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RESEARCH ARTICLE
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"EVALUATING ANTIDIABETIC DRUG THERAPIES IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME: BIOCHEMICAL IMPACT AND CARDIOVASCULAR BENEFITS OF SGLT2 INHIBITORS - A CROSS-SECTIONAL STUDY"

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Background: Polycystic Ovary Syndrome (PCOS) is a hormonal disorder often associated with insulin resistance. Anti diabetic drugs i.e, SGLT2 inhibitors ,Metformin and Vildagliptin are antidiabetic medications that improve biochemical markers and clinical outcomes in polycystic ovary syndrome patients. **Objective:** To compare the effectiveness and biochemical impact of anti diabetic drugs i.e Metformin, Vildagliptin,SGLT2 inhibitors in women with PCOS and also explore the cardiovascular benefits of SGLT2 inhibitors. **Methodology:** This cross-sectional study included women with polycystic ovary syndrome (PCOS) treated with either SGLT2 inhibitors, Metformin and Vildagliptin. Biochemical parameters, including insulin sensitivity, androgen levels, and lipid profiles were measured and assess the cardiovascular protective effects of SGLT2 inhibitors. **Results** Both Metformin and Vildagliptin improved insulin sensitivity and reduced androgen levels, but Metformin showed greater efficacy in weight reduction and improvement in lipid profiles and SGLT2 inhibitors has cardiovascular protective effects. **Conclusion:** Antidiabetic drugs are effective in improving biochemical markers in PCOS patients as well as Metformin and SGLT2 inhibitors has additional benefits on heart and lipid profiles may make it a preferred choice for cardiovascular patients.

Keywords: Polycystic Ovary Syndrome, Metformin, Vildagliptin, Insulin Resistance, SGLT2 inhibitors

INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting 5-10% of women of reproductive age. The diagnosis of polycystic ovary syndrome is based on diverse clinical manifestations, including chronic anovulation or oligo-ovulation, hyperandrogenism and the presence of polycystic ovaries on ultrasound[1,2]. As the leading cause of female infertility, Polycystic ovary syndrome is also associated with an increased risk of developing diabetes mellitus, cardiovascular disease and endometrial cancer[3].

The exact pathophysiology of polycystic ovary syndrome remains unclear, insulin resistance and the resulting compensatory hyperinsulinemia are believed to play a crucial role in the development of the disorder[4-7]. Insulin resistance is a common feature of polycystic ovary syndrome affecting both normal-weight and overweight women and is thought to contribute significantly to the hyperandrogenism and infertility associated with the condition which causes increase risk of developing diabetes, with an onset age 30 years earlier than the general population[8].

Hyperinsulinemia not only increases the risk of cardiovascular disease directly but also indirectly through its impact on lipid metabolism. Given the significance of insulin resistance in PCOS, insulin sensitizers have emerged as a promising therapeutic approach[9,10]. Metformin and SGLT2 inhibitors are two such agents that reduce insulin resistance through different mechanisms. Metformin, a biguanide, decreases hepatic glucose production, lowers circulating insulin levels, and improves peripheral glucose utilization. In contrast, Sodium glucoae co-transporter inhibitors (SGLT2) inhibitors improve glucose level in body, promote glucose excretion, reducing blood glucose levels. Beyond glycemic control, these agents have demonstrated cardiovascular benefits, including reduced risk of major adverse cardiovascular events (MACE), heart failure hospitalizations and kidney disease progression. The mechanisms underlying these benefits are multifaceted, involving diuresis, natriuresis, and potential direct effects on the cardiovascular system[11]. Clinical trials have consistently shown that SGLT2 inhibitors improved cardiovascular outcomes in patients with type 2 diabetes andreduced cardiovascular risk. As such, SGLT2 inhibitors are increasingly recognized as a valuable treatment option for patients with type 2 diabetes and cardiovascular disease.

Vildagliptin, a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor, has been shown to improve glycemic control in patients with type 2 diabetes by enhancing alpha- and beta-cell responses to glucose. Clinical studies have demonstrated the efficacy of Vildagliptin as monotherapy or in combination with other antidiabetic agents or insulin in achieving better blood glucose control[12,13]. Furthermore, Vildagliptin has a favorable safety profile, making it a viable treatment option for patients with type 2 diabetes.

