Sridharan and Sivaramakrishnan
Diabetology & Metabolic Syndrome (2025) 17:168
https://doi.org/10.1186/s13098-025-01730-8

Diabetology &
Metabolic Syndrome

RESEARCH

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Expanding therapeutic horizons: glucagon-like peptide-1 receptor agonists and sodium glucose transporter-2 inhibitors in poly cystic ovarian syndrome: a comprehensive review including systematic review and network meta-analysis of randomized clinical trials

Kannan Sridharan[1*] and Gowri Sivaramakrishnan[2]

Abstract

Background Polycystic ovary syndrome (PCOS) is a complex endocrine characterized by hyperandrogenism, hormonal imbalances, and metabolic disruptions, leading to reproductive complications and increased risk of cardiometabolic diseases. While lifestyle modifications are the cornerstone of PCOS management, pharmacological interventions, including metformin, oral contraceptives, and anti-androgens, are commonly utilized. Recently, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) have shown promising results in PCOS management.

Methods This study conducted a comprehensive review of randomized clinical trials evaluating the effects of GLP-1 RAs and SGLT2is in women with PCOS. A systematic literature search was performed, and network meta-analysis using random-effects model that generated mixed treatment comparison estimates was employed to assess the comparative efficacy of these drug classes on clinical (menstrual frequency, pregnancy rate and proportion of patients with regular menstrual cycles), anthropometric, hormonal, and metabolic parameters. Additionally, a systematic review of preclinical studies investigating GLP-1 RAs and SGLT2is in animal models of PCOS was undertaken.

Results This comprehensive meta-analysis included 27 RCTs (1642 participants). GLP-1 RAs (alone and in combination with metformin) were observed to improve menstrual frequencies. GLP-1 RAs showed significant reductions in all anthropometric parameters, while SGLT2is was observed to improve wait hip ratio (WHR) and android gynoid fat (AGF) ratio (in addition to reduced body weight observed with SGLT2is/metformin combination). Reductions in WHR and AGF ratio were better with SGLT2is compared to GLP-1 RAs. The combination of GLP-1 RAs and SGLT2is was observed to have superior efficacy in reducing body weight, percent fat mass, and AGF ratio compared to GLP-1 RAs alone. Regarding hormonal parameters, GLP-1 RAs were observed with significant improvement in free androgen

*Correspondence:
Kannan Sridharan
skannandr@gmail.com
Full list of author information is available at the end of the article

index (FAI), free testosterone, androstenedione, and sex hormone binding globulin levels. SGLT2is was observed with significant improvements in FAI and total testosterone, outperforming GLP-1 RAs in reducing these parameters. Regarding metabolic parameters, GLP-1 RAs significantly improved triglycerides, markers of insulin resistance and fasting and postprandial plasma glucose. SGLT2is was associated with significant improvements in homeostatic model assessment for insulin resistance (HOMA-IR) and fasting plasma glucose, and in combination with metformin, SGLT2is significantly improved triglycerides. SGLT2is outperformed GLP-1 RAs in reducing LDL cholesterol and HOMA-IR. The combination of SGLT2is and GLP-1 RAs was better than GLP-1 RAs in reducing triglycerides and fasting plasma glucose. However, the strength of evidence for these findings was very low. Systematic assessment of animal studies revealed a potential association of several molecular pathways, including AMPK-α, SIRT1, FDX, PI3K/AKT, endothelial adhesion molecules (VCAM, ICAM, and E-selectin), STAR, and CYP17A1, with the therapeutic effects of GLP-1 RAs and SGLT2is in PCOS. Both drug classes were associated with significant improvements in ovarian morphology in animal studies.

Conclusion This systematic review and meta-analysis advance our understanding of GLP-1 RAs and SGLT2is in PCOS management. While both drug classes demonstrate efficacy in metabolic parameters, their distinct mechanisms offer unique therapeutic advantages. SGLT2is excel in improving hormonal profiles and insulin resistance, whereas GLP-1 RAs show consistent benefits in weight management. The enhanced efficacy of combination therapy suggests a potential paradigm shift in PCOS treatment strategies, moving beyond traditional monotherapy approaches. These findings support the therapeutic potential of both drug classes, individually or combined, in PCOS management, providing a foundation for more personalized treatment approaches.

Keywords GLP-1 analogs, SGLT2 inhibitors, PCOS, Metabolic syndrome

Introduction

Polycystic ovary syndrome (PCOS) affects 6–20% of reproductive-age women across different ethnic populations [1]. As the leading cause of female infertility, PCOS is characterized by hyperandrogenism, hormonal imbalances, and metabolic disruptions that impair ovulatory function and menstrual regularity [2]. Beyond reproductive issues, PCOS increases the risks of type 2 diabetes, cardiovascular diseases, metabolic syndrome, and mental health disorders, significantly impacting quality of life and healthcare utilization [3].

Despite decades of research, PCOS etiology remains unclear. While genetic polymorphisms and gut microbiota alterations have been identified, their complex interactions in PCOS pathogenesis are poorly understood [4]. This knowledge gap has led to symptom-focused treatments rather than addressing root causes, with strategies tailored to specific clinical manifestations and reproductive goals [1]. Management primarily emphasizes lifestyle modifications, particularly weight reduction, as approximately 80% of PCOS patients are overweight or obese [5].

Current pharmacological treatments include metformin, oral contraceptives, anti-androgens, insulin sensitizers, ovulation inducers, statins, and various supplements [6]. Recently, two novel drug classes have gained attention: glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium glucose transporter-2 inhibitors (SGLT2is), showing promise in PCOS clinical trials due to their effects on metabolic abnormalities [7].

GLP-1 RAs, synthetic analogues of endogenous GLP-1, stimulate insulin secretion while inhibiting glucagon release, with additional benefits in gastric emptying and appetite suppression [8, 9]. SGLT2is work by inhibiting glucose reabsorption in proximal renal tubules, demonstrating various pleotropic effects beyond glycemic control [10, 11]. Both drug classes have seen substantial clinical adoption, with prescriptions increasing dramatically between 2015 and 2020 [12, 13].

Clinical trials of these medications in PCOS patients have shown improvements in metabolic and hormonal parameters [14, 15]. A meta-analysis of four trials with 158 participants demonstrated significant reductions in body weight, fasting plasma glucose, and insulin resistance [16]. Additional analyses have documented improvements in various anthropometric and endocrine parameters [17, 18]. However, existing meta-analyses have limitations, including inadequate consideration of concurrent metformin use and lack of evidence strength grading. The absence of direct comparative trials between GLP-1 RAs and SGLT2is in PCOS necessitates network meta-analysis to generate effect estimates through common comparators [19]. Additionally, a comprehensive review of preclinical studies in PCOS animal models is needed to understand underlying mechanisms. This study aims to address these gaps through an extensive review of clinical trials with

network meta-analysis, complemented by a systematic review of preclinical studies with SGLT2is and GLP-1 RAs.

Methods

Search strategy

This meta-analysis protocol is registered in the Open Science Framework [20]. A comprehensive literature search was conducted across multiple electronic databases including PubMed, Cochrane Central Register of Controlled Trials, and Google Scholar. The detailed search strategy, incorporating Medical Subject Headings (MeSH) terms, keywords, and their combinations, is outlined in Electronic Supplementary Table 1. The final database search was executed on January 10, 2025, without imposing restrictions on publication year or language to ensure maximum capture of relevant studies. Conference proceedings were excluded due to potential limitations in methodological reporting. Additionally, reference lists of eligible studies were manually screened to identify additional relevant publications. This network meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement with network meta-analysis extension guidelines [21].

Eligibility criteria

We included only randomized clinical trials that met the following criteria.

Population Women diagnosed as PCOS. We did not restrict studies that have diagnosed PCOS using Rotterdam criteria.

Intervention The following GLP-1 RAs were included in this study: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide. The following SGLT2is were considered in this study: canagliflozin, bexagliflozin, licogliflozin, empagliflozin, luseogliflozin, dapagliflozin, enavogliflozin, remogliflozin, ertugliflozin, ipragliflozin, henagliflozin, remogliflozin, tofogliflfozin and sotagliflozin. Studies were eligible to be included if atleast one of the treatment arms were either GLP-1 RAs or SGLT2is or their combinations.

