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EFFECTS OF EMPAGLIFLOZIN ON METABOLIC PARAMETERS IN POLYCYSTIC OVARY SYNDROME

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Abstract

Background: *Polycystic ovary syndrome (PCOS) is a common hormonal disorder with metabolic complications. While metformin is widely used, newer drugs like empagliflozin show promise. Due to limited local data, this study evaluated empagliflozin's effects on metabolic parameters in women with PCOS in a local population.*

Objective: *To compare the effect of empagliflozin on metabolic parameters in polycystic ovary syndrome in comparison with metformin in terms of mean difference in body mass index and fasting blood glucose (8 hrs fasting).*

Duration: *25-11-2024 to 25-05-2025*

Methodology: *Following approval from the Ethical Review Board, 60 PCOS patients from DHQ hospital Sheikhupura were enrolled and randomly assigned to two groups using the lottery method: Group A received empagliflozin 25 mg daily, and Group B received metformin SR 1500 mg daily for 12 weeks. Baseline and 12-week BMI and fasting glucose levels were recorded. BMI was calculated using the standard formula, and blood glucose was measured from a single hospital lab by one operator to minimize bias.*

Results: *This study on 60 PCOS patients (mean age 32.73 ± 6.28 years, BMI 29.95 ± 3.02) showed greater BMI reductions (−1.80 vs. −1.01 kg/m²) and glucose (−16.27 vs. −13.83 mg/dL) reductions with empagliflozin than metformin. Subgroup trends favored empagliflozin, though some lacked statistical significance due to limited sample sizes.*

Conclusion: *Empagliflozin demonstrated superior efficacy over metformin in reducing BMI and fasting blood glucose in women with PCOS over 12 weeks. Although end-treatment values were comparable, the magnitude of reduction was significantly greater with empagliflozin. Subgroup trends favored empagliflozin, though some lacked statistical significance, likely due to limited sample sizes.*

INTRODUCTION

It is a prevalent endocrine disorder affecting women of reproductive age, with a reported prevalence ranging from 6.8% to 18%.[1] It is characterized by excessive androgen production from the ovaries and/or adrenal glands, often due to intrinsic ovarian abnormalities in steroidogenesis as well as extrinsic factors such as hyperinsulinemia.[2] A hallmark feature of PCOS is the presence of an increased number of antral follicles, typically arrested in development at 5 to 8 mm in diameter, compared to healthy controls.[2,3] Although the precise etiopathogenesis of PCOS remains unclear, insulin resistance and the resulting

hormonal imbalance, particularly hyperandrogenism, are widely recognized as modifiable contributors.[4] Insulin resistance in PCOS arises from post-receptor defects in insulin signaling, leading to impaired glucose tolerance, dyslipidemia, and hypertension, all of which increase the risk of cardiovascular disease.[4,5] Therefore, screening for metabolic syndrome and glucose intolerance is essential in the management of women with PCOS.[5]

While symptom management has traditionally been the focus, recent therapeutic strategies aim to address insulin resistance, thereby indirectly improving hyperandrogenism and its metabolic consequences.[3] Common treatments include lifestyle interventions, oral contraceptives, anti-androgens, ovulation induction agents, and insulin sensitizers such as metformin.[5] Metformin, introduced in 1994 for PCOS management, has shown efficacy in improving endocrine function, regulating ovulation, and promoting weight loss in overweight women.[6] Empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor approved for type 2 diabetes, is a newer agent with an insulin-independent mechanism of action.[7] By enhancing urinary glucose excretion, it offers metabolic benefits without increasing hypoglycemia risk, making it a promising therapeutic option for PCOS patients.[7,8]

Javed et al. in a study in the United Kingdom reported mean change in metabolic parameters in PCOS women as BMI (-1.4±3.2 vs. 1.2±2.3 kg/m2; p-value=0.005), BMR (-1.8±2.9 vs. 0.1±1.9 kcal; p-value=0.020), fasting glucose (-0.8±5.8 vs. -2.3±8.0 mmol/L; p-value=0.508), total cholesterol (TC) (-1.6±13.7 vs. -2.2±8.5 mmol/L; p-value=0.869), low density lipoproteins cholesterol (LDLC) (2.7±30.2 vs. -3.4±9.6 mmol/L; p-value=0.395), high density lipoproteins cholesterol (HDLC) (-0.6±9.2 vs. -3.4±9.6 mmol/L; p-value=0.358) respectively between empagliflozin and metformin group.[8] The mean change in BMI was 1.3±0.3 in empagliflozin and 0.6±0.3 in control group.[9] Mean change in fasting blood glucose in empagliflozin group was 4±4.[10] Mean change in BMI in metformin group was 1.02±0.04.[11] The evidence is limited to a single study only and there is no locally published material on the subject matter. Therefore, purpose of this study is to repeat this trial so as to ascertain effect of empagliflozin on metabolic parameters in PCOS women. If significant results are observed, it will help to choose a better treatment regime for PCOS in future practice.