In this study, these antidiabetic medications offered therapeutic benefits beyond glycemic control, potentially addressing some of the underlying pathophysiological mechanisms driving the disorder and especially , SGLT2 inhibitors improved cardiovascular outcomes in patients with type 2 diabetes and reduced cardiovascular risk.. However, further research is needed to fully elucidate the effects of these agents on polycystic ovary syndrome outcomes.

METHODOLOGY

A cross sectional included 105 patients and were randomized in 3 study groups All patients were assessed by history taking, clinical examinations and were investigated by routine investigation to check for general condition. Fasting Serum (free testosterone, dehydroepiandrosterone (DHEA) and, insulin leves) and Glycosylated hemoglobin (Hb A1c) were assessed and evaluated for hirsutism at baseline and at the end of the study using the modified Ferriman-Gallwey (F-G) score.

Ethical considerations

The study was approved by the institutional IRB of Dow University of Health Sciences.

STATISTICAL ANALYSIS

Data analysis using SPSS Version 22 included calculating means, standard deviations, frequencies, and percentages. Chi-square tests compared treatment efficacy between groups with effect modifiers controlled through stratification. A p-value of ≤ 0.05 was considered significant.

RESULTS

The study compared the demographic, clinical, and biochemical characteristics of the study groups using one-way analysis of variance (ANOVA).

Table1 showed the demographic features & Biochemical Parameters of study participants

	Group 1 SGLT 2 inhibitors	Group 2 Vildaglipti n	Group 3 Metformin	p value
Age	25.5 ± 4.0	24.5 ± 3.6	23.2 ± 4.3	0.058
BMI	27.5 ± 5.2	28.0 ± 5.1	25.8 ± 5.7	0.199
Ferriman-Gallwey (F-G) score	12.0 ± 7.4	11.8 ± 7.9	12.3 ± 7.4	0.961
Free testosterone (0.6 - 6.8 pg/ml)	4.4 ± 2.7	5.4 ± 2.5	5.5 ± 2.0	0.121
DHEA (44 - 332 µg/dL)	263.7 ± 117.4	271.9 ± 126.5	280.7 ± 132.2	0.852
Fasting Insulin (<25 µ IU/L)	27.9 ± 8.7	28.9 ± 8.1	29.8 ± 10.6	0.711
Hb A 1c (<5.7%)	4.4 ± 0.6	4.8 ± 0.7	4.7 ± 0.8	0.102
LDL (up to 140 mg/dl)	129.6 ± 27.3	133.6 ± 32.5	127.6 ± 28.9	0.691

The efficacy of SGLT2 inhibitors was evaluated in Group 1demonstrated significant reductions in several key parameters following treatment.Specifically, paired t-test analysis revealed statistically significant decreases in body mass index (BMI), Ferriman-Gallwey score, free testosterone levels, dehydroepiandrosterone (DHEA) levels, fasting insulin levels, and glycosylated hemoglobin (HbA1c) levels. However, the reduction in cholesterol and low-density lipoprotein (LDL) levels reached statistical significance.

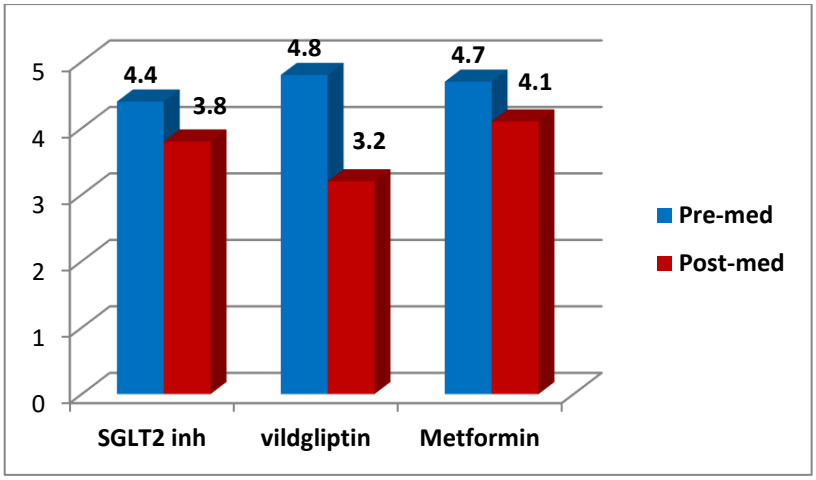

Fig 1 showed the pre medication and post medication effect on Hb A1c

Furthermore, the impact of SGLT2 inhibitors on menstrual irregularities was assessed using the Chi-Square test .The results showed a significant reduction in oligomenorrhea and amenorrhea, indicating a notable improvement in menstrual cyclicity.