Control Placebo/other active drugs/standard of care.

Outcomes The following outcomes were assessed in this study:

Clinical parameters: menstrual frequency, pregnancy rate and proportion of patients with regular menstrual cycles.

Anthropometric parameters: BMI, body weight, WC, waist hip ratio (WHR), percent fat mass, visceral adipose tissue (VAT) mass and volume, systolic blood pressure (SBP), diastolic blood pressure (DBP) and android gynoid fat (AGF) ratio.

Hormonal parameters: Free androgen index (FAI), total testosterone, free testosterone, androstenedione, luteinizing hormone, follicle stimulating hormone (FSH), estradiol, progesterone and SHBG.

Metabolic parameters: total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, free fatty acids (FFA), HOMA-IR, fasting and 2 h insulin, fasting and 2 h post-prandial glucose, glycosylated hemoglobin (HbA1c), highly sensitive c-reactive protein (hsCRP), insulin secretion-sensitivity index (ISSI), ISS following oral glucose tolerance test (ISOGTT), lipoprotein (a) [Lp (a)], adiponectin, apolipoprotein A1, and apolipoprotein B.

All the above outcomes were assessed both as post-interventional values (at the end of last follow-up duration) and change-from-baseline values (pre-intervention values subtracted from the post-interventional values).

Study procedure

Independent literature searches were conducted by two investigators. Data extraction included trial identification, publication year, participant demographics (age, BMI), detailed intervention characteristics (drug name, dosage, administration frequency, and duration), and all specified outcomes. Disagreements in data extraction or interpretation were resolved through structured discussion until consensus was achieved.

The methodological quality assessment utilized the Cochrane risk of bias tool, evaluating seven domains: (1) random sequence generation; (2) allocation concealment; (3) participant and personnel blinding; (4) outcome assessment blinding; (5) outcome data completeness; (6) selective reporting; and (7) other bias [22]. Every domain in the risk of bias tool was assessed as one of the following: low, unclear or high risk.

Statistical analysis employed a random-effects model to generate direct, indirect, and mixed treatment comparison estimates. Direct estimates were derived from head-to-head trials, while indirect estimates were obtained through a common comparator across the included trials. For example, if a clinical trial has compared two interventions A and B, and another clinical has compared B and C, indirect effect estimates were obtained by pooling these trials through a common comparator (intervention B). These were subsequently combined to generate mixed comparison estimates using frequentist approach through weighted averages. As the outcomes were numerical variables, the primary effect measure employed was weighted mean difference (WMD) with 95% confidence intervals (95% CI). For studies reporting median and interquartile ranges, mean and standard deviation were estimated using the

methodology described by Wan et al. [23]. We analyzed two types of measurements: post-intervention values, which were taken on the last follow-up day; and change-from-baseline values, that were calculated by subtracting baseline measurements from the last follow-up day measurements. Between-evidence consistency was evaluated using H statistics, with inconsistency categorized as mild (< 3), modest (3–6), or large (> 6) [24]. Considering the fewer numbers of studies (< 10) pooled for each outcome measure, publication bias could not be assessed. All the statistical tests were two-sided, and p-values ≤ 0.05 were considered significant. Mixed comparison pooled estimates were generated using MetaXL© software [25]. Evidence quality was assessed using the GRADE working group approach [22].

Clinical trials.gov

A comprehensive search of clinicaltrials.gov was conducted using the search terms"polycystic ovary syndrome","PCOS", and"polycystic ovarian syndrome", with the final search performed on January 12, 2025 [26]. Data extraction included intervention details, outcome measures (primary, secondary, and other), target age groups, trial phases, study design characteristics, planned sample sizes, and trial locations.

Animal studies

The systematic review of preclinical studies included investigations of GLP-1 RAs and SGLT2is in PCOS animal models. Data extraction encompassed animal species, PCOS induction methodology, therapeutic effects (anthropometric, metabolic, hormonal, and ovarian parameters), and elucidated molecular pathways involved in the therapeutic response.

Results

Search results

The systematic literature search yielded 124 articles, of which 27 randomized clinical trials (published across 30 articles) [27–56] satisfied the predefined eligibility criteria (Fig. 1). The final analysis encompassed data from 1,642 participants, with three studies [27, 32, 55] excluded from the meta-analysis due to their reporting of outcomes as least square means. Table 1 presents the comprehensive characteristics of the included trials. Rotterdam criteria were employed for PCOS diagnosis in 26 articles, while the remaining study [29, 35, 39, 51] utilized National Institute of Health recommendations.

The intervention distribution comprised five clinical trials investigating SGLT2is, 21 evaluating GLP-1 RAs, and one trial comparing both drug classes. Within the SGLT2i category, the following agents were studied: canagliflozin (two trials), empagliflozin (two trials), licogliflozin (one trial), and a combination of empagliflozin/cyproterone acetate (one trial). The GLP-1 RAs investigations included: exenatide (five trials), liraglutide (eight trials), dulaglutide (one trial), semaglutide (two trials), liraglutide/metformin combination (five trials), exenatide/metformin combination (one trial), and exenatide/cyproterone acetate combination (one trial). The single comparative trial between drug classes evaluated exenatide against dapagliflozin.

Comparator interventions were diverse, including metformin (15 trials), placebo (eight trials), GLP-1 RAs/metformin combination (two trials), metformin/clomifene citrate combination (one trial), metformin/cyproterone acetate combination (one trial), cyproterone acetate/ethinyl estradiol combination (one trial), phentermine/topiramate combination (one trial), and calorie-restricted diet (one trial). Figure 2 illustrates the risk of bias assessment, demonstrating predominantly low risk across most domains, with blinding being the notable exception where higher risk was observed.

Pooled estimates for clinical outcomes in PCOS women

The analysis of post-interventional menstrual frequency incorporated seven studies encompassing 435 participants, primarily evaluating GLP-1 RAs, metformin, GLP-1 RAs/metformin combinations, and roflumilast (Fig. 3A). Forest plot analysis revealed significant improvements in menstrual frequency across all active interventions compared to placebo: GLP-1 RAs demonstrated a WMD of 3.58 (95% CI 3.54, 4.16), metformin showed a WMD of 3.76 (95% CI 3.42, 4.1), GLP-1 RAs/metformin combination achieved a WMD of 3.95 (95% CI 3.48, 4.42), and roflumilast exhibited a WMD of 3.99 (95% CI 3.63, 4.35) (Fig. 3B). The analysis revealed mild inconsistency between direct and indirect evidence ($H = 1$).

The assessment of regular menstrual cycles included three distinct comparative analyses: exenatide versus metformin with clomifene citrate, canagliflozin/metformin versus metformin alone, and liraglutide/metformin versus cyproterone acetate/ethinyl estradiol. Ovulation and pregnancy rates were reported in only one study. The heterogeneity in comparator groups precluded the execution of a network meta-analysis for these clinical outcomes. Notably, the paucity of SGLT2i studies prevented the analysis of clinical outcomes for this drug class independently.

