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

Jiaqi Zhang, Chuan Xing, Bing He

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 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. Approximately 30%–60% of patients with PCOS are overweight or obese, and 95% of them have insulin resistance (IR). PCOS typically has an early onset. Therefore, metabolic abnormalities associated with PCOS, such as IR, are often linked to impaired glucose metabolism, diabetes mellitus, aberrant adipokine production of adipose tissue, low-grade systemic inflammation and cardiovascular diseases.

These comorbidities could have long-lasting effects on the health of patients with PCOS. 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. A recent meta-analysis has also confirmed that diets are advantageous for weight loss and improved IR. 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 dehydroepiandrostosterone 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 chemotactant 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 results will be initially imported into EndNote. The search results will be initially imported into EndNote. The search strategy will contain medical subject headings and keywords 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. 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 Cochrane-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 V15.1 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. 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.

Acknowledgements
We want to thank Haolu Wang and Abdullah Shopit for their assistance in editing the manuscript, especially regarding the grammar, formatting, and punctuation. Furthermore, we thank the editors and reviewers for their professional comments. Finally, we thank Zhijie Liao and Wei Yan for input during the revision period.

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.

Patient consent for publication
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
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REFERENCES


### PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Page</th>
</tr>
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<tbody>
<tr>
<td><strong>ADMINISTRATIVE INFORMATION</strong></td>
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<td>Title:</td>
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<td>Identify the report as a protocol of a systematic review</td>
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<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
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<td>Authors:</td>
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<tr>
<td>Contact</td>
<td>3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
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<tr>
<td>Contributions</td>
<td>3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
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<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
<td>6</td>
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<td>Support:</td>
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<td>Sources</td>
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<td>Indicate sources of financial or other support for the review</td>
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<td>Sponsor</td>
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<td>Role of sponsor or funder</td>
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<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
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<td>Rationale</td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
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<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
<td>2-3</td>
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<tr>
<td><strong>METHODS</strong></td>
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<td>3-4</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review</td>
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<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage</td>
<td>4</td>
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<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated</td>
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<td>Study records:</td>
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<td>Data management</td>
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<td>Describe the mechanism(s) that will be used to manage records and data throughout the review</td>
<td>4-5</td>
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<tr>
<td>Selection process</td>
<td>11b</td>
<td>State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)</td>
<td>4-5</td>
</tr>
<tr>
<td>Data collection process</td>
<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators</td>
<td>5</td>
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<td>Data items</td>
<td>12</td>
<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications</td>
<td>5</td>
</tr>
<tr>
<td>Outcomes and prioritization</td>
<td>13</td>
<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</td>
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<tr>
<td>Risk of bias in individual studies</td>
<td>14</td>
<td>Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis</td>
<td>5</td>
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<tr>
<td>Data synthesis</td>
<td>15a</td>
<td>Describe criteria under which study data will be quantitatively synthesised</td>
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<td>15b</td>
<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)</td>
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<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
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<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
<td>5</td>
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<tr>
<td>Meta-bias(es)</td>
<td>16</td>
<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
<td>5</td>
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<tr>
<td>Confidence in cumulative evidence</td>
<td>17</td>
<td>Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
<td>5-6</td>
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</table>

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

### Table S2 Search strategy as used in MEDLINE via PubMed

<table>
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<tr>
<th>#1</th>
<th>(((Polycystic ovary syndrome[MeSH Terms]) OR (PCOS[Text Word])) OR (PCOD[Text Word])) OR (Polycystic ovar*[Text Word])) OR (Stein-Leventhal Syndrome[Title/Abstract])</th>
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