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COMPARISON OF METFORMIN AND METFORMIN PLUS DAPAGLIFLOZINE FOR TREATING METABOLIC SYNDROME IN PATIENTS WITH POLY CYSTIC OVARIAN SYNDROME (PCOS)

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is commonly associated with metabolic syndrome, including insulin resistance and obesity. This study compares the effects of Metformin alone versus Metformin plus Dapagliflozin on metabolic parameters in women with PCOS.

Methods: A 12-week randomized controlled trial was conducted at Lady Willingdon Hospital, Lahore, involving 40 women with PCOS. Participants received either Metformin alone (Group A) or Metformin with Dapagliflozin (Group B). Weight, HbA1c, fasting glucose, insulin, and lipid profiles were assessed at baseline and after 12 weeks.

Results: Group B showed significantly greater reductions in weight (-8.3 ± 1.1 kg vs. -2.9 ± 0.8 kg; $p < 0.001$) and HbA1c (-0.5% vs. -0.2%; $p = 0.002$). Improvements in glucose, insulin, LDL-C, HDL-C, and triglycerides were also more significant in Group B ($p < 0.01$).

Conclusion: The combination of Metformin and Dapagliflozin was more effective than Metformin alone in improving metabolic outcomes in PCOS. It may be a promising strategy for managing metabolic syndrome in these patients.

1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) refers to a complex disorder with the variability of phenotypes usually characterized by anovulatory, irregular menstruation, hyperandrogenic, polycystic ovaries, and metabolic components [**1**]. It is a common endocrinopathy that affects up to five women

of reproductive age [**2**]. PCOS is also associated with insulin resistance, obesity, chronic systemic inflammation, and dyslipidemia which collectively enhance the risk of cardiovascular disease [**3**].

About 50% of PCOS patients are overweight or obese i.e., having a higher propensity of central adiposity due to glucose tolerance and insulin sensitivity. An increased visceral fat deposition indicates a high association with PCOS severity and induces high serum androgen production [**4**]. Oral hormonal contraceptives (OHC) are the first choice of treatment in hyperandrogenic PCOS women who do not desire conception. Additionally, insulin sensitizers counteract unfavorable consequences of OHC and provide additional benefits in treating PCOS [**5**].

Dapagliflozin is a sodium-glucose cotransporter type 2 inhibitor (SGLT2) that is vital in lowering blood glucose levels. It blocks the reabsorption of glucose in the proximal tubule of the kidney and increases the glucose excretion rate [**6**]. Having sustained effects on glycated hemoglobin and glycemia reduction, it has currently been used in the management of diabetes type II patients [**7**, **8**]. The role of dapagliflozin in reducing blood pressure and decreasing weight has been reported [**9**]. Its adverse effects include the risk of genital tract infections and euglycemic ketoacidosis [**10**]. Metformin is an insulin-sensitizing agent that plays a vital role in controlling blood sugar levels, widely used in T2D treatment. Some studies also report its effect on weight loss [**11**]. Some of the previous reported are as follows: A 12-week randomized control trial reported a 2.7% reduction in body weight by dapagliflozin compared to that of 1.7% by metformin [**12**].

Ferreira-Hermosillo et al reported a decrease in body weight of 1.1± 3.39 kg by metformin and 3.6± 4.22 kg by dapagliflozin after treatment of one year on 2847 patients [**13**]. Elkind-Hirsch et al reported a significant weight loss difference between the patients treated with metformin alone i.e., (4.4 + 18 kg) vs metformin plus dapagliflozin i.e., (21.5 + 14kg). This study shows that combined therapy is more effective in reducing weight [**14**].

. MATERIAL AND METHODS

. Study design and settings

The study design is Prospective Randomized Control Trial and the study was conducted at Lady Willingdon Hospital Lahore (Gynae Unit-I). Duration of Study was 6 months. A sample size of 38 (considered as 40) participants was calculated taking a 1% level of significance, 99% power of the test, 3.8 population standard deviation, 14.44 population variance, 21.5 test value of the weight loss mean in group DAPA+MET and 4.4 as anticipated weight loss mean in group MET [14]. Each group will contain 20 patients.

$$n = \frac{2\sigma^2(z_{1-\alpha} + z_{1+\beta})^2}{(\mu_1 - \mu_2)^2}$$

Sample technique used is Non-Probability Consecutive Sampling.