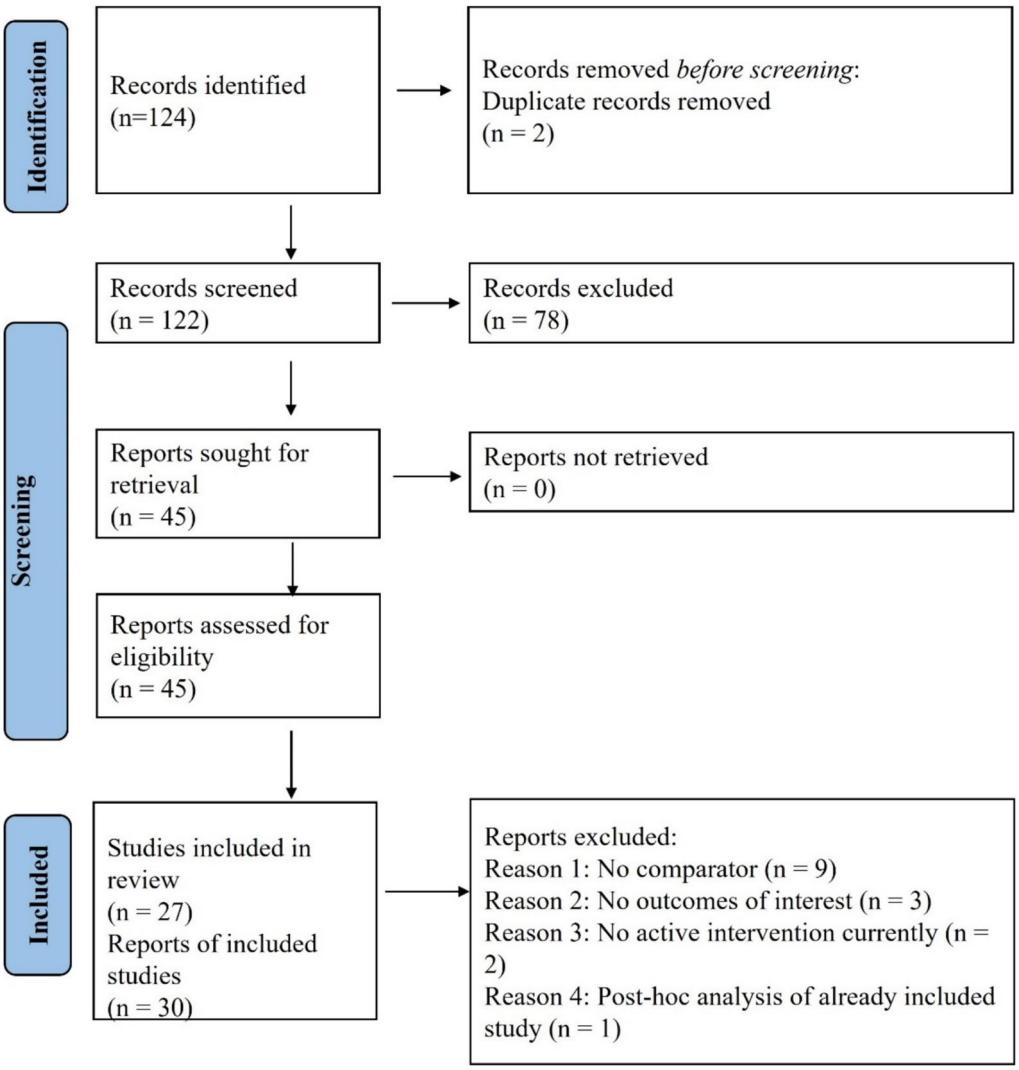

Fig. 1 PRISMA flow chart of included trials. A total of 30 reports of 27 studies were included in the meta-analysis

Pooled estimates for anthropometric parameters in PCOS in women

BMI: Analysis of BMI changes incorporated nine studies (388 participants), predominantly comparing GLP-1 RAs/metformin combinations with metformin monotherapy and GLP-1 RAs alone (Electronic Supplementary Fig. 1). Significant BMI reductions versus placebo were demonstrated across multiple interventions: GLP-1 RAs/metformin (WMD: −2.34; 95% CI −3.52, −1.16), GLP-1 RAs (WMD: −2.01; 95% CI −2.16, −1.85), SGLT2is/metformin (WMD: −1.5; 95% CI −2.7, −0.3), and metformin (WMD: −1.21; 95% CI −2.03, −0.38) (Fig. 4A). Post-interventional BMI analysis revealed significant reductions only with phentermine/topiramate (WMD: −2.96; 95% CI −5.82, −0.09; Electronic Supplementary Fig. 2). Mixed treatment comparisons against GLP-1 RAs showed no significant differences for SGLT2is/metformin (WMD: 0.51; 95% CI −0.68, 1.7) or GLP-1 RAs/metformin (WMD: −0.06; 95% CI −1.03, 0.92).

Body weight: Ten studies (554 participants) evaluated body weight changes (Electronic Supplementary Fig. 3). Compared to placebo, significant weight reductions were observed with GLP-1 RAs/metformin (WMD: − 6.65; 95% CI −10.35, −2.95), GLP-1 RAs (WMD: −5.85; 95% CI −7.31, −4.38), SGLT2is/metformin (WMD: −4.74; 95% CI −7.49, −1.99), and metformin (WMD: −3.93; 95% CI −5.4, −2.46) (Fig. 3B). Analysis of post-interventional body weights across 18 studies (904 participants) demonstrated significant reductions with phentermine/topiramate (WMD: −11.99; 95% CI −20.31, −3.68), GLP-1 RAs/SGLT2is (WMD: −10.99; 95% CI −19.22, −2.76), GLP-1 RAs/metformin (WMD: −9.5; 95% CI −18.08, −9.01), and GLP-1 RAs (WMD: −8.59; 95% CI −16.65, −0.54). In comparison to GLP-1 RAs, superior weight

Table 1 Key characteristics of randomized clinical trials included in the systematic review and meta-analysis

Study ID	Patient	Intervention	Control	Outcomes
Cai 2021 [27]	PCOS as defined by Rotterdam criteria with insulin resistance	Canagliflozin 100 mg/day for 12 weeks	Metformin 1.5–2 g/day for 12 weeks	Changes in HOMA-IR, anthropometric measurements, menstrual frequency, sex hormone levels, metabolic variables and body fat distribution
El Gohary 2023 [28]	Obese/overweight PCOS women as defined by Rotterdam criteria	Empagliflozin metformin 12.5/500 mg with clomiphene citrate 50 mg twice daily for 3 cycles from day 2 of the natural or the withdrawal cycle for 5 days	Metformin 500 mg continuously once daily plus clomiphene citrate 50 mg twice daily for 3 cycles from day 2 of the natural or the withdrawal cycle for 5 days	HOMA-IR and sex hormone levels and ovarian volume
Elkind-Hirsch 2021 [29]	Obese PCOS women as defined by modified National Institutes of Health 1990 criteria	Group 1: Exenatide 2 mg/week (n = 20) Group 2: Dapagliflozin 10 mg/day (n = 17) Group 3: Exenatide 2 mg/week with Dapagliflozin 10 mg/day (n = 20) Group 4: Dapagliflozin 10 mg/day with metformin 2000 extended release/day (n = 19) for 24 weeks	Phentermine 7.5 mg/day with topiramate 46 mg extended release/day for 24 weeks (n = 16)	Metabolic parameters, body composition, and sex hormones
Javed 2019 [30] & Javed 2020 [31]	Obese/overweight PCOS women as defined by Rotterdam criteria	Empagliflozin (25 mg/day) for 12 weeks	Metformin (1.5 g/day) for 12 weeks	HOMA-IR, anthropometric measurements, sex hormone levels, metabolic parameters, endothelial microparticles[a] and body fat distribution
Tan 2021 [32]	Overweight/obese PCOS women as defined by Rotterdam criteria	Licogliflozin 50 mg three times daily for 14 days	Placebo for 14 days	Insulin resistance, anthropometric measurements, sex hormone levels, and metabolic parameters
Zhang 2022 [33]	Overweight/obese PCOS women as defined by Rotterdam criteria	Canagliflozin 100 mg/day with metformin 1000 mg twice daily for 3 months (n = 21)	Metformin 1000 mg twice daily for 3 months (n = 20)	Changes in menstrual pattern, anthropometric parameters, hormone levels, and metabolic parameters
Elkind-Hirsch 2008 [34]	Overweight/obese PCOS women as defined by Rotterdam criteria	Exenatide (10 µg twice daily) and exenatide (10 µg twice daily) with extended-release metformin (1000 mg twice daily) for 24 week	Extended-release metformin (1000 mg twice daily) for 24 week	Changes in menstrual cyclicity, hormonal parameters, metabolic profiles, and inflammatory markers
Elkind-Hirsch 2022 [35]	Obese PCOS women as defined by modified National Institutes of Health 1990 criteria	Liraglutide 3 mg/day for 32 weeks	Placebo for 32 weeks	Changes in anthropometric parameters, hormone, and metabolic parameters
Frossing 2017 [36] & Frossing 2018 [37]	Overweight/obese PCOS women as defined by Rotterdam criteria with or without insulin resistance	Liraglutide 1.8 mg/day for 26 weeks	Placebo for 26 weeks	Changes in anthropometric parameters, hormone, and metabolic parameters
Gan 2023 [38]	Obese PCOS women as defined by Rotterdam criteria	Exenatide 2 mg SC once weekly with metformin orally 400 mg thrice daily for 12 weeks	Metformin orally 400 mg thrice daily for 12 weeks	Changes in anthropometric parameters, hormone, and metabolic parameters

