ABSTRACT

Introduction Polycystic ovary syndrome (PCOS) is a heterogeneous reproductive endocrine disorder. Several ongoing trials test sodium-glucose cotransporter-2 (SGLT-2) inhibitors for women with PCOS. However, their effectiveness has not been fully elucidated owing to the lack of high-confidence evidence. Our group agrees with the statement that SGLT-2 inhibition could treat PCOS as it is supported by reports demonstrating the benefits of SGLT-2 inhibition on metabolic status and weight control. Moreover, the functions of chronic inflammation amelioration and cardiovascular system protection make it a more attractive candidate for PCOS therapy. Therefore, to provide physicians with a reference, we intend to perform a meta-analysis on the efficacy and safety of SGLT-2 inhibitors on the endocrine and metabolic profiles of patients with PCOS.

Methods and analysis We will search for randomised controlled trials performed until September 2022 using PubMed, Web of Science, EMBASE, the Cochrane Library, Google Scholar, the PhRMA Clinical Study Results Database (www.clinicaltrials.gov), the China National Knowledge Infrastructure, the Wanfang, the Weipu and the China biomedical literature databases. The outcomes will include androgen-associated outcomes, body fat, glucose and lipid homeostasis, inflammatory outcomes and adverse events. In addition, two investigators will independently assess methodological quality using the revised Cochrane risk-of-bias tool 2. The analysis will be performed using RevMan V.5.3 software, and subgroup and sensitivity analyses and a meta-regression will be used to determine the heterogeneity source.

Ethics and dissemination Ethical approval is not required because this is a meta-analysis. We will disseminate these results by publishing them in a peer-reviewed journal.

PROSPERO registration number CRD42021281176.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous reproductive endocrine disorder associated with oligomenorrhea or amenorrhea, hyperandrogenaemia and polycystic ovaries, according to the Rotterdam criteria.\(^1\)\(^2\) Approximately 30%–60% of patients with PCOS are overweight or obese, and 95% of them have insulin resistance (IR).\(^3\)\(^4\) PCOS typically has an early onset.\(^5\) Therefore, metabolic abnormalities associated with PCOS, such as IR, are often linked to impaired glucose metabolism, diabetes mellitus, aberrant adipokine production of adipose tissue,\(^6\)\(^7\) low-grade systematic inflammation and cardiovascular diseases.\(^8\) These comorbidities could have long-lasting effects on the health of patients with PCOS.\(^9\) Therefore, improving weight control, IR and long-term comorbidities, such as chronic inflammation and cardiovascular events, could be the key to managing PCOS.

Our research team found that time-restricted feeding may help reduce body fat and improve IR in patients with PCOS.\(^9\) A recent meta-analysis has also confirmed that diets are advantageous for weight loss and improved IR.\(^10\) However, managing patients
with PCOS is challenging because it may be impossible to monitor their behaviour and provide standardised diets continuously.

Alleviating IR is an appealing target for PCOS treatment, and several insulin-sensitisers have been developed to control PCOS. Metformin is the most common oral insulin sensitiser for patients with PCOS, which reduces hyperinsulinaemia and hyperandrogenaemia. Metformin promotes weight loss in overweight and obese patients. However, metformin monotherapy requires at least 1000 mg/day for 25.5 weeks to produce curative effects for PCOS and is likely accompanied by side effects, such as gastrointestinal issues. Glucagon-like peptide-1 receptor agonists (GLP1-RAs) reduce body mass index (BMI) and improve IR in women with PCOS. Patients tend to prefer orally administrated drugs rather than injection drugs, which are invasive and may involve potential pain and infection at the injection site.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are relatively novel glucose-lowering medications that have been extensively investigated and gradually introduced into clinical practice. They potentially reduce plasma glucose levels by blocking glucose reabsorption in the renal proximal tubule of patients with diabetes. SGLT-2 inhibition has also shown positive effects on reducing body weight, blood pressure, cardiovascular and renal complications, attenuating beta-cells exhaustion and relieving oxidative damage and inflammation.

