

## Comparing The Effects of Metformin vs. Sodium-Glucose Co-transporter-2 Inhibitor

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Submitted: 15-15-2023

Accepted: 25-12-2023

### ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder characterized by metabolic disturbances, including insulin resistance and obesity, combined with cardiovascular complications such as hypertension affecting many women worldwide. An analysis of information from randomized controlled trials and systematic reviews was used to assess whether insulin sensitizer drugs such as Metformin and SGLT2 inhibitors can treat PCOS metabolic (insulin resistance, obesity) and cardiovascular (HTN) dysfunction. Insulin resistance, body weight, lipid profile, blood pressure, and glucose levels were key parameters investigated in PCOS patients. The analysis revealed that Metformin and SGLT-2 inhibitors significantly improve insulin resistance and reduce obesity in women with PCOS. SGLT-2 inhibitors indicated significant cardiovascular benefits in diabetic patients, demonstrating promise in addressing PCOS's cardiovascular aspects compared to Metformin. These medications positively affected glucose metabolism, weight management, lipid profile levels, and blood pressure regulation. Overall, there is insufficient data to assess the difference in PCOS women's metabolic or cardiovascular parameters. This review also highlights that further research should aim to refine treatment protocols of both medications and individualized therapeutic needs in women with PCOS. This will improve the understanding of the efficacy of Metformin and SGLT-2 inhibitors in women with PCOS.

### I. INTRODUCTION

Research Question: How insulin sensitizer drugs such as Metformin and SGLT2 inhibitors can be used to treat PCOS metabolic (insulin resistance, obesity) and cardiovascular (HTN) dysfunction?

### Pathophysiology of PCOS

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS is a heterogeneous disorder characterized by hyperandrogenism and chronic anovulation (Witchel et al., 2019). The underlying pathophysiology of PCOS is still unclear; however, specific genetic traits, deficient maturation of ovarian follicles, insulin resistance, and changing gonadotropin secretions are the most predominant etiological factors (Marinkovic-Radosevic et al., 2021).

The diagnosis of PCOS is a diagnosis of exclusion and is characterized by having two or more symptoms, including irregular menstrual periods, polycystic ovaries, and hyperandrogenism. Symptoms of PCOS typically arise during the early pubertal years. Morbidities associated with PCOS include obesity, impaired glucose tolerance, metabolic syndrome, infertility, type 2 diabetes mellitus, depression, and increased risk of cardiovascular disease. About two-thirds of females with PCOS have insulin resistance and a high prevalence of obesity, which correlates with hyperandrogenemia and metabolic disorders (Rasquin Leon LI et al., 2022). Therefore, the goal for treating PCOS includes decreasing hyperandrogenemia, managing menstrual dysfunction, preventing endometrial dysplasia, increasing fertility, and regulating metabolic factors (Rasquin Leon LI et al., 2022).

Metabolic and cardiovascular complications are related to this condition. The main treatment includes lifestyle intervention and drugs such as metformin, thiazolidinediones, and oral contraceptive pills. These measures do not successfully address the long-term metabolic consequences in PCOS patients. Therefore, sodium-glucose co-transporter-2 (SGLT-2) inhibitors such as empagliflozin, which are a new class of antidiabetic medications, could be a new

treatment option for PCOS patients due to beneficial glycemic and cardiovascular effects, as well as on weight, BMI, waist and hip circumference, and total body fat (Marinkovic-Radosevic et al., 2021). This literature review focuses on comparing the safety and efficacy of metformin and SGLT-2 inhibitors in PCOS patients, their beneficial effects on blood glucose and the cardiovascular system, which are often a problem in women affected by PCOS, and how they improve comorbidities such as hypertension, insulin resistance, and obesity.

### Metformin

Metformin is a biguanide insulin sensitizer that can improve insulin action. It is often used as a first-line treatment for type 2 diabetes mellitus. The mechanism of action of metformin involves the inhibition of hepatic gluconeogenesis, increased glucose uptake, and increased insulin sensitivity in the peripheral tissues (Abdalla et al., 2020). The common side effects associated with this medication are nausea, vomiting, diarrhea, and abdominal bloating. Metformin has been used since 1994 as an insulin sensitizer for patients with PCOS. Studies have found that metformin can improve endocrine disorders, regulate ovarian function, and reduce the weight of overweight patients with PCOS (Guan et al., 2020).