Table 1 (continued)

Study ID	Patient	Intervention	Control	Outcomes
Jensterle 2015a [39]	PCOS diagnosed by the National Institute of Child Health and Human Development criteria	Liraglutide 1.2 mg SC once daily for 12 weeks	Metformin 1000 mg twice daily for 12 weeks	Menstrual frequencies, anthropometric parameters, hormone, and metabolic parameters
Jensterle 2015b [40]	Obese PCOS women as defined by Rotterdam criteria	Group 1: Liraglutide 1.2 mg SC once daily for 12 weeks Group 2: Roflumilast 500 µg orally once daily	Metformin 1000 mg twice daily for 12 weeks	Menstrual frequencies, anthropometric parameters, hormone, and metabolic parameters
Jensterle 2016 [41]	Obese PCOS women as defined by Rotterdam criteria	Liraglutide 0.6 mg/day SC increased to 1.2 mg/day after 1 week for 12 weeks	Liraglutide 1.2 mg SC with oral metformin 1000 mg once daily for 12 weeks	Anthropometric parameters, hormone, and metabolic parameters
Jensterle 2017 [42]	Obese PCOS women as defined by Rotterdam criteria	Liraglutide 0.6 mg/day SC increased to 3 mg/day for 12 weeks	Liraglutide 1.2 mg SC with oral metformin 2000 mg once daily for 12 weeks	Anthropometric parameters, hormone, and metabolic parameters
Jensterle 2021 [43]	Obese PCOS women as defined by Rotterdam criteria	Semaglutide started at 0.5/week for the first 4 weeks, and increased to 1 mg/week for the remaining 12 weeks	Placebo for 26 weeks	Anthropometric parameters, hormone, metabolic, and tongue fat parameters
Jensterle 2022 [44]	Obese PCOS women as defined by Rotterdam criteria	Semaglutide 0.25 mg weekly for the first 2 weeks, titrated to 0.5 mg/week for 2 weeks and then was increased to 1.0 mg once weekly for the remaining treatment period for 8 weeks	Placebo for 12 weeks	Anthropometric parameters, hormone, and metabolic parameters
Liao 2024 [45]	Obese/overweight PCOS women as defined by Rotterdam criteria	Liraglutide 0.6 mg/day, increased to 1.2 mg/day after one week, with a maximum dose of 1.8 mg/day SC with metformin 1500 mg/day for 12 weeks	Cyproterone acetate 2 mg/day with ethinyl estradiol 35 µg/day for 12 weeks	Anthropometric, menstrual, hormone, and metabolic parameters
Liu 2017 [46]	Obese/overweight PCOS women as defined by Rotterdam criteria	Exenatide 10 µg/day SC for a week and then escalated to 10 µg twice daily for 12 weeks	Metformin 1000 mg twice daily for 12 weeks	Anthropometric, menstrual, hormone, metabolic and proteomic analysis parameters
Ma 2021 [47]	Obese/overweight PCOS women as defined by Rotterdam criteria	Exenatide 2 mg weekly with metformin 500 mg thrice daily for 12 weeks	Metformin 500 mg thrice daily for 12 weeks	Anthropometric, hormone, and metabolic parameters
Nylander 2017 [48] & Nylander 2017b [49]	Obese/overweight PCOS women as defined by Rotterdam criteria	Liraglutide 1.8 mg/day SC, starting at 0.6 mg/day and 1.2 mg/day for the first and second week, respectively for 26 weeks	Placebo for 26 weeks	Anthropometric, hormone, metabolic, ovarian and thrombotic parameters
Salamun 2018 [50]	Obese/overweight PCOS women as defined by Rotterdam criteria	Liraglutide 1.2 mg SC once daily with metformin 1000 mg twice daily for 12 weeks	Metformin 1000 mg twice daily for 12 weeks	Anthropometric, hormone, metabolic, and in vitro fertilization parameters

Table 1 (continued)

Study ID	Patient	Intervention	Control	Outcomes
Sever 2014 [51]	Obese/overweight PCOS women as diagnosed by National Institute of Child Health and Human Development	Liraglutide 1.2 mg SC daily for one group and another received liraglutide (1.2 mg daily) with metformin orally 1000 mg twice daily	Metformin orally 1000 mg twice daily	Anthropometric, hormone, and metabolic parameters
Tao 2021 [52]	Obese/overweight PCOS women as defined by Rotterdam criteria	Exenatide 10–20 µg/day for one group and combined liraglutide (10–20 µg/day) with metformin 1.5–2 g/day orally for another group for 12 weeks	Metformin 1.5–2 g/day orally for 12 weeks	Anthropometric, hormone, and metabolic parameters
Wang 2017 [53]	Normal or overweight infertile women with oligomenorrhea, amenorrhea or irregular uterine bleeding with any two of the following: 1) hairy, acne, high androgenic manifestations or hyperandrogenism. With ovarian polycystic changes examined using ultrasound and 3) With insulin resistance as determined by HOMA-IR	Exenatide 5 µg twice daily for 1 month after which 10 µg twice daily for 2 months after which cyproterone acetate 50 mg/day for 5 days	Metformin 250 mg twice daily increased to 2000 mg/day with cyproterone acetate 50 mg/day for 5 days	Anthropometric, hormone, and metabolic parameters, and angiotensin levels
Xing 2022 [54]	Obese/overweight PCOS women as defined by Rotterdam criteria	Liraglutide 1.2 mg/day with metformin 1000 mg twice daily for 12 weeks	Metformin 1000 mg twice daily for 12 weeks	Anthropometric, menstrual, hormone, and metabolic parameters
Zhang 2023 [55]	Obese/overweight PCOS women as defined by Rotterdam criteria	Dulaglutide (1.5 mg SC weekly) with calorie-restricted diet	Calorie-restricted diet	Menstrual frequency, metabolic profiles, hormonal parameters, liver fat, and body composition
Zheng 2017 [56]	Obese/overweight PCOS women as defined by Rotterdam criteria	Exenatide 10 µg twice daily SC for 12 weeks	Metformin 1000 mg orally twice daily for 12 weeks	Anthropometric, menstrual, hormone, and metabolic parameters

PCOS: Polycystic ovarian syndrome; HOMA-IR: Homeostatic model of assessment of insulin resistance; a: includes intercellular adhesion molecule 1, vascular cell adhesion molecule 1, E-selectin, endoglin and vascular endothelial growth factor and platelet endothelial cell adhesion molecule 1; and SC: subcutaneous

