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Sodium-glucose cotransporter-2 inhibitors for improving endocrine and metabolic profiles in overweight and obese individuals with polycystic ovary syndrome: a meta-analysis protocol

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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 Chinese biomedical literature databases. The outcomes will include androgen-associated outcomes, body fat, glucose and lipid homoeostasis, 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.

Strengths and limitations of this study

► This will be the first time that meta-analysis is used to collect evidence related to the efficacy and safety of sodium-glucose cotransporter-2 inhibition supplementation on polycystic ovary syndrome.

► We carefully developed the search strategy and defined the inclusion/exclusion criteria to ensure that relevant literature will not be missed.

► Two reviewers will independently conduct the study selection, data extraction, and risk of bias analysis. If there is no consensus, a clinical epidemiologist will arbitrate.

► We will only include randomised controlled trials, but we cannot ensure that all included studies are of high quality.

► If potentially eligible studies are initially scarce, completing the analysis may be delayed.

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.[5] 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

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous reproductive endocrine disorder associated with oligomenorrhoea or amenorrhoea, hyperandrogenaemia and polycystic ovaries, according to the Rotterdam

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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.[2] Metformin is the most common oral insulin sensitiser for patients with PCOS, which reduces hyperinsulinaemia and hyperandrogenaemia.[11] Metformin promotes weight loss in overweight and obese patients.[12] 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.[13 14] Glucagon-like peptide-1 receptor agonists (GLP1-RAs) reduce body mass index (BMI) and improve IR in women with PCOS.[15] However, patients tend to prefer orally administered drugs rather than injection drugs, which are invasive and may involve potential pain and infection at the injection site.[16]

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.[17–19] 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.[20–23]

Currently, several reports have investigated the use of SGLT-2 inhibitors for PCOS, such as empagliflozin, licogliflozin and dapagliflozin.[20 24–27] In PCOS mouse models displaying hyperandrogenism, empagliflozin was found to be beneficial in reducing blood pressure and the amount of fat.[20] 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.[24] 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.[25]

The underlying mechanisms of SGLT-2 inhibition in PCOS have not been fully clarified. Marinkovic-Radosevic *et al* suggested that SGLT-2 inhibitors indirectly improved the metabolic status (eg, glucose and lipid homoeostasis) 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.[28] 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.[20] 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,[22] since chronic low-grade inflammation accompanies

PCOS.[29 30] SGLT-2 inhibition can reduce the occurrence of cardiovascular events,[31] and its use has been expanded to patients with diabetes and chronic kidney diseases.[32] 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.[21 23] Moreover, the functions of chronic inflammation amelioration and cardiovascular system protection make it a more attractive therapy candidate.[33 34] 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,[35] 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,[36] the 1990 National Institutes of Health in 1990 criteria[37] or the 2009 Androgen Excess Society criteria.[38]
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 chemoattractant 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 2.[39] 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 χ^2 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 (eg, 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.[40] 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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