A study comparing metformin and lifestyle modifications in patients with PCOS found a significant BMI reduction in both groups. However, androgen level reduction was only observed in the metformin group (Abdalla et al., 2020). This drug has limited effects on improving glucose metabolism and total cholesterol and provides no cardiovascular benefits to PCOS patients. Long-term use of metformin may result in the development of vitamin B12 deficiency. A contraindication to taking metformin includes severe renal dysfunction, which requires the patient's renal function to be assessed periodically (Corcoran C, Jacobs TF, 2022). Intolerance, contraindications, and associated adverse events should be considered before prescribing metformin to patients with PCOS.

### SGLT-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, which include bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, are a class of antidiabetic drugs typically used in the

management of type 2 diabetes mellitus. In this literature review, we will focus on empagliflozin and dapagliflozin. The mechanism of action of SGLT-2 inhibitors is to inhibit glucose and sodium reabsorption and to promote glucose urine excretion in the proximal convoluted tubule (Lee et al., 2020). It may also increase insulin sensitivity, increase muscle glucose reuptake, decrease hepatic gluconeogenesis, and improve insulin release from pancreatic beta-cells (Marinkovic-Radosevic et al., 2021). The mechanism of action of SGLT-2 inhibitors is solely glucose-dependent and insulin-independent, reducing the risk of hypoglycemia.

In a 12-week randomized open-label study of empagliflozin versus metformin in obese women with PCOS, treatment with empagliflozin demonstrated significant improvement in anthropometric parameters and body composition. Still, no changes were observed in the metabolic parameters (Javed et al., 2019). These mechanisms may help patients with PCOS and improve metabolic concerns. In addition to the metabolic benefits in PCOS patients, there are cardioprotective and renal benefits of SGLT-2 inhibitors (Marinkovic-Radosevic et al., 2021). This is important when treating patients with PCOS with increased cardiovascular disease risk. Common adverse drug events associated with SGLT-2 inhibitors are genital infections, urinary tract infections, vulvovaginal candidiasis, and vulvovaginitis (Mosley et al., 2015).

### Compare and contrast between Metformin and SGLT-2 inhibitors

One research study investigated how pharmacological options helped manage endothelial microparticles (EMP) levels in women with PCOS. The study was a 12-week randomized trial that followed 39 overweight/obese women who received empagliflozin or metformin. The study's results indicated that metformin and SGLT-2 inhibitors (e.g., empagliflozin and dapagliflozin) enhance endothelial function and lower the risk of cardiovascular disease in women with PCOS. Still, the two medications had no significant difference (Zeeshan Javed et al., 2020). Metformin and SGLT-2 inhibitors are not recommended during pregnancy and breastfeeding. Metformin is not recommended for pregnant women since it can readily cross the placenta from mother to fetus, raising concern for its potential effects on the developing fetus (Hyer et al., 2018). One example of

these adverse effects is the infant becoming large for their gestational age. However, some studies have shown that pregnant women with PCOS who take metformin lower the risk of adverse effects and obesity in their children compared to the women who do not take the medication (Fornes et al., 2022). In addition, it has been shown that metformin helps induce ovulation and reduce miscarriages and was found to cause no increase in birth defects in individuals with PCOS (Hyer, Jyoti, Shehata, 2018). Yet, the same cannot be said for SGLT-2 inhibitors as they are considered category C medication. This is due to the adverse effects SGLT-2 inhibitors have on renal development and maturation, which has been noted in animal studies (Mosley et al., 2015).