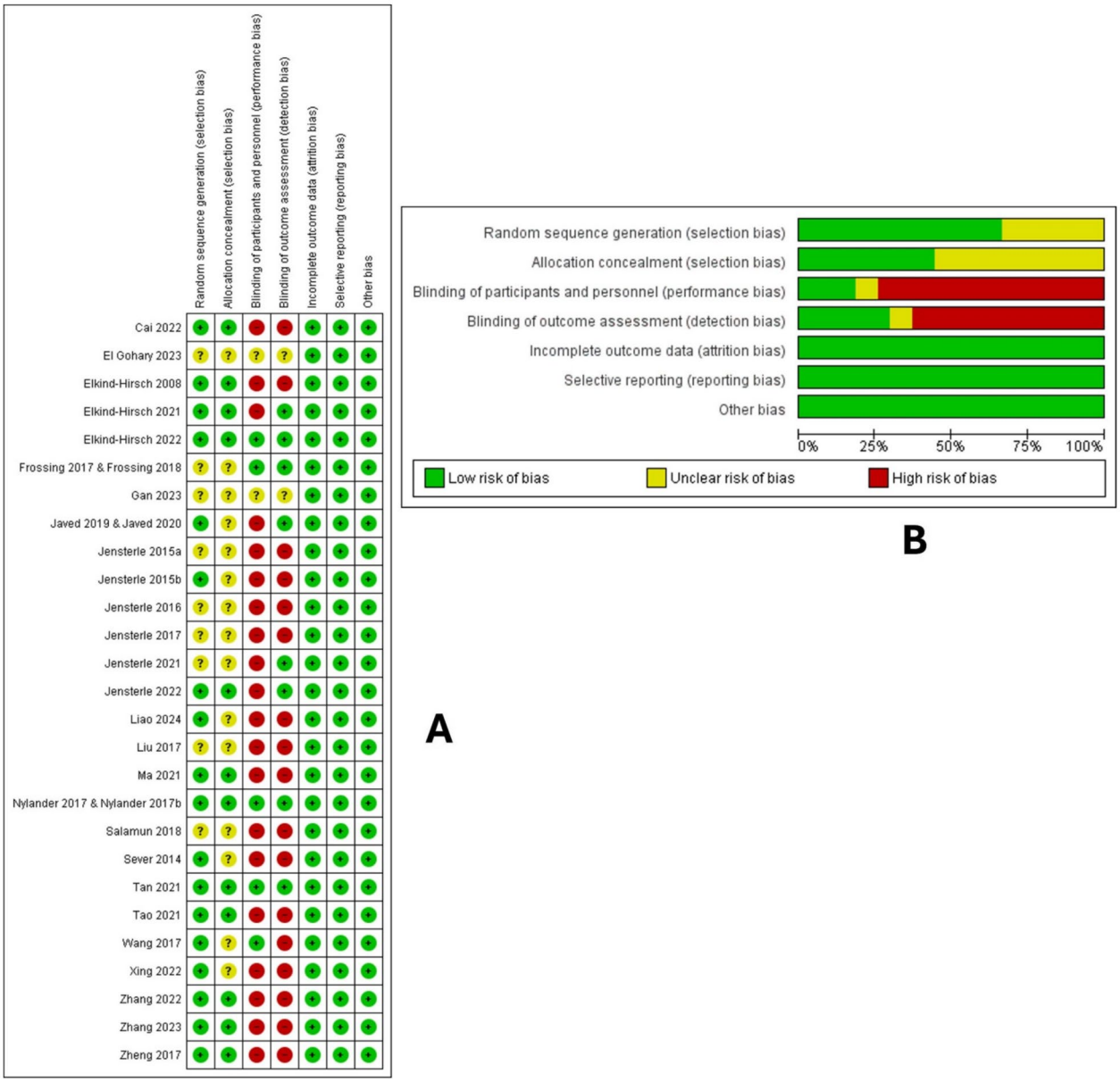

Fig. 2 Risk of bias of included studies. **A**: Risk of bias of individual domains for each study. Green circles indicate low risk, yellow color indicates unclear risk, and red color indicates high risk of bias. **B**: Green bars indicate low risk of bias; yellow color indicates an unclear risk and red color indicates high risk of bias

reductions were achieved with phentermine/topiramate (WMD: −3.4; 95% CI −5.16, −1.64) and GLP-1 Ras/SGLT2is (WMD: −2.4; 95% CI −3.91, −0.89).

Waist circumference: Seven studies (297 participants) analyzed WC changes, revealing significant reductions with GLP-1 RAs (WMD: −6.37; 95% CI −10, −2.74), GLP-1 RAs/metformin (WMD: −7.59; 95% CI −12.93, −2.25), and metformin (WMD: −4.77; 95% CI −9.06, −0.48) (Fig. 4C). Post-interventional WC analysis showed no significant differences between interventions, including GLP-1 RAs versus SGLT2is.

WHR: WHR change analysis included two studies (110 participants), showing no significant differences versus metformin for GLP-1 RAs/metformin (0; 95% CI −0.02, 0.03) or cyproterone acetate/ethinyl estradiol (0.01; 95% CI −0.03, 0.05). Post-interventional WHR analysis across five studies (423 participants; Electronic Supplementary Fig. 4) demonstrated significant reductions versus metformin for phentermine/topiramate (WMD: −0.07;

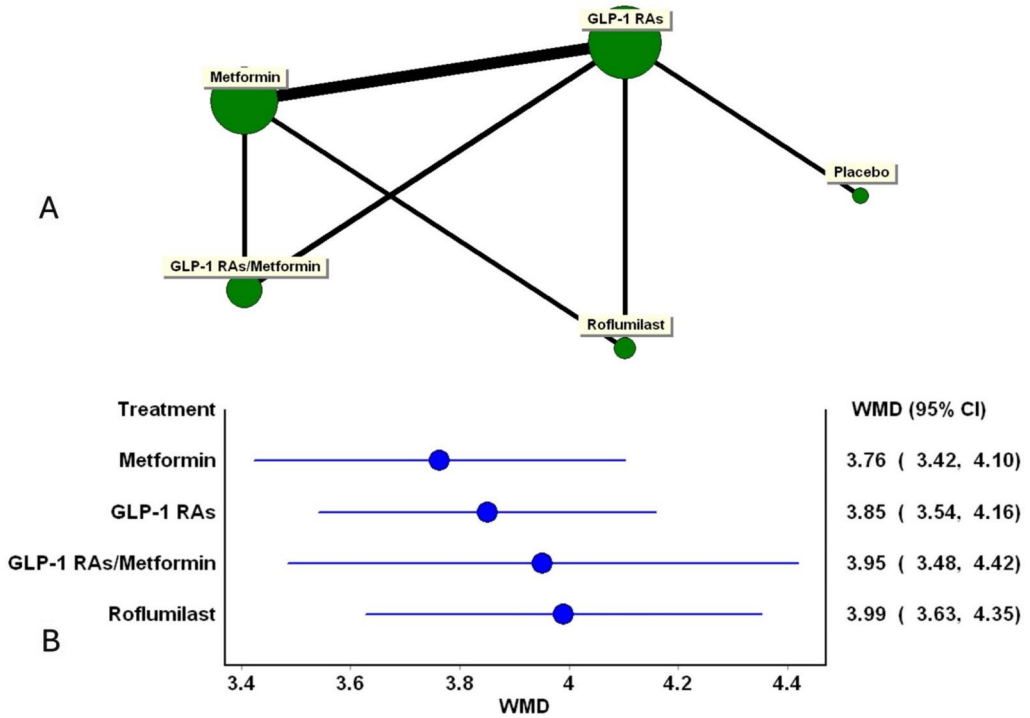

Fig. 3 Network and Forest plots for menstrual frequency compared to placebo. **A**: Network plot for interventions evaluating the menstrual frequency. Green circles represent the relative numbers of studies evaluating the specific interventions and the thickness of lines represents the relative numbers of studies evaluating the connected interventions. **B**: Forest plot of interventions evaluating menstrual frequency compared to placebo. Blue circles represent the point estimates and horizontal blue lines represent the 95% confidence intervals for the interventions in comparison with placebo

95% CI −0.05), SGLT2is/metformin (WMD: −0.05; 95% CI −0.07, −0.03), SGLT2is (WMD: −0.05; 95% CI −0.07, −0.03), and GLP-1 Ras (WMD: −0.02; 95% CI −0.04, 0) (Fig. 3D). In comparison to GLP-1 Ras, SGLT2is (WMD: −0.03; 95% CI −0.04, −0.02), SGLT2is/metformin (WMD: −0.03; 95% CI −0.04, −0.02), and phentermine/topiramate (WMD: −0.04; 95% CI −0.07, −0.01) were associated with significant reductions in the WHR.