Currently, several reports have investigated the use of SGLT-2 inhibitors for PCOS, such as empagliflozin, licogliflozin and dapagliflozin. In PCOS mouse models displaying hyperandrogenism, empagliflozin was found to be beneficial in reducing blood pressure and the amount of fat. Tan et al found that 50 mg of licogliflozin three times per day for 2 weeks improved hyperinsulinaemia and hyperandrogenaemia compared with a placebo in obese patients with PCOS. Moreover, a randomised, single-blinded, comparative 24-week study of patients with PCOS found that 10 mg of dapagliflozin (DAPA) daily, 10 mg of DAPA daily with 2 mg of exenatide weekly, or 10 mg of DAPA daily with 2000 mg of metformin daily significantly reduced patients’ weight and waistline.

The underlying mechanisms of SGLT-2 inhibition in PCOS have not been fully clarified. Marinkovic-Radosavic et al suggested that SGLT-2 inhibitors indirectly improved the metabolic status (eg, glucose and lipid homeostasis) in patients with PCOS by inhibiting glucose and sodium reabsorption in the proximal tubule of the kidney and by reducing the liver fat and visceral adipose tissue. In another study, it is suggested that empagliflozin could reduce blood pressure in PCOS rats via amelioration of the androgen-induced increase in intrarenal ACE expression and activity. Li et al reported that the antioxidative effect of SGLT-2 inhibition might be partially mediated by sodium-hydrogen exchanger 1 and nicotinamide adenine dinucleotide phosphate oxidase inhibition, since chronic low-grade inflammation accompanies PCOS. SGLT-2 inhibition can reduce the occurrence of cardiovascular events, and its use has been expanded to patients with diabetes and chronic kidney diseases. Therefore, it is promising that inhibiting SGLT-2 may also manage the long-term health consequences of PCOS.

The effectiveness of SGLT-2 inhibitors for PCOS has not been fully elucidated owing to the lack of high-confidence evidence. Several clinical trials are underway. We agree with the statement that SGLT-2 inhibition could be a potential PCOS treatment option, supported by the reports demonstrating its improvements in metabolic status and weight control. Moreover, the functions of chronic inflammation amelioration and cardiovascular system protection make it a more attractive therapy candidate. Hence, we have designed this meta-analysis to review and estimate the efficacy and safety of SGLT-2 inhibitors on the endocrine and metabolic profiles of patients with PCOS to provide a reference for physicians.

MATERIALS AND METHODS

Protocol

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines, this protocol will be conducted. The PRISMA-P checklist has been included in online supplemental table S1.

Inclusion criteria

1. Study type: Randomised controlled trials, regardless of the blinding method. No language restrictions will be applied.
2. Participants: Overweight or obese (BMI ≥24 kg/m2) individuals with PCOS aged 18–45 years old with no limits regarding ethnicity and duration. PCOS will be defined based on the 2003 Rotterdam criteria, the 1990 National Institutes of Health in 1990 criteria or the 2009 Androgen Excess Society criteria.
3. Interventions: Four interventions and comparison types will be considered:
   A. SGLT-2 inhibition versus lifestyle modification.
   B. SGLT-2 inhibition versus other pharmaceutical therapy.
   C. SGLT-2 inhibition plus lifestyle modification versus lifestyle modification.
   D. SGLT-2 inhibition plus other pharmaceutical therapy versus other pharmaceutical therapy.

We refer to ‘lifestyle modifications’ as dietary patterns, exercise and behavioural therapy, while ‘other pharmaceutical therapies’ are metformin, thiazolidinedione, orlistat and GLP1-RAs. The duration and forms of lifestyle modifications in intervention type (A) should be identical to those in type (C). Similarly, the pharmaceutical intervention categories and dosages should be consistent between intervention types (B) and (D).

Furthermore, the participants in intervention types (A) and (C) should be free of other medical interventions (except SGLT-2 inhibition) throughout the experimental
period in the intervention and control arms. Also, lifestyle modifications should not be allowed in intervention types (B) or (D). Participants receiving concurrent lifestyle modifications and pharmaceutical therapy in either arm will be excluded. We will control for potential confounders to ensure the entire study is eligible for any two comparisons.