## II. METHODS

### Overview:

This systematic review addresses the efficacy of how metformin and SGLT2 inhibitors act on metabolic and cardiovascular markers in women diagnosed with PCOS when compared to one another. We included randomized controlled trials of 39 overweight women diagnosed with PCOS being placed on metformin or an SGLT2-i for 12 weeks. The research was reported according to PRISMA recommendations (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). When required by the Institutional Review Board (IRB), written informed consent was received from every participant. A randomized open-label parallel study was performed to minimize subjective bias in the design.

### Identification and retrieval of primary studies:

We searched PubMed, Clinicaltrials.gov, NIH, and AHA journals and text words: "Metformin in PCOS," "SGLT2-inhibitors in PCOS", "PCOS treatment," "SGLT2-I vs. Metformin in PCOS," "Metabolic effects of metformin in PCOS," "Metabolic effects of SGLT-2 inhibitors in PCOS". Databases were searched within a ten-year window (2013-2023). Our literature search included women with PCOS treating metabolic and cardiovascular symptoms with either Metformin or SGLT2 inhibitors. It was limited to peer-reviewed English-language articles available in full PDF text.

### Study selection, study quality, and data extraction:

We determine whether a study met the inclusion and exclusion criteria, collect information to assess the methodological validity of each study included, and extract data from the included studies using the structure and standardized data extraction forms. Information extracted included a description of the study, such as the authors, country, year of publication, article publisher, setting, diagnostic criteria for PCOS, inclusion and exclusion criteria, length of trial, primary and secondary outcomes, sample size, and study participant dropout rate. It includes the description of participants, such as mean age, BMI, ethnicity, age at PCOS diagnosis, and comorbidities. It includes the intervention, such as lifestyle modification type and duration, metformin dose and duration, and SGLT-2 inhibitors. The study results are according to the outcomes outlined above.

### Exclusion Criteria:

To obtain information about the efficacy of how metformin and SGLT2 inhibitors act on metabolic and cardiovascular markers in women diagnosed with PCOS when compared to one another. We did not include clinical trials, reviews, cohort studies, and case-control studies that were duplicate publications, involved animal samples, or involved patients with non-classical 21-hydroxylase deficiency, hyperprolactinemia, Cushing's disease, androgen-secreting tumors, chronic adrenal insufficiency, anemia, or previous bariatric surgeries. We also didn't include subjects with a confirmed diagnosis of diabetes or pre-diabetes, ongoing, inadequately controlled thyroid disorder, history or presence of malignant neoplasms within the last five years (except basal and squamous cell skin cancer and in-situ carcinoma) and acute or chronic pancreatitis, who are on any of the following medications within three months of recruitment: Metformin or other insulin-sensitizing medications (e.g., pioglitazone), Hormonal contraceptives (e.g., birth control pills, hormone-releasing implants, etc.), Anti-androgens (e.g., spironolactone, flutamide, finasteride, etc.), Clomiphene citrate or estrogen modulators such as letrozole, GnRH modulators such as leuprolide, Minoxidil. To avoid any disorder which, in the investigator's opinion, might jeopardize the subject's safety, we decided to avoid studies that may include pregnant females, breastfeeding or

intending to become pregnant (including IVF or ICSI) or of childbearing potential, not using adequate contraceptive methods, severe hepatic impairment (ALT >3 times ULN), women with a history of recurrent urinary tract infections, hematocrit above the upper limit of the normal range, involved in another medicinal trial (CTIMP) within the past four weeks and any known hypersensitivity to the Investigational Medicinal Products or any of their excipients.

#### **Inclusion Criteria:**

We sought reports of controlled trials, cohort studies, and case-control studies that provided data on the efficacy of how metformin and SGLT2 inhibitors act on metabolic and cardiovascular markers in women diagnosed with PCOS when compared to one another. We included only randomized control studies that enrolled women aged 18-45 years (inclusive) with a confirmed diagnosis of PCOS based on Rotterdam criteria, presence of both irregular periods and biochemical hyperandrogenemia, polycystic ovary by ultrasonography, metformin or an SGLT2-I being the main intervention in the study group, body mass index (BMI)  $\geq 25$ , the study reporting at least one metabolic parameter, and confirmation of negative pregnancy test during screening visit and agreement to use barrier contraception during the study period.