Percent fat mass: Three studies (266 participants) were assessed for analyzing changes in percent fat mass and no significant reductions were observed with GLP-1 RAs/metformin (WMD: −1.07%; 95% CI −1.88, −0.26) and GLP-1 RAs (WMD: −0.87%; 95% CI −1.07, −0.67) but not with metformin alone (WMD: 2.69%; 95% CI 2.48, 2.9). Seven studies (451 participants) were pooled for analyzing differences in post-interventional percent fat mass (Electronic Supplementary Fig. 5). Significant reductions were observed with GLP-1 RAs/metformin (WMD: −4.25%; 95% CI −6.21, −2.29), GLP-1 RAs/SGLT2is (WMD: −3.2%; 95% CI −3.98, −2.42), phentermine/topiramate (WMD: −2.8%; 95% CI −3.65, −1.95), GLP-1 RAs (WMD: −1.9; 95% CI −2.27, −1.53), SGLT2is/metformin (WMD: −1.9%; 95% CI −2.68, −1.12), SGLT2is (WMD: −1.6%; 95% CI −2.43, −0.77), and metformin (WMD: −1.34%; 95% CI −2.37, −0.31) (Fig. 3E).

In comparison to GLP-1 RAs, GLP-1 RAs/SGLT2is (WMD: −1.3%; 95% CI −1.88, −0.72), and phentermine/topiramate (WMD: −0.9%; 95% CI −1.53, −0.27) were associated with significant reductions in the percent fat mass.

VAT mass: Two studies (65 participants; Electronic Supplementary Fig. 6) were pooled for analyzing the changes in VAT mass and significant reduction was observed with GLP-1 RAs (WMD: −104 g; 95% CI −180.31, −27.69) compared to placebo (Fig. 3F). Four studies (131 participants) were pooled for the analysis of post-interventional VAT mass and no significant differences were observed with metformin (WMD: −163.8 g; 95% CI −429.38, 101.78), GLP-1 RAs (WMD: −134 g; 95% CI −311.88, 40.88), and GLP-1 RAs/metformin (WMD: −128.92 g; 95% CI −347.94, 90.11) compared to placebo.

VAT surface area: Only one study each assessed the changes and post-interventional VAT surface area and so pooled estimates could not be generated for this outcome.

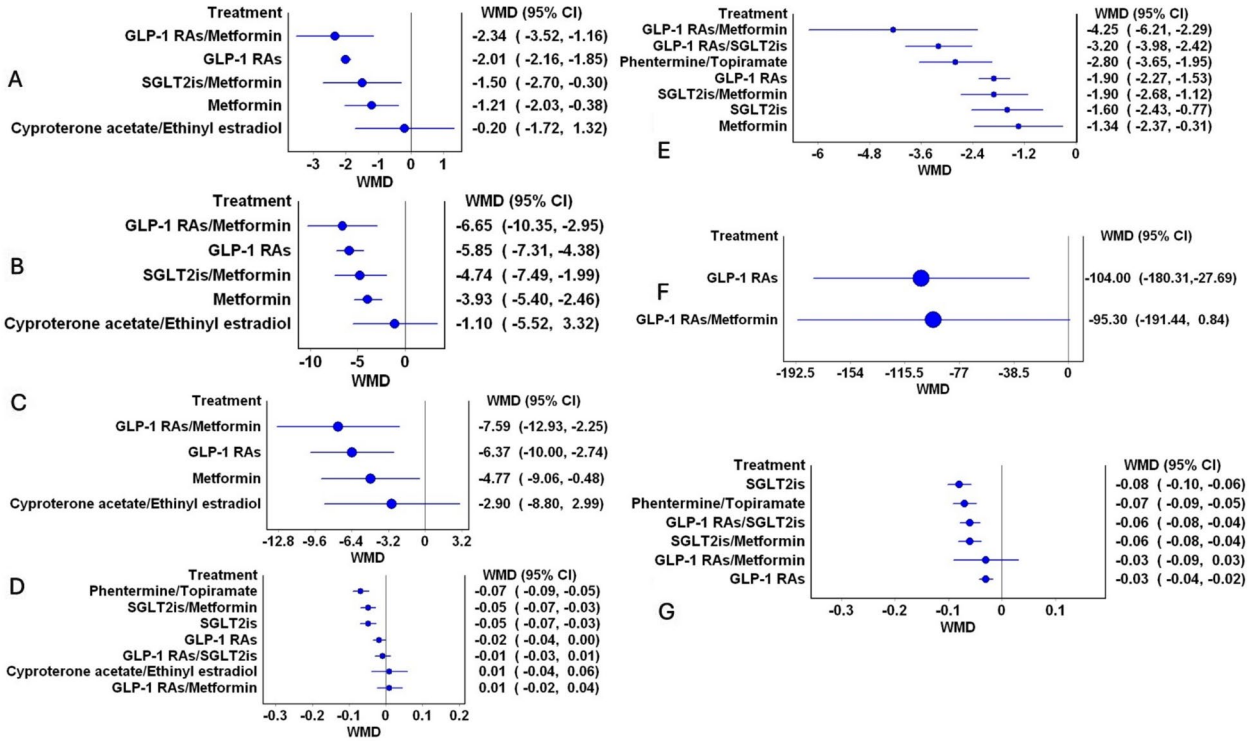

Fig. 4 Comparison of anthropometric parameters between GLP-1 RAs, SGLT2is and comparator drugs used in clinical trials with placebo. Blue circles represent the point estimates and horizontal blue line represents 95% CI. Central vertical black line represents the line of no difference. Changes in BMI (**A**); body weight (**B**), waist circumference (**C**), and visceral adipose tissue (**F**); and post-interventional waist hip ratio (**D**), percent fat mass (**E**), and android gynoid ratio (**G**)

AGF ratio: Three studies (202 participants) were pooled for analysis of post-interventional AGF ratio (Electronic Supplementary Fig. 7). Significant reductions in the AGF ratios were observed with SGLT2is (WMD: −0.08; 95% CI −0.1, −0.06), phentermine/topiramate (WMD: −0.07; 95% CI −0.09, −0.05), GLP-1 RAs/SGLT2is (WMD: −0.06; 95% CI −0.08, −0.04), SGLT2is/metformin (WMD: −0.06; 95% CI −0.08, −0.04), and GLP-1 RAs (WMD: −0.03; 95% CI −0.04, −0.02) (Fig. 4G).

In comparison with GLP-1 Ras, significantly reductions in the post-interventional AGF ratios were observed with the following interventions: SGLT2is (WMD: −0.05; 95% CI −0.06, −0.04), phentermine/topiramate (WMD: −0.04; 95% CI −0.05, −0.03), SGLT2is/metformin (WMD: −0.03; 95% CI −0.04, −0.02), and GLP-1 RAs/SGLT2is (WMD: −0.03; 95% CI −0.04, −0.02).

Pooled estimates for hormonal parameters in PCOS women

FAI: Thirteen studies (852 participants) were pooled for the analysis of post-interventional FAI values (Electronic Supplementary Fig. 8). Significantly reduced FAI was observed with the following drugs: SGLT2is (WMD: −1; 95% CI −1.6, −0.39), phentermine/topiramate (WMD: −0.7; 95% CI −1.31, −0.08) and GLP-1 RAs (WMD: −0.4; 95% CI −0.75, −0.05) (Fig. 5A). Due to lack of a common comparator, pooled estimates could not be generated for the changes in FAI.

Compared to GLP-1 RAs, SGLT2is (WMD: −0.57; 95% CI −0.97, −0.18) were associated with a better reduction in post-interventional FAI.

Total testosterone: Seven studies (327 participants) were pooled for the analysis of changes in total testosterone levels (Electronic Supplementary Fig. 9). Significantly reduced total testosterone levels were observed with the following interventions compared to placebo: cyproterone acetate/ethinyl estradiol (WMD: −24.79; 95% CI −43.55, −6.03), SGLT2is/metformin (WMD: −24.14; 95% CI −39.44, −8.84), GLP-1 RAs/metformin (WMD: −9.19; 95% CI −17.86, −0.52), metformin (WMD: −9.14; 95% CI −17.81, −0.47), and GLP-1 RAs (WMD: −6.32; 95% CI −8, −4.64) (Fig. 5B). Nineteen studies (1105 participants) were pooled for the analysis of post-interventional testosterone levels (Electronic Supplementary Fig. 10). Significantly reduced post-interventional testosterone was observed only with SGLT2is (WMD: −7.18; 95% CI −12.03, −2.32).