. Sample Selection

Inclusion criteria for research consists of these points; women of age 18 to 40 years, BMI > 25kg/m2, women with PCOS as per Rotterdam criteria, negative serum pregnancy test before enrollment. Exclusion criteria include; pregnant ladies, ladies intended to become pregnant, breastfeeding mothers and ladies not agree to birth control, women having three month old medication history having oral contraceptive pills, SGLT-2 inhibitors, glucagon-like peptide-1 receptor agonists, and MET, women having medical record of comorbidities such as diabetes, abnormal thyroid function-hyperthyroidism or hypothyroidism, androgen secreting tumor, congenital adrenal hyperplasia and Cushing syndrome and also women with UTI infections and gastrointestinal problems will be excluded. Approval for this study was

taken from Lady Willingdon Hospital ethical committee, Department of Obstetrics and Gynaecology, dated August 5th , 2024 (Reference no: 1673-7-LWH-OBG).

c. Data Collection Process

Prior to initiating the study, ethical clearance from the Institutional Review Board will be secured. Participants will be recruited from an eligible pool of women aged 18 to 40 years with a BMI greater than 30 kg/m^2 and diagnosed with PCOS based on the Rotterdam criteria. Exclusion criteria will be rigorously applied. Once consented, participants will undergo a comprehensive baseline assessment including anthropometric measurements and clinical tests. They will be randomized into two groups; (A) to receive metformin alone and (B) metformin combined with dapagliflozin. The intervention will last for 12 weeks, during which adherence to the medication regimen and any lifestyle guidelines will be monitored. Follow-up assessments will occur after12 weeks, where the same measurements (weight and Hb1Ac) taken at baseline will be repeated. The patient compliance will be ensured through clear communication and reminders.

d. Data Analysis Process

The quantitative variable like age, BMI will be presented as mean ± SD. Qualitative variables including menstrual frequency will be determined. Both groups will be compared for mean decrease in weight/BMI, mean decrease in triglyceride levels using independent sample t-test. Effect modifiers like age, duration of PCOS will be addressed through satisfaction.

3. RESULTS

A total of 40 patients diagnosed with polycystic ovarian syndrome (PCOS) and metabolic syndrome were randomized into two equal groups. Group A received Metformin monotherapy, while Group B was administered a combination of Metformin and Dapagliflozin. Baseline characteristics such as age (Group A: 29.4 ± 5.2 years; Group B: 28.7 ± 4.9 years), BMI (33.1 ± 2.4 kg/m² vs. 33.6 ± 2.6 kg/m²), body weight (84.2 ± 6.5 kg vs. 85.0 ± 7.2 kg), and HbA1c (6.1 ± 0.4% vs. 6.2 ± 0.5%) showed no statistically significant difference between the groups ($p > 0.05$), indicating comparability at baseline (**Table 1**). After 12 weeks of intervention, Group B exhibited a significantly greater reduction in body weight compared to Group A. The mean weight loss in Group B was 8.3 ± 1.1 kg, while Group A showed a mean weight loss of only 2.9 ± 0.8 kg ($p < 0.001$). This corresponds to a 9.8% weight reduction in Group B compared to 3.4% in Group A (**Table 2**). The mean reduction in HbA1c was also more pronounced in the combination therapy group (0.5 ± 0.1%) compared to Metformin monotherapy (0.2 ± 0.1%), and this difference was statistically significant ($p = 0.002$) (**Table 3**).

Metabolic profile analysis revealed that fasting blood glucose levels decreased from 6.9 to 5.6 mmol/L in Group B and from 6.8 to 6.1 mmol/L in Group A ($p = 0.001$). Fasting insulin levels were reduced more significantly in Group B (14.5 → 10.1 mmol/L) than in Group A (14.2 → 12.0 mmol/L), with a p-value of 0.007. Lipid parameters improved more favorably in Group B, including a greater reduction in LDL-C (3.7 → 2.9 mmol/L) and triglycerides (2.3 → 1.5 mmol/L), and a greater increase in HDL-C (1.1 → 1.4 mmol/L), all showing statistical significance ($p < 0.005$) (**Table 4**).