4. Target outcomes: The outcomes will be divided into five groups:
   A. Androgen-associated outcomes: total testosterone, the free androgen index, androstenedione, sex hormone-binding globulin and dehydroepiandrosterone sulfate.
   B. Body fat outcomes, BMI and the waist-to-hip ratio.
   C. Glucose and lipid homoeostasis outcomes: the fasting insulin level and fasting blood glucose levels, the homoeostatic model assessment of insulin resistance, triglyceride, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol.
   D. Inflammatory outcomes: C reactive protein, high-sensitivity C reactive protein and macrophage chemotactrant protein-1.
   E. Adverse events.

Exclusion criteria
1. Target population: Women who give birth during the study period or those with severe comorbidities.
2. Duplicated studies.
3. Outcomes that include missing data or studies without target outcomes.

Search strategy
We will search PubMed, Web of Science, EMBASE, the Cochrane Library, the PhRMA Clinical Study Results Database (www.clinicaltrials.gov), Google Scholar, the China National Knowledge Infrastructure, the Wanfang, the Weipu and Chinese biomedical literature databases for trials up to and including September 2022. The search strategy will contain medical subject headings and words for SGLT-2 inhibitors and PCOS; an experienced medical librarian (QZW) will assist in the selection. The detailed search strategy for use in MEDLINE via PubMed is listed in online supplemental table S2, but a modified search strategy will be applied to other electronic databases.

Data collection and analysis

Studies selection
The search results will be initially imported into EndNote V.9, and duplicates will be discarded. Two investigators (JZ and CX) will independently screen and cross-check the records by first examining the titles and abstracts. Studies not meeting the inclusion criteria will be excluded. Next, two researchers will independently perform a full-text scan to verify whether the studies meet the inclusion criteria. A clinical epidemiologist (ZQL) will arbitrate regarding any differences in opinions.

Data extraction
Two reviewers (JZ and CX) will independently extract the data using a standardised data extraction form. Descriptive information will be collected for each study, including the authors, country, publication year, age of enrolled participants, PCOS diagnostic criteria, BMI, interventions and controls (including type and dosage), experimental duration, and primary and secondary outcome efficiency. If a consensus is not reached during the initial meetings, a clinical epidemiologist (ZQL) will arbitrate.

Risk of bias assessment
Two investigators (JZ and CX) will independently assess methodological quality using the revised Cochrane risk-of-bias tool. This tool includes the following domains: ‘randomisation process,’ ‘deviations from intended interventions,’ ‘missing outcome data,’ ‘measurement of the outcome’ and ‘selective reporting of results.’ Each item will be classified as ‘high bias risk,’ ‘low bias risk,’ or ‘some concerns.’ Disagreements, should they arise, will be resolved by a clinical epidemiologist (ZQL).

Statistical analysis

Data synthesis
The analysis will be performed using RevMan V.5.3 software. Continuous data will be analysed using standardised mean differences to express the effect size as these parameters could eliminate the diversity dimensions. The relative risk will be used to express dichotomous data, with 95% CIs and an α error of 0.05. The random-effects method will be used to pool the data based on the Cochran-Mantel-Haenszel method if high heterogeneity is determined using the χ2 test.

Dealing with missing data
If necessary, we will contact the corresponding author for missing data, more detailed data or the full text.

Subgroup analysis, sensitivity analysis and meta-regression
A subgroup analysis will be used to assess the effects of various factors and specific analytical details to address heterogeneity. These analyses may be performed based on several factors, such as the various timings of the interventions, the different drugs used, the BMI of patients (obese or overweight) or variable diagnostic criteria.

A sensitivity analysis will also be used to dissect heterogeneity after removing articles with a high bias risk. Once the number of eligible trials exceeds ten, a meta-regression will be performed using STATA V.15.1 software to explore other aspects that may affect the final results (e.g., the study region or differential diagnostic criteria).