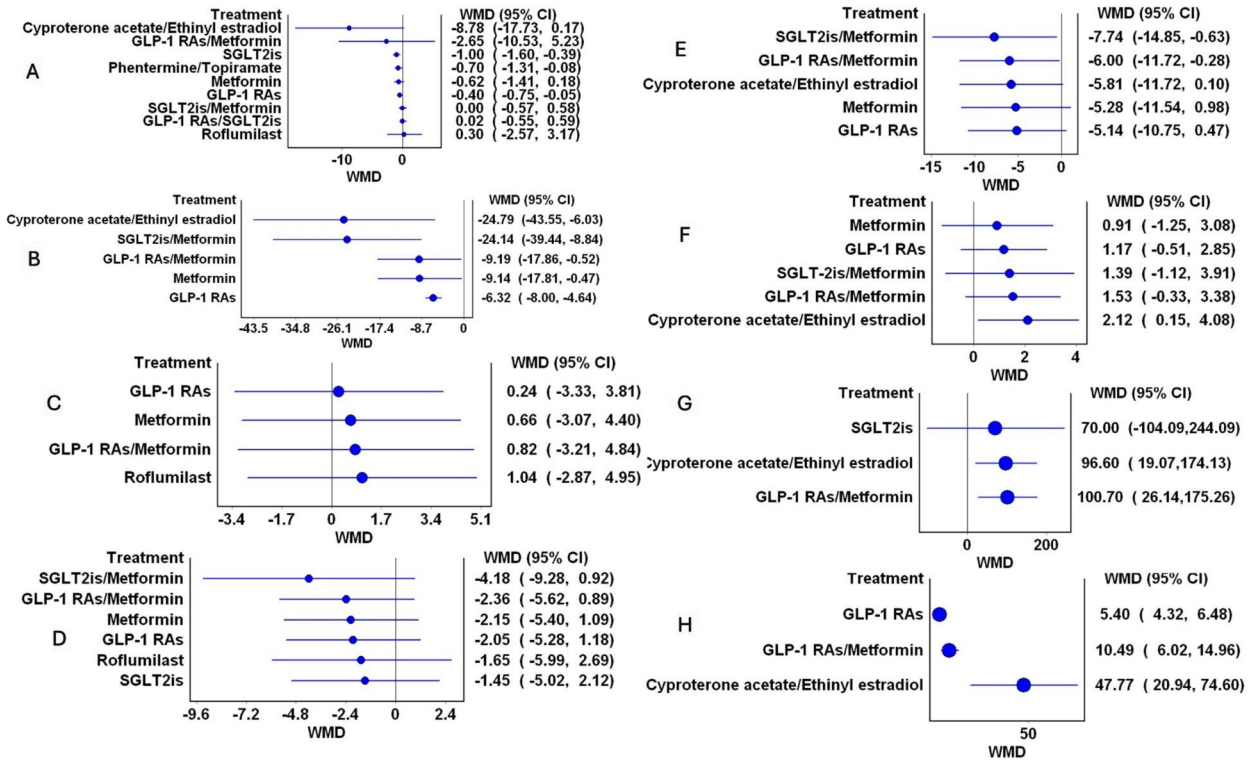

Fig. 5 Forest plots of interventions for outcome parameters related to hormonal changes in PCOS women. Blue circles represent the point estimates and horizontal blue line represents 95% CI. Central vertical black line represents the line of no difference. Post-interventional FAI(**A**), free testosterone (**C**), androstenedione (**D**), LH (**E**), FSH (**F**), and estradiol (**G**). Figures **B** and **H** represent changes in total testosterone and SHBG, respectively

In comparison with GLP-1 RAs, SGLT2is were associated with significantly reduced changes in total testosterone levels (WMD: −3.74; 95% CI −5.94, −1.55).

Free testosterone: Three studies (173 participants) were pooled for the analysis of changes in free testosterone (Electronic Supplementary Fig. 11). Significantly reduced changes in free testosterone levels were observed with GLP-1 RAs (WMD: −0.01; 95% CI −0.01, −0.01). Six studies (185 participants) were pooled for the analysis of post-interventional free testosterone (Electronic Supplementary Fig. 12) and no significant differences were observed for any of the drugs compared to placebo (Fig. 5C).

Androstenedione: Three studies (136 participants) were pooled for the analysis of changes in androstenedione (Electronic Supplementary Fig. 13). Significantly reduced changes in androstenedione levels were observed with GLP- RAs (WMD: −1.45; 95% CI −2.31, −0.59) and GLP-1 RAs/metformin (WMD: −3.8; 95% CI −5.46, −2.14). Nine studies (416 participants) were pooled for the analysis of post-interventional androstenedione levels (Electronic Supplementary Fig. 14) and no significant differences were observed with any of the drugs compared to placebo (Fig. 5D).

No significant differences were observed in the post-interventional androstenedione levels with SGLT2is compared to GLP-1 RAs (WMD: 0.6; 95% CI −0.92, 2.12).

LH: Five studies (259 participants) were pooled for the analysis of changes in LH (Electronic Supplementary Fig. 15). No significant differences were observed with cyproterone acetate/ethinyl estradiol (WMD: −3.44; 95% CI −8.36, 1.48), GLP-1 RAs/metformin (WMD: −304; 95% CI −7.17, 1.09), SGLT2is/metformin (WMD-2.73; 95% CI −11.84, 6.38), GLP-1 RAs (WMD: −2.64; 95% CI −5.78, 0.5) and metformin (WMD: −1.29; 95% CI −8.78, 6.2). Nine studies (506 participants) were pooled for analysis of post-interventional LH (Electronic Supplementary Fig. 16). Compared to placebo, SGLT2is/metformin (WMD: −7.74; 95% CI −14.85, −0.63) and GLP-1 RAs/metformin (WMD: −6; 95% CI −11.72, −0.28) were associated with associated with significantly lower LH compared to placebo (Fig. 5E).

No significant differences in LH levels were observed with SGLT2is/metformin (WMD: −2.6; 95% CI −6.98, 1.77) compared to GLP-1 RAs.

FSH: Five studies (259 participants) were pooled for the analysis of changes in FSH levels (Electronic