. DISCUSSION

This study evaluated and compared the effectiveness of Metformin monotherapy versus combination therapy with Metformin and Dapagliflozin in managing metabolic syndrome among women with PCOS. The results clearly demonstrate that the combination therapy was significantly superior in improving weight, glycemic parameters, and lipid profiles over the 12-week trial period. The findings are in line with earlier studies suggesting the enhanced

effectiveness of dual therapy in improving metabolic outcomes in PCOS. For instance, Elkind-Hirsch et al. (2020) highlighted significant reductions in body weight and HbA1c among overweight women treated with the combination therapy post-gestational diabetes mellitus [**14**]. Ferreira-Hermosillo et al. (2020) similarly reported greater weight reduction in patients receiving both Metformin and Dapagliflozin compared to Metformin alone [**13**].

The improved outcomes in our study can be attributed to the complementary mechanisms of both drugs. Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, increases urinary glucose excretion, thereby promoting glycemic control independently of insulin. When paired with Metformin, an insulin sensitizer, this mechanism enhances insulin sensitivity, lowers glucose levels, and facilitates weight loss more effectively than either drug alone. Additionally, recent studies have begun to explore the role of SGLT2 inhibitors in managing the broader metabolic complications of PCOS. Ryder et al. (2021) investigated the use of Empagliflozin in overweight and obese women with PCOS and found favorable effects on weight and visceral adiposity, suggesting potential class-wide benefits of SGLT2 inhibitors in PCOS management [**15**]. This supports the outcomes seen in our trial using Dapagliflozin. Furthermore, Lempesis et al. (2023) emphasized the cardiovascular benefits of SGLT2 inhibitors in women with PCOS, highlighting their role in improving lipid parameters and potentially reducing long-term cardiovascular risk [**16**].

In addition to these cardiometabolic improvements, Rakic et al. (2023) have also proposed that SGLT2 inhibitors may improve hormonal balance and inflammatory status in PCOS by reducing oxidative stress and regulating mitochondrial function [**17**]. These mechanisms might further explain the broad-spectrum metabolic benefits seen in our study with combination therapy. The observed improvements in LDL-C, HDL-C, and triglyceride levels in our study reinforce the notion that addressing both insulin resistance and dyslipidemia is critical in managing PCOS. Given the established connection between PCOS, metabolic syndrome, and cardiovascular disease, the dual-drug approach could offer a more comprehensive management strategy, especially for women who are overweight or obese.

Nonetheless, it is important to acknowledge limitations. The sample size was small, and the duration of the study was limited to 12 weeks. Additionally, this study did not assess ovulation rate, androgen levels, or menstrual regularity, which are also important clinical endpoints in PCOS. Long-term studies involving a larger cohort and assessment of hormonal and reproductive outcomes are necessary to fully establish the efficacy and safety of Dapagliflozin in PCOS. In conclusion, combination therapy with Metformin and Dapagliflozin was more effective than Metformin alone in reducing weight and improving glycemic and lipid profiles in women with PCOS and metabolic syndrome. This approach shows promise for the metabolic management of PCOS, though further research is needed to determine its long-term impact on reproductive health and overall disease progression.

. CONCLUSION

This study demonstrates that the combination of Metformin and Dapagliflozin is significantly more effective than Metformin alone in improving key metabolic parameters in women with polycystic ovarian syndrome (PCOS) and metabolic syndrome. Patients receiving combination therapy experienced greater reductions in body weight, HbA1c levels, fasting glucose, insulin levels, and lipid abnormalities over a 12-week period. These findings suggest that adding Dapagliflozin to Metformin may offer a more comprehensive and targeted approach to

managing the metabolic disturbances commonly associated with PCOS. Given the complex interplay of insulin resistance, obesity, and cardiovascular risk in PCOS, the enhanced metabolic benefits observed with combination therapy hold promising clinical implications. However, larger-scale and longer-term studies are warranted to validate these results, assess safety profiles, and explore additional outcomes such as hormonal regulation, menstrual cyclicity, ovulation, and fertility potential. Until then, Metformin combined with Dapagliflozin may be considered a valuable treatment option for improving metabolic health in select PCOS patients with coexisting metabolic syndrome.

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Ethical Approval: Approval for this study was taken from Lady Willingdon Hospital ethical committee, Department of Obstetrics and Gynaecology, dated August 5th , 2024.

Conflict of Interest: The authors declare no potential conflict of interest.

Consent for Publication: All authors approved the manuscript for publication.