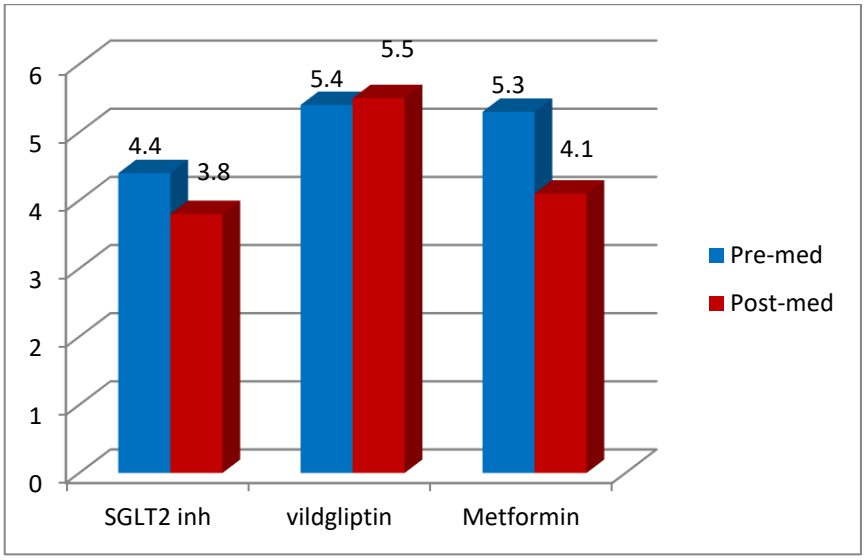

Fig 2 showed the pre medication and post medication effect on free testosterone level

The effects of Vildagliptin were evaluated in Group 2 showed significant reductions in BMI and HbA1c levels following treatment. However, the reduction in LDL levels was not statistically significant.

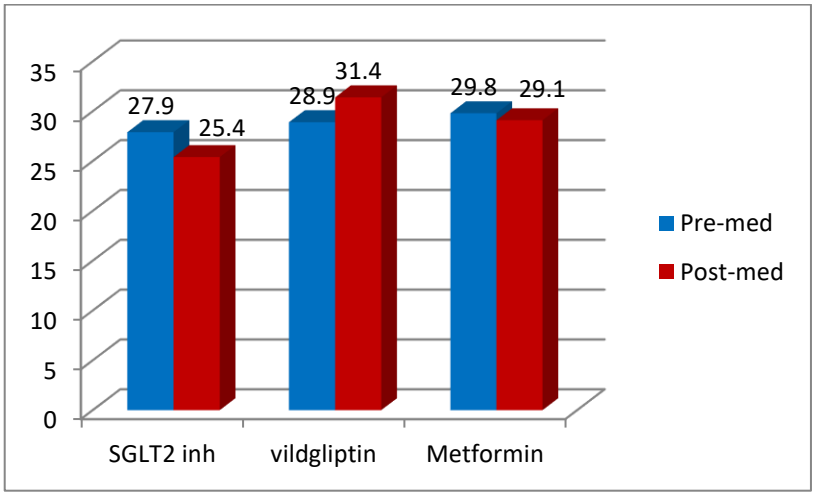

Fig 3 showed the pre medication and post medication effect on fasting insulin level

Notably, Vildagliptin treatment was associated with increases in Ferriman-Gallwey score, free testosterone levels, DHEA levels and fasting insulin levels, although these changes did not reach statistical significance in the context of the study's objectives.

