.001$). These findings align with literature, who also observed enhanced weight loss in MET + LIRA therapy compared to metformin alone (11). The superior outcomes with MET + LIRA can be attributed to liraglutide's multifaceted mechanisms, including appetite suppression, delayed gastric emptying, and modulation of insulin sensitivity, which complement metformin's effects (12, 13).

Demographic factors, including age and marital status, provided additional insights into treatment responses. Group B patients were slightly older (mean age: 28.34 ± 6.82 years) than Group A (22.66 ± 6.91 years), and the majority of participants in both groups were unmarried (Group A: 68.5%; Group B: 57.1%). These differences suggest that older and unmarried women with PCOS may benefit from combination therapy, possibly due to greater motivation for metabolic improvement and better adherence to treatment protocols (14). This observation is consistent with Lyu et al., who noted that demographic factors, such as age and urban lifestyle, diet, behavior can influence treatment efficacy in PCOS populations (11, 15).

The duration of the disease emerged as a significant determinant of treatment effectiveness. Patients with a disease duration exceeding 12 months exhibited more pronounced improvements in weight, BMI, and metabolic parameters, particularly in the MET + LIRA group. This finding aligns with literature which emphasized that prolonged metabolic dysfunctions in PCOS require more intensive and synergistic therapeutic strategies (16). Chronic exposure to insulin resistance and systemic inflammation in long-standing PCOS likely amplifies the benefits of liraglutide's anti-inflammatory and metabolic effects (17).

Both treatment groups showed significant improvements in metabolic parameters, with the MET + LIRA group achieving superior outcomes. Notably, the MET + LIRA group experienced greater reductions in waist circumference (10.40 ± 2.39 cm vs. 8.61 ± 2.98 cm) and triglycerides (39.0 ± 10.61 mg/dl vs. 29.51 ± 13.08 mg/dl), alongside more pronounced increases in HDL levels (8.77 ± 2.59 mg/dl vs. 7.62 ± 2.3 mg/dl). These results align with Andersen et al., who emphasized the effectiveness of GLP-1 receptor agonists in improving lipid profiles and reducing central adiposity (18). However, the improvement in waist circumference contrasts with findings in literature who observed no significant advantage of MET + LIRA on central adiposity (19). This difference may be attributed to variations in baseline BMI, as the higher BMI in this cohort likely amplified liraglutide's impact on reducing visceral fat.

Fasting blood glucose levels significantly decreased in both treatment groups; however, hypertension parameters, such as mean arterial pressure, showed no statistically significant improvement, even in the MET + LIRA group. This finding is aligned with studies, which observed blood pressure reductions with GLP-1 receptor agonists with metformin was not significant (20). The lack of significant impact may be attributed to the short intervention period of 12 weeks, potentially insufficient to produce notable changes in cardiovascular outcomes or it could be due the effect is very minimal and doesn't reflect its significances in patient with PCOS.

CONCLUSION

This study reinforces the enhanced efficacy of MET + LIRA combination therapy in managing metabolic syndrome in PCOS patients, particularly among older individuals and those with longer disease durations. While the findings are largely consistent with existing literature, differences in outcomes, such as those related to blood pressure, highlight the need for longer, multicenter studies. Future research should investigate the long-term impacts of this combination therapy on both metabolic and reproductive health outcomes while considering demographic and disease duration factors to optimize therapeutic strategies.

Limitation

The limitations of study include relatively small sample size, could have selection bias due to specific demography, limited duration follow ups to 12 weeks and doesn't account for potential side effects associated with metformin and Liraglutide.

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