### **III. RESULTS**

#### **Search results:**

In our electronic database search, we used the keywords (PCOS, metformin in PCOS, SGLT-2 inhibitors in PCOS, metabolic syndrome, insulin resistance, PCOS effect on endocrine markers, and PCOS effect on cardiovascular markers). We obtained 30 articles from PubMed, 100 articles from Clinicaltrials.gov, 50 from NIH, and 60 from AHA. Then, we reviewed the abstract retrieved for eligible

criteria. We excluded some articles that did not satisfy the eligibility criteria. At the end of the process, we included fifteen studies of 8 randomized controlled trials; the other was an experimental study. Seven studies compared the effects of empagliflozin versus metformin (Javed et al., 2019; Lee et al., 2020; Abdalla et al., 2020; Cignarella et al., 2020; Marinkovic-Radosevic et al., 2021; Anam et al., 2022), two studies compared canagliflozin combined with metformin versus metformin monotherapy (Cai et al., 2022; Zhang et al., 2022), and one study compared the effects of dapagliflozin versus metformin (Mosley et al., 2015), one study addressed options including Metformin and SGLT-2 inhibitors for managing the metabolic aspects of PCOS (Abdalla et al, 2020), and one study studying the effects of metformin monotherapy in women with PCOS and their BMI (Guan et al., 2020). Overall, the studies showed a small to no difference in the effect of metabolic and cardiovascular markers in women with PCOS when comparing Metformin and SGLT-2 inhibitors.

#### **Qualitative Synthesis:**

We summarized the clinical and methodological characteristics of the included studies, such as the number and characteristics of study participants, including factors that may impact the generalizability of results to real-world settings (e.g., comorbidities in studies of older patients, race/ethnicity in conditions where disparities exist, or lifestyles including diet and exercise). We also included studies that contained clinical settings, interventions, primary and secondary outcome measures, and follow-up periods. We investigated the description of the overall body of evidence across the following domains: risk of bias, consistency, precision, directness, reporting bias, and strength of association.