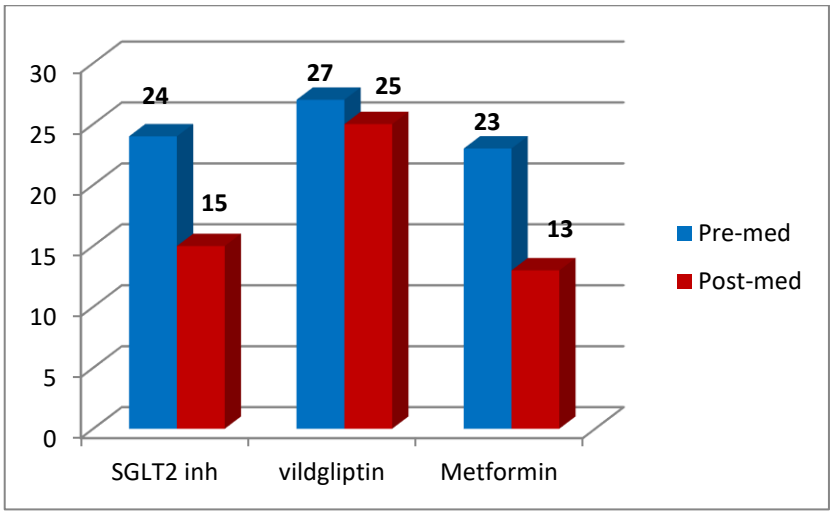

Fig 4 showed the pre medication and post medication effect on patients with menstrual irregularities

The effect of Vildagliptin on the menstrual irregularities in group 2, Chi Square test shows no significant change of the rate of oligomenorrhea and amenorrhea i.e. no significant regaining of menstrual cyclicity.

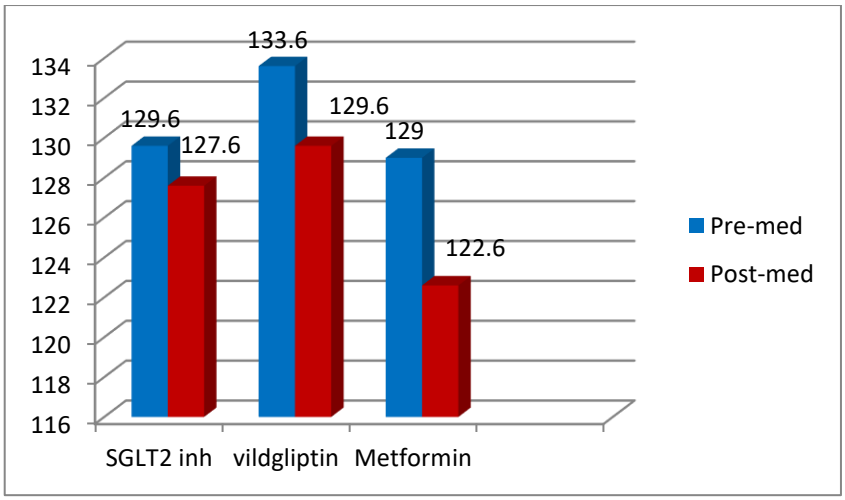

Fig 5 showed the pre medication and post medication effect on lipid profile

Assessment of the effect of the drug Metformin on the study variables in group 3 using paired T test shows significant reduction of BMI, Ferriman-Gallwey score, free testosterone level and HbA1C level.

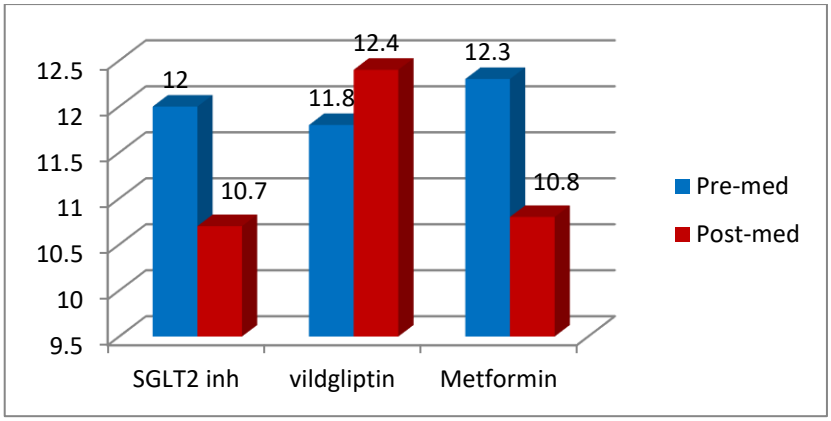

Fig 6 showed the pre medication and post medication effect on Ferriman-Gallwey (F-G) score

But no significant reduction of DHEA level, fasting insulin level. Also there is non-significant elevation of LDL level. The effect of Metformin on the menstrual irregularities in group 3, Chi Square test shows significant reduction of oligomenorrhea and amenorrhea i.e. significant regaining of menstrual cyclicity.