METHODOLOGY

This randomized controlled trial was conducted at the Department of Obstetrics and Gynaecology, DHQ Hospital, Sheikhupura, over a period of six months following ethical approval. A total of 60 women diagnosed with PCOS based on the Rotterdam criteria were included. These criteria required the presence of any two of the following: oligo-anovulation (menstrual cycles <28 or >32 days), hyperandrogenism (DHEA-S >200 µg/dL), and polycystic ovarian morphology (≥12 follicles measuring 2-9 mm or ovarian volume >10 mL). The sample size was calculated with 90% confidence interval and 70% power, based on expected mean BMI changes between the empagliflozin and metformin groups.[8] Non probability consecutive sampling was used. Women aged 20-45 years who met the inclusion criteria were selected, while those on hormonal or anti-diabetic drugs, pregnant or lactating, or with chronic illnesses such as liver disease or hyperthyroidism were excluded. After obtaining informed consent, patients were randomly allocated to two groups using the lottery method. Group A received empagliflozin 25 mg daily, while Group B was treated with metformin SR 1500 mg daily, both for 12 weeks. Baseline and post-treatment values were recorded for BMI, calculated using weight in kilograms divided by height in meters squared (kg/m²), and fasting blood glucose levels measured after 8 hours of fasting. Blood samples were analyzed at a single hospital laboratory by one technician to ensure consistency and reduce bias. Data were analyzed using SPSS version 25. Numerical variables including age, BMI, and blood glucose levels were expressed as mean ± standard deviation (SD), and independent t-tests were applied to compare mean differences between the groups. A p-value ≤0.05 was considered statistically significant. Categorical variables such as obesity status were summarized as frequencies and percentages. Data were stratified for age and obesity to assess effect modifiers, and post-stratification analysis was also performed using the independent sample t-test.

RESULTS

The study included a total of 60 participants aged between 20 and 45 years, with a mean age of 32.73 ± 6.28 years. Among them, 26 participants (43.3%) were in the 20–30 years age group, while 34 participants (56.7%) were aged between 31 and 45 years. The mean BMI of the participants was 29.95 ± 3.02, with 35 individuals (58.3%) classified as obese and 25 (41.7%) as non-obese. The mean fasting blood sugar level was recorded at 132.63 ± 4.22 mg/dL. Data is given in Table 1.0. At baseline both the groups were statistically comparable for all the variables (p-value>0.05), as shown in Table 2.0. After 12 weeks of treatment, the mean BMI in Group A (empagliflozin) was 28.47 ± 2.99 kg/m², while in Group B (metformin) it was 28.63 ± 2.99 kg/m², with no statistically significant difference between the groups (p = 0.873). However, the mean reduction in BMI was significantly greater in Group A (-1.800 ± 0.47 kg/m²) compared to Group B (-1.013 ± 0.53 kg/m²), with a highly significant difference (p = 0.000). Similarly, the post-treatment blood sugar levels were 116.73 ± 4.35 mg/dL in Group A and 118.43 ± 5.36 mg/dL in Group B, showing no significant difference (p = 0.183). However, the mean reduction in blood sugar level was significantly greater in the empagliflozin group (-16.27 ± 2.50 mg/dL) compared to the metformin group (-13.83 ± 1.78 mg/dL), with the difference being statistically significant (p = 0.000). Data is given in Table 3.0. Mean difference in BMI and blood sugar level was stratified for sub groups of age and BMI wherein group A maintained its supremacy over group B but statistical significance could not be achieved in all the sub groups which may however be associated with small sample size in sub groups.

Table 1.0: Demographic Characteristics of Women Suffering from PCOS

Characteristics	Total (n=60)
Age (20-45years)	32.73±6.28
• 20-30 years	26 (43.3%)
• 31-45 years	34 (56.7%)
BMI	29.95±3.02
• Obese	35 (58.3%)
• Non-Obese	25 (41.7%)
Blood Sugar Level (mg/dl)	132.63±4.22

Table 2.0: Comparison of Baseline Characteristics between the Groups

Characteristics	Group A (n=30)	Group B (n=30)	p-value
Age (20-45years)	32.30±6.14	33.17±6.49	0.597
• 20-30 years	12 (40.0%)	14 (46.7%)	0.602
• 31-45 years	18 (60.0%)	16 (53.3%)	
BMI	30.27±2.92	29.63±3.13	0.414
• Obese	19 (63.3%)	16 (53.3%)	0.432
• Non-Obese	11 (36.7%)	14 (46.7%)	
Blood Sugar Level (mg/dl)	133.00±3.80	132.27±4.65	0.506

Table 3 .0: Comparison of Study Mean BMI and Blood Sugar After 12 weeks of Treatment and Comparison of Mean Difference

Study Variable	Group A (n=30)	Group B (n=30)	p-value

BMI (kg/m^2)			
• After 12 weeks treatment	28.47±2.99	28.63±2.99	0.873
• Mean Difference	-1.800±0.47	-1.013±0.53	0.000
Blood Sugar Level (mg/dl)			
• After 12 weeks treatment	116.73±4.35	118.43±5.36	0.183
• Mean Difference	-16.27±2.50	-13.83±1.78	0.000

DISCUSSION

PCOS is a common endocrine disorder in women of reproductive age, associated with insulin resistance, obesity, and metabolic dysfunction.[12,13] Traditionally, treatments such as metformin have been used to improve insulin sensitivity and manage symptoms.[14,15] Recently, newer agents like empagliflozin, a SGLT2 inhibitor, have shown potential metabolic benefits. However, there is limited data on the use of empagliflozin in PCOS, and most available studies are from non-local populations.[8-11] To address this gap, the present study was conducted to evaluate the effects of empagliflozin on metabolic parameters in women with PCOS in a local population setting.