**Table 1**  
 Studies on the effects of SGLT-2 inhibitors vs. Metformin on PCOS

Study Number	Study Description	Study design	Total number of subjects	Type of SGLT-2 inhibitors involved	Type of comorbidity	Results of Metformin monotherapy on PCOS	Results of SGLT-2 inhibitors therapy on PCOS
Abdalla et al. (2021)	A review of therapeutic options for managing the metabolic aspects of polycystic ovary syndrome	Systemic review	7029	Empagliflozin and dapagliflozin	Cardiovascular disease Obesity T2DM	reducing weight and improving lipid profiles	reduced the need for dialysis and decreased dialysis from renal causes
Azam, A. K., & Inzocch, S. F. (2022)	Newest Glucose-Lowering Medications and Potential Role in Metabolic Management of PCOS	Systemic review	n/a	Empagliflozin	Cardiovascular disease T2DM	Improve weight loss, hyperandrogenism, and reproductive health	Reduce weight, improve reproductive health, decrease risk of developing T2DM, improve CV outcomes
Cai et al. (2022)	The safety and efficacy of canagliflozin in comparison to metformin in PCOS patients with insulin resistance	RCT	33	canagliflozin	Insulin resistance	normal pattern, reduced body weight and total fat mass, and decreased triglyceride levels	Also reducing waist and abdominal circumference and waist level
Cipriello et al. (2023)	Pharmacological Approaches to Controlling Cardio-metabolic Risk in Women with PCOS	Systemic review	n/a	Empagliflozin	Cardiovascular disease Obesity	improve lipid profile as well by increasing HDL-C and reducing TG levels	reducing weight, BMI, waist and hip circumferences, and total body fat
Ferzan et al. (2022)	The association between polycystic ovary syndrome with or without metformin and the pregnancy	RCT	405,947	n/a	Pregnant Diabetes	Reduce rates of pre-eclampsia, macrosomia and large for gestational age	n/a
Giam et al. (2022)	The Effect of Metformin on Polycystic Ovary Syndrome in Overweight Women	Systemic review	n/a	n/a	Obesity	improved endocrine and metabolic indicators, including testosterone, follicle-stimulating hormone, luteinizing hormone, and low-density lipoprotein cholesterol	n/a
Hyerr et al. (2018)	Metformin in Pregnancy	RCT	400	n/a	Pregnancy T2DM Obesity	reducing GDM, gestational hypertension, proteinuria	n/a
Javed et al. (2019)	Effects of empagliflozin on metabolic parameters in PCOS patients	RCT	39	Empagliflozin	Obesity Cardiovascular disease	Some improvement in anthropometric parameters and body composition	Significant improvement in body proportions and composition in overweight women in 12 weeks
Liu et al. (2020)	SGLT2 Inhibitor Cardiovascular Outcomes	Systemic review	n/a	Canagliflozin, dapagliflozin, and empagliflozin	cardiovascular disease (including coronary artery disease and heart failure), liver disease, renal impairment, obesity, and hypertension	n/a	Dual therapy with metformin was superior in improving endothelial function and arterial stiffness. Monotherapy showed no effect on reactive hyperemia index
Martinez-Rodriguez, J et al. (2021)	Evaluating new treatment options for PCOS: review on SGLT-2 inhibitor	Systematic review	n/a	Empagliflozin	Insulin resistance	n/a	Further research needs to be done to assess the efficacy of SGLT-2 inhibitors for PCOS as of now the metformin option is likely more efficacious, mechanism and oral administration
Mosley, J et al. (2019)	SGLT-2 inhibitors in the management of T2DM	Systematic review	n/a	Canagliflozin, dapagliflozin, empagliflozin	T2DM	n/a	Article discusses the background, MHA and benefits of SGLT-2 inhibitors. This background information gives better insight in how SGLT-2 inhibitors could potentially work on women with PCOS
Raupach et al. (2022)	Overview on PCOS	Systematic review	n/a	Not specific to name	Insulin resistance, weight loss, cardiovascular effects, fat mass reduction, hormonal and metabolic	Improve menstrual cycles, abnormal waist to hip ratio, and vascular markers in non-obese women with PCOS. Can help treat hyperandrogenism mildly	SGLT-2 inhibitors work in increasing urinary glucose excretion, improve weight loss and cardiovascular risk with T2DM patients. There's less data supporting that these effects would be the same in obese patients
Winkel, S. (2019)	Pathophysiology, Presentation, and Treatment of Adipose Gain with PCOS	Systemic review	n/a	n/a	Overweight, obesity, impaired glucose tolerance and T2DM, depression, anxiety, eating disorders and disordered eating, and altered body image	improvement of BMI, beneficial effects on hemostasis, triglycerides, and high-density lipoprotein cholesterol	n/a
Zhou, J. (2020)	Effects of empagliflozin vs metformin on endothelial microparticles in overweight/obese women with PCOS	RCT	38	empagliflozin	Overweight, obesity, CV disease	VCAM-1 EMPs (P = 0.001) increased significantly after 12 weeks of treatment, whereas all other EMPs remained unchanged	ICAM-1 (P = 0.004), E-selectin (P = 0.016) and VCAM-1 (P = 0.001) EMPs increased significantly following 12 weeks of treatment, but no change were seen in PECAM-1 (P = 0.93) or EMPs (P = 0.15) EMPs
Zhang, J (2022)	Canagliflozin combined with metformin versus metformin monotherapy for endocrine and metabolic profiles women with PCOS	RCT	36	Canagliflozin	T2DM, thyroid dysfunction, hypercalcaemia, endocrine-secreting tumours, congenital adrenal hyperplasia, and Cushing syndrome	weight reduction, decreased serum testosterone levels, lipid metabolism disorder amelioration, and endothelial function improvement	reduce fat mass, and blood pressure, ameliorate glucose homeostasis, alleviate oxidative damage and inflammation, and protect the cardiovascular system

Note. The above table simplifies the clinical studies where SGLT2 inhibitors and/or Metformin were used as therapy in patients with PCOS and studies that explain in depth the significance of