DISCUSSION

Polycystic ovary syndrome (PCOS) is a complex and multifaceted endocrine disorder affecting women of reproductive age. Characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries, PCOS is a leading cause of infertility and menstrual irregularities[12-14]. Beyond its reproductive implications, PCOS is also associated with metabolic complications, including insulin resistance, obesity, and an increased risk of developing type 2 diabetes and cardiovascular disease[14,15]. The heterogeneity of PCOS symptoms and underlying pathophysiology presents a challenge for diagnosis and treatment, underscoring the need for a comprehensive and individualized approach to managing this condition.

The management of polycystic ovary syndrome (PCOS) involves a multifaceted approach, incorporating various pharmacological agents to address the complex pathophysiology of the disorder[16]. Metformin, a well-established treatment for PCOS, has been shown to improve insulin sensitivity, reduce androgen levels, and regulate menstrual cyclicity. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, a newer class of antidiabetic agents, have demonstrated promising results in PCOS management[17-19]. By promoting glucose excretion and improving insulin sensitivity, SGLT2 inhibitors have been shown to reduce body mass index (BMI), improve hormonal profiles, and regulate menstrual cyclicity. Additionally, SGLT2 inhibitors have cardioprotective effects, including reductions in low-density lipoprotein (LDL) ,total cholesterol, which may be beneficial for women with PCOS who are at increased risk of cardiovascular disease[20].

In addition to these metabolic benefits, SGLT2 inhibitors also demonstrated cardioprotective effects, significant improvement in menstrual cyclicity, with a notable reduction in oligomenorrhea and amenorrhea[21]. These findings suggest that SGLT2 inhibitors may be an effective therapeutic option for managing hypercholesteremia, PCOS, particularly in women with insulin resistance and menstrual irregularities.

The cardioprotective effects of SGLT2 inhibitors, as evidenced by significant reductions in LDL levels may provide additional benefits for women with PCOS who are at increased risk of cardiovascular disease. Overall, the findings of this study suggest that SGLT2 inhibitors may be a valuable treatment option for PCOS, offering a unique combination of metabolic and cardiovascular benefits.

Vildagliptin enhances glucose-dependent insulin secretion, suppresses glucagon release and improves glycemic control. It has been shown to be effective in reducing HbA1c levels and improving glucose tolerance. In contrast, Vildagliptin treatment resulted in significant reductions in BMI and HbA1c levels but had limited effects on hormonal parameters and menstrual irregularities[22]. The lack of significant improvement in insulin sensitivity with Vildagliptin may

be attributed to its mechanism of action, which primarily involves increasing insulin release rather than improving insulin sensitivity.

This study evaluated the efficacy of various oral hypoglycemic medications, including newer agents, in managing polycystic ovary syndrome (PCOS) as alternatives to Metformin. The results showed that SGLT2 inhibitors demonstrated significant improvements in several key parameters, including body mass index (BMI), Ferriman-Gallwey score, free testosterone levels, dehydroepiandrosterone (DHEA) levels, fasting insulin levels and glycosylated hemoglobin (HbA1c) levels. Notably, SGLT2 inhibitors also showed a significant reduction in cholesterol and low-density lipoprotein (LDL) levels, which is consistent with their known cardioprotective effects.

CONCLUSION

In conclusion, this study demonstrated the efficacy of SGLT2 inhibitors, Vildagliptin, and Metformin in women with polycystic ovary syndrome (PCOS). SGLT2 inhibitors showed significant cardioprotective effects and improvements in lipid profiles, BMI, hormonal profiles, and menstrual cyclicity, while Vildagliptin demonstrated significant reductions in BMI and HbA1c levels but had limited effects on hormonal parameters and menstrual irregularities. Metformin treatment resulted in significant improvements in BMI, hormonal profiles, and menstrual cyclicity. These findings suggest that SGLT2 inhibitors and Metformin may be effective therapeutic options for managing PCOS, particularly in women with insulin resistance and menstrual irregularities. However, further studies are needed to confirm these results and determine the long-term efficacy and safety of these treatments.

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