This study enrolled 60 women aged 20–45 years, with a mean age of 32.73 ± 6.28 years. The mean BMI was 29.95 ± 3.02, and the mean fasting blood sugar level was 132.63 ± 4.22 mg/dL. At baseline, both treatment groups were statistically comparable ($p > 0.05$). After 12 weeks, the mean BMI was 28.47 ± 2.99 kg/m² in the empagliflozin group and 28.63 ± 2.99 kg/m² in the metformin group ($p = 0.873$), but the BMI reduction was significantly greater with empagliflozin ($p = 0.000$). Blood sugar reduction also favored empagliflozin ($p = 0.000$). Subgroup analysis showed similar trends without consistent statistical significance.

A comparison of the findings of this study with existing literature reveals a growing body of evidence supporting the metabolic benefits of empagliflozin over metformin. In a study conducted by Javed et al. in the United Kingdom, univariate analysis demonstrated significantly greater reductions in several anthropometric parameters in the empagliflozin group compared to the metformin group. These included weight (−1.4 ± 3.2% vs. 1.2 ± 2.3%; $P = 0.006$), body mass index (−1.4 ± 3.2% vs. 1.1 ± 2.2%; $P = 0.006$), waist circumference (−1.6 ± 2.8% vs. 0.2 ± 2.1%; $P = 0.029$), and hip circumference (−2.0 ± 3.0% vs. 1.1 ± 1.9%; $P = 0.001$). Additionally, improvements in basal metabolic rate (−1.8 ± 2.9% vs. 0.1 ± 1.9%; $P = 0.024$) and fat mass (−0.7 ± 4.9% vs. 3.2 ± 5.0%; $P = 0.023$) were noted in the empagliflozin group. These differences remained significant even after adjustment for covariates using linear regression analysis.[8] However, Javed et al. reported no significant differences in hormonal or other metabolic parameters between the two groups.[8]

Another relevant study by Kuchay et al. highlighted empagliflozin's role in reducing hepatic fat content when used alongside standard diabetes therapy. The mean difference in MRI-proton density fat fraction (MRI-PDFF) between the empagliflozin and control groups was 24.0%, with a highly significant P value of <0.0001. Within-group analysis showed that MRI-PDFF decreased from 16.2% to 11.3% in the empagliflozin group ($P < 0.0001$), while no significant change was observed in the control group (16.4% to 15.5%; $P = 0.057$). Moreover, the empagliflozin group showed a significant reduction in serum ALT levels ($P = 0.005$), although changes in AST ($P = 0.212$) and GGT ($P = 0.057$) were not statistically significant.[9]

Supporting these metabolic effects at the renal level, Al-Jobori et al. studied the impact of empagliflozin on maximal renal glucose transport (TmG) in patients with and without type 2 diabetes. At baseline, TmG was significantly higher in diabetic patients compared to non-diabetic subjects (459 ± 53 vs. 337 ± 25 mg/min; $P < 0.05$). Following 48 hours of treatment, empagliflozin reduced TmG by 44 ± 7% in diabetic patients and by 53 ± 6% in non-diabetic individuals ($P < 0.001$ for both). By day 14, further reductions of 65 ± 5% and 75 ± 3%, respectively, were observed. Additionally, empagliflozin significantly lowered the plasma glucose concentration threshold for glycosuria in both groups to levels below 40 mg/dL, well beneath the normal fasting plasma glucose range.[10]

Tanaka et al. reported that empagliflozin significantly enhanced metabolic outcomes, including glycemic control and weight reduction, particularly when used

in combination with metformin, suggesting a potential synergistic effect in patients with insulin resistance.[16]

CONCLUSION

Empagliflozin demonstrated superior efficacy over metformin in reducing BMI and fasting blood glucose in women with PCOS over 12 weeks. Although end-treatment values were comparable, the magnitude of reduction was significantly greater with empagliflozin. Subgroup trends favored empagliflozin, though some lacked statistical significance, likely due to limited sample sizes.

LIMITATIONS & RECOMMENDATIONS

This study is among the few to evaluate empagliflozin in a local PCOS population, offering valuable comparative data against metformin. Strengths include a randomized design and clearly defined metabolic outcomes. However, limitations include a small sample size and short follow-up duration, which may affect generalizability and subgroup analysis power. Future studies should explore long-term effects, hormonal outcomes, and broader populations to establish empagliflozin's full therapeutic potential in PCOS management.

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Authors Contribution

Author 1

Substantial contributions to study design, acquisition of data
Analysis & Interpretation of Data, Manuscript writing
Has given final approval of the version to be published
Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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