Publication bias and selective outcome reporting bias
If the number of included trials exceeds ten, funnel plots and an Egger’s test will be employed to determine publication bias. We will also review the initial trial registries or published protocols to detect possible selective outcome reporting bias if available. Otherwise, we will compare the methods and results in the publications.
Grading quality of evidence
The Grading of Recommendations Assessment, Development and Evaluation will be used to assess the confidence in cumulative evidence. For this tool, each outcome will be evaluated for the risk of bias, heterogeneity, indirectness, imprecision and publication biases, and the results will be categorised into four levels: high, moderate, low and very low.

Amendments
If amendments to this protocol are made, the final reports will describe the details.

Patient and public involvement
There will be no patient or public involvement in this study.

Ethics and dissemination
Ethical approval is not required as this study is a meta-analysis. We will disseminate these results by publishing them in a peer-reviewed journal.

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Contributors
JZ and CX designed the study protocol and the search strategy. JZ drafted the protocol and registered it on the PROSPERO database. CX screened and edited the literature. BH reviewed and edited the final manuscript. All the authors read and approved the final protocol.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Supplemental material
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REFERENCES
1 Glintborg D, Altinkok ML, Ravn P, et al. Adrenal activity and metabolic risk during randomized escitalopram or placebo treatment in PCOS. Endocr Connect 2018;7:479–89.
2 Cignarella A, Mioni R, Sabbadini C, et al. Pharmacological approaches to controlling cardiometabolic risk in women with PCOS. Int J Mol Sci 2020;21: doi:10.3390/ijms21249554. [Epub ahead of print: 15 Dec 2020]
3 Wang F-F, Wu Y, Zhu Y-H, et al. Pharmacologic therapy to induce weight loss in women who have obesity/overweight with polycystic ovary syndrome: a systematic review and network meta-analysis. Obes Rev 2018;19:1424–45.
4 Stepto NK, Cassar S, Joham AE, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulinaemic clamp. Hum Reprod 2013;28:777–84.
5 Bates GW, Legro RS. Longterm management of polycystic ovarian syndrome (PCOS). Mol Cell Endocrinol 2013;373:91–7.
6 Kokosar M, Benrick A, Perflyev A, et al. A single bout of electroacupuncture remodels epigenetic and transcriptional changes in adipose tissue in polycystic ovary syndrome. Sci Rep 2018;8:1878.
7 Root-Bernstein R, Podufaly A, Dillon PF. Estradiol binds to insulin and insulin receptor decreasing insulin binding in vitro. Front Endocrinol 2014;5:118.
8 Delitalia AP, Capobianco G, Delitalia G, et al. Polycystic ovary syndrome, adipose tissue and metabolic syndrome. Arch Gynecol Obstet 2017;296:405–19.
9 Li C, Xing C, Zhang J, et al. Eight-hour time-restricted feeding improves endocrine and metabolic profiles in women with anovulatory polycystic ovary syndrome. J Transl Med 2021;19:148.
10 Shang Y, Zhou H, Hu M, et al. Effect of diet on insulin resistance in polycystic ovary syndrome. J Clin Endocrinol Metab 2020;105:doi:10.1210/clinem/dgaae25S. [Epub ahead of print: 01 10 2020].
11 Zhang Q, Li S, Li L, et al. Metformin treatment and homocysteine: a systematic review and meta-analysis of randomized controlled trials. Nutrients 2016;8: doi:10.3390/nu8120798. [Epub ahead of print: 09 Dec 2016].
12 Hui F, Zhang Y, Ren T, et al. Role of metformin in overweight and obese people without diabetes: a systematic review and network meta-analysis. Eur J Clin Pharmacol 2019;75:437–50.