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Tables and figures

Table 1: Baseline Characteristics of Patients in Both Groups Before Treatment Initiation

Parameter	Group A (Metformin)	Group B (Met + Dapagliflozin)	p-value
Age (years)	29.4 ± 5.2	28.7 ± 4.9	0.62
BMI (kg/m²)	33.1 ± 2.4	33.6 ± 2.6	0.48
Weight (kg)	84.2 ± 6.5	85.0 ± 7.2	0.70
HbA1c (%)	6.1 ± 0.4	6.2 ± 0.5	0.44

Table 2: Comparison of Weight Reduction Between Study Groups

Group	Baseline Weight (kg)	Final Weight (kg)	Mean Change (kg)	% Reduction	p-value
Group A (Metformin)	84.2 ± 6.5	81.3 ± 6.1	-2.9 ± 0.8	3.4%	—
Group B (Met + Dapagliflozin)	85.0 ± 7.2	76.7 ± 6.8	-8.3 ± 1.1	9.8%	<0.001

Table 3: Comparison of HbA1c Reduction Between Treatment Groups

Group	Baseline HbA1c (%)	Final HbA1c (%)	Mean Change	p-value
Group A (Metformin)	6.1 ± 0.4	5.9 ± 0.3	-0.2 ± 0.1	—
Group B (Met + Dapagliflozin)	6.2 ± 0.5	5.7 ± 0.3	-0.5 ± 0.1	0.002

Table 4: Effects on Metabolic Parameters in Both Groups

Parameter	Group A (Metformin)	Group B (Met + Dapagliflozin)	p-value
Fasting Glucose (mmol/L)	6.8 → 6.1	6.9 → 5.6	0.001
Fasting Insulin (mmol/L)	14.2 → 12.0	14.5 → 10.1	0.007
LDL-C (mmol/L)	3.6 → 3.2	3.7 → 2.9	0.005
HDL-C (mmol/L)	1.1 → 1.2	1.1 → 1.4	0.004
Triglycerides (mmol/L)	2.2 → 1.9	2.3 → 1.5	0.001