PCOS, SGLT-2 inhibitors, and Metformin. The table includes the authors, the year the study was published, and a quick description of each study. In addition, the study design (RCT or systematic review) and the total number of subjects from each study were included. The table further helps distinguish the different types of SGLT-2 inhibitors involved in each study and the results, if applicable. SGLT-2 inhibitors, Sodium-glucose Cotransporter-2; T2DM, Type 2 Diabetes Mellitus; CV, Cardiovascular; PCOS, Polycystic Ovarian Syndrome; RCT, Randomized Controlled Trial; HDL-C, High-density Lipoprotein Cholesterol; TG, Triglycerides; GDM, Gestational Diabetes Mellitus; MOA, Mechanism of Action; BMI, Body Mass Index; VCAM-1, Vascular Cell Adhesion Molecule-1; ICAM-1, Intracellular Adhesion Molecule 1; EMPs, Endothelial

Microparticles; PECAM-1, platelet Endothelial Cell Adhesion Molecule-1.

#### IV. DISCUSSION

In this review, we evaluated whether insulin sensitizer drugs such as Metformin and SGLT2 inhibitors can treat PCOS metabolic (insulin resistance, obesity) and cardiovascular (HTN) dysfunction. Fifteen studies, including randomized controlled trials and systematic reviews, were reviewed in this paper. Between the two insulin sensitizer drugs studied, Metformin and SGLT2 inhibitors, the comparisons showed no difference in the metabolic or cardiovascular parameters, suggesting a similar pattern of changes in both treatment methods.

Metformin, a widely used medication, has effectively improved insulin resistance and reduced obesity in women with PCOS (Guan et al., 2020; Abdalla et al., 2020). It has been shown to positively impact metabolic parameters, such as glucose metabolism and lipid profiles (Abdalla et al., 2020).

Additionally, metformin is considered safe to use in some pregnancies and reduces certain risks of pregnancy complications (Fornes et al., 2022; Hyer et al., 2018), which is a crucial consideration for women of childbearing age with PCOS. However, metformin may not provide significant cardiovascular benefits.

SGLT2 inhibitors, on the other hand, like canagliflozin and empagliflozin, have shown promising results in improving metabolic parameters, like improving insulin sensitivity and reducing fasting glucose levels in women with PCOS (Javed et al., 2019; Zhang et al., 2022). These medications reduce insulin resistance, promote weight loss, and improve cardiovascular risk factors like HTN. SGLT2 inhibitors also have indicated significant cardiovascular benefits in diabetic patients (Lee et al., 2020), which may be advantageous for women with PCOS who usually have an increased risk of cardiovascular complications. It is important to consider patient risk factors, like metabolic and cardiovascular history, potential side effects, and their preference when choosing between metformin and SGLT2 inhibitors.

The long-term cardiovascular and metabolic risk following SGLT2 inhibitors and metformin remains to be determined in PCOS. However, studies using these drugs support cardioprotective effects in patients without PCOS. Many of these trials were short in duration, lasting approximately 12 weeks; treatments over a longer duration may be needed to determine the long-term effectiveness of metformin and SGLT2 inhibitors.

## V. CONCLUSION

In conclusion, the use of Metformin and SGLT2 inhibitors in managing metabolic and cardiovascular aspects of PCOS in women has been the subject of several studies. Much research and discussion have been conducted on these treatment options for the PCOS community, including lifestyle modifications (diet and exercise) and medical and surgical treatment.

Overall, both metformin and SGLT2 inhibitors have their benefits in managing PCOS. Metformin might be preferred in some cases due to its safety during pregnancy and its longer history of use in these studies. At the same time, SGLT2 inhibitors offer potential cardiovascular and weight loss benefits. They might be more beneficial for overweight patients, but they are relatively newer and

require more research for PCOS-specific outcomes. Ultimately, the choice between Metformin and SGLT2 inhibitors should be based on the patient's needs, risk factors, and response to treatment. Further long-term research is required to improve our understanding of the effectiveness of metformin and SGLT2 inhibitors as treatments for women diagnosed with PCOS.

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