13 Chen X, He S, Wang D. Effects of metformin on body weight in polycystic ovary syndrome patients: model-based meta-analysis. Expert Rev Clin Pharmacol 2021;14:121–30.
14 Bargiota A, Di Iani–Kandarakis E. The effects of old, new and emerging medicines on metabolic aberrations in PCOS. Ther Adv Endocrinol Metab 2012;3:27–47.
15 Han Y, Li Y, He B, Clip–1 receptor agonists versus metformin in PCOS: a systematic review and meta-analysis. Reprod Biomed Online 2019;39:332–40.
16 Song SO, Kim KJ, Lee B-W, et al. Tolerability, effectiveness and predictive parameters for the therapeutic usefulness of exenatide in obese, Korean patients with type 2 diabetes. J Diabetes Investig 2014;5:554–62.
17 Bonora BM, Vigili de Kreutzenbergh S, Avogaro A, et al. Effects of the SGLT2 inhibitor dapagliflozin on cardiac function evaluated by impedance cardiography in patients with type 2 diabetes. secondary analysis of a randomized placebo-controlled trial. Cardiovasc Diabetol 2019;18:106.
18 Kameszki M, Kusaball T, Komaki K, et al. Comprehensive renoprotective effects of iragliflozin on early diabetic nephropathy in mice. Sci Rep 2018;8:4029.
19 Tanaka A, Shimabukuro M, Okada Y, et al. Rationale and design of an investigator-initiated, multicenter, prospective open-label, randomized trial to evaluate the effect of iragliflozin on endothelial dysfunction in type 2 diabetes and chronic kidney disease: the proceed trial. Cardiovasc Diabetol 2020;19:85.
20 Pruett JE, Torres Fernandez ED, Everman SJ, et al. Impact of SGLT-2 inhibition on cardiometabolic abnormalities in a rat model of polycystic ovary syndrome. Int J Mol Sci 2021;22: doi:10.3390/ijms22052576. [Epub ahead of print: 04 Mar 2021].
21 Miura H, Sakaguchi K, Okada Y, et al. Effects of iragliflozin on glycemic control, appetite and its related hormones: a prospective, multicenter, open-label study (SOAR-KOBE study). J Diabetes Invest 2019;10:1254–61.
22 Li X, Römer G, Kerindongo RP, et al. Sodium glucose co-transporter 2 inhibitors ameliorate endothelium barrier dysfunction induced by cyclic stretch through inhibition of reactive oxygen species. Int J Mol Sci 2021;22: doi:10.3390/ijms22116044. [Epub ahead of print: 03 Jun 2021].
23 Bays HE, Weinstein R, Law G, et al. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. Obesity 2014;22:1042–9.
24 Tan S, Ignatenko S, Wagner F, et al. Licogliflozin versus placebo in women with polycystic ovary syndrome: a randomized, double-blind, phase 2 trial. Diabetes Obes Metab 2021;23:2595-2599.
25 Elkind-Hirsch KE, Chappell N, Seidemann E, et al. Exenatide, dapagliflozin, or Phentermine/Topiramate differentially affect metabolic profiles in polycystic ovary syndrome. J Clin Endocrinol Metab 2021;106:3019-3033.

26 Javed Z, Papageorgiou M, Deshmukh H, et al. Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: a randomized controlled study. Clin Endocrinol 2019;90:805-13.

27 Javed Z, Papageorgiou M, Madden LA, et al. The effects of empagliflozin vs metformin on endothelial microparticles in overweight/obese women with polycystic ovary syndrome. Endocr Connect 2020;9:563-9.

28 Marinkovic-Radosevic J, Cigrovski Berkovic M, Kruetz E, et al. Exploring new treatment options for polycystic ovary syndrome: review of a novel antidiabetic agent SGLT2 inhibitor. World J Diabetes 2021;12:932-8.

29 Han R, Gong X, Zhu Y, et al. Relationship of PD-1 (PDCD1) and PD-L1 (CD274) single nucleotide polymorphisms with polycystic ovary syndrome. Biomed Res Int 2021;2021:9596358.

30 Li L, Zhu J, Ye F, et al. Upregulation of the IncRNA SRLR in polycystic ovary syndrome regulates cell apoptosis and IL-6 expression. Cell Biochem Funct 2020;38:880-5.

31 Sato T, Arzawa Y, Yuasa S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. Cardiovasc Diabetol 2018;17:6.