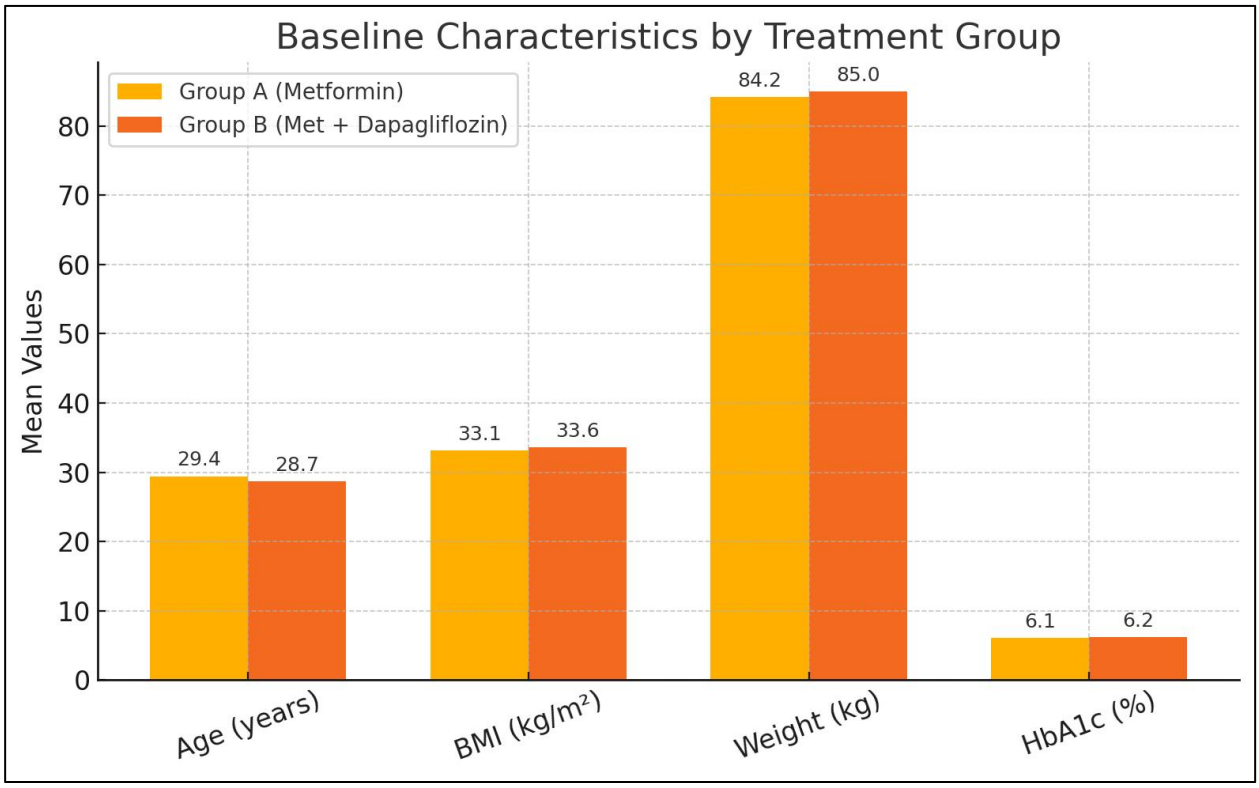

Figure 1: Baseline characteristics of both treatment groups showing comparable values

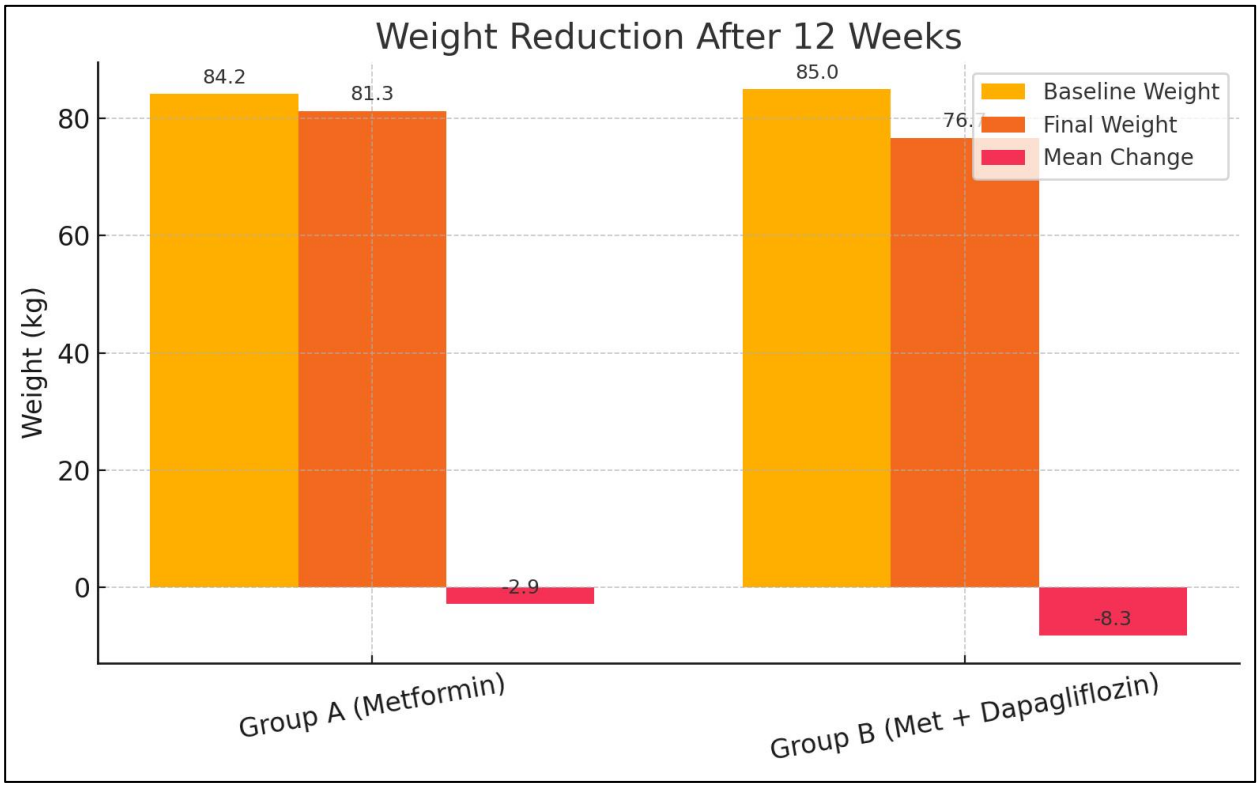

Figure 2: Weight reduction over 12 weeks in both groups. Group B showed greater weight loss compared to Group A