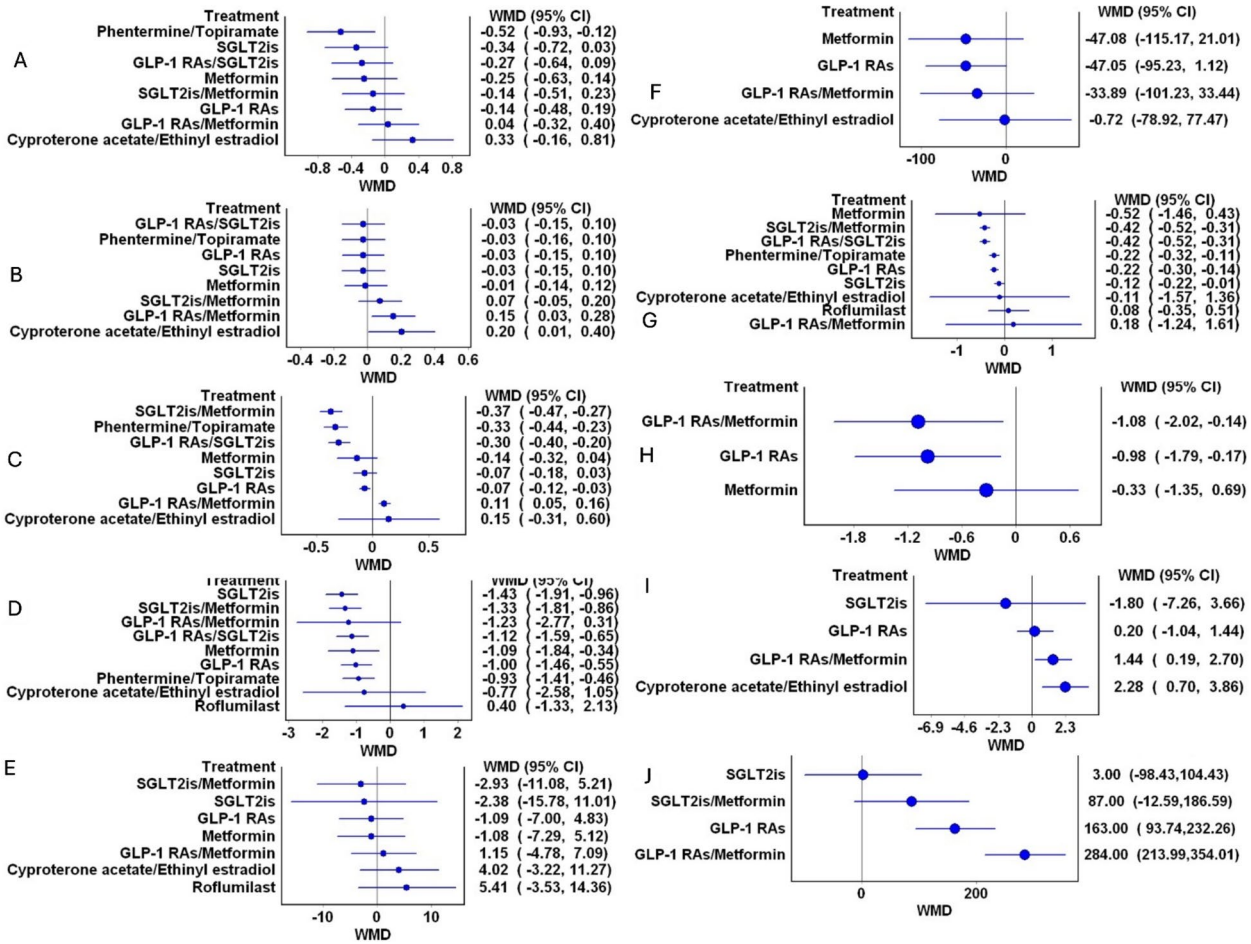

Fig. 6 Forest plot for metabolic parameters in PCOS women. Blue circles represent the point estimates and horizontal blue line represents 95% CI. Central vertical black line represents the line of no difference. Post-interventional LDL cholesterol (**A**), HDL cholesterol (**B**), trigylcerides (**C**), HOMA-IR (**D**), fating insulin (**E**), two-hour insulin (**F**), fating plasma glucose (**G**), post-prandial glucose (**H**), hsCRP (**I**) and ISSI (**J**)

Supplementary Fig. 17) and no significant differences were observed with GLP-1 RAs/metformin (WMD: −0.67; 95% CI −2.5, 1.16), GLP-1 RAs (WMD: −0.47; 95% CI −1.6, 0.66), SGLT2is/metformin (WMD: −0.43; 95% CI −3.4, 2.54), metformin (WMD: −0.36; 95% CI −2.96, 2.24) and cyproterone acetate/ethinyl estradiol (WMD: −0.14; 95% CI −2.18, 1.9) compared to placebo. Seven studies (393 participants) were pooled for the analysis of post-interventional FSH values (Electronic Supplementary Fig. 18) and only cyproterone acetate (WMD: 2.12; 95% CI 0.15, 4.08) was associated with increased FSH compared to placebo (Fig. 5F).

Estradiol: Two studies (110 participants) were included for the analysis of changes in serum estradiol levels (Electronic Supplementary Fig. 19). No significant differences were observed with cyproterone acetate/ethinyl estradiol (WMD: −3.1; 95% CI −122.89, 116.69) and GLP-1 RAs/metformin (WMD: −0.2; 95% CI −116.38, 115.98) compared to metformin. Four studies (201 participants) were pooled for the analysis of post-interventional estradiol levels (Electronic Supplementary Fig. 20). Compared to metformin, GLP-1 RAs/metformin (WMD: 100.7; 95% CI 26.14, 175.26) and cyproterone acetate/ethinyl estradiol (WMD: 96.6; 95% CI 19.07, 174.13) were associated with significantly increased estradiol levels (Fig. 5G).

Progesterone: Only one study has assessed changes in progesterone level and so pooled estimates could not be generated for this outcome. Two studies (112 participants) were pooled for the estimation of post-intervention serum progesterone levels (Electronic Supplementary Fig. 21). Compared to metformin, no significant differences were observed with either cyproterone acetate/ethinyl estradiol (WMD: 0.59; 95% CI −13.28, 14.46) or GLP-1 RAs/metformin (WMD: 0.75; 95% CI −13.09, 14.59).

SHBG: Four studies (201 participants) were pooled for the analysis of changes in SHBG (Electronic

Supplementary Fig. 22). GLP-1 RAs (WMD: 5.4; 95% CI 4.32, 6.48), GLP-1 RAs/metformin (WMD: 10.49; 95% CI 6.02, 14.96) and cyproterone acetate/ethinyl estradiol (WMD: 47.77; 95% CI 20.94, 74.6) were observed with elevated SHBG compared to placebo (Fig. 4H). Thirteen studies (737 participants) were pooled for the analysis of post-intervention SHBG (Electronic Supplementary Fig. 23). Only cyproterone acetate/ethinyl estradiol (WMD: 42.5; 95% CI 10.09, 74.91) was associated with a significantly higher SHBG value compared to placebo.

Pooled estimates for metabolic parameters in PCOS women

Total cholesterol: Four studies (191 participants) were pooled for the analysis of changes in total cholesterol (Electronic Supplementary Fig. 24). No significant differences were observed in total cholesterol with SGLT2is/metformin (WMD: 0.05; 95% CI −0.23, 0.33), and GLP-1 Ras/metformin (WMD: 0.27; 95% CI −0.08, 0.61) compared to metformin while cyproterone acetate/ethinyl estradiol (WMD: 0.81; 95% CI 0.27, 1.34) was associated with an elevated total cholesterol. Fifteen studies (902 participants) were pooled for analysis of post-interventional total cholesterol (Electronic Supplementary Fig. 25) and only phentermine/topiramate (WMD: −0.66; 95% CI −1.27, −0.04) were observed with significantly reduced levels.

LDL cholesterol: Four studies (191 participants) were pooled for the analysis of changes in total cholesterol (Electronic Supplementary Fig. 26). Compared to metformin, no significant changes were observed in the LDL cholesterol changes with SGLT2is/metformin (WMD: 0.07; 95% CI −0.23, 0.37), GLP-1 RAs/metformin (WMD: 0.1; 95% CI −0.21, 0.41), and cyproterone acetate/ethinyl estradiol (WMD: 0.49; 95% CI −0.07, 1.05). Fifteen studies (902 participants) were pooled for analysis of post-interventional LDL cholesterol values (Electronic Supplementary Fig. 27). Only phentermine/topiramate (WMD: −0.52; 95% CI −0.93, −0.12) was observed with significantly reduced LDL cholesterol compared to placebo (Fig. 6A).

Compared to GLP-1 Ras, SGLT2is were associated with significantly lower post-intervention LDL cholesterol (WMD: −0.2; 95% CI −0.33, −0.07).

HDL cholesterol: Three studies (150 participants) were pooled for the analysis of changes in HDL cholesterol (Electronic Supplementary Fig. 28). Compared to metformin, no significant differences were observed either with cyproterone acetate/ethinyl estradiol (WMD: 0; 95% CI −0.28, 0.27) or GLP-1 RAs/metformin (WMD: 0.08; 95% CI −0.02, 0.17). Twelve studies (671 participants) were pooled for the analysis of post-interventional HDL cholesterol (Electronic Supplementary Fig. 29). GLP-1 RAs/metformin (WMD: 0.15; 95% CI 0.03, 0.28) and cyproterone acetate/ethinyl estradiol (WMD: 0.2; 95% CI 0.01, 0.4) were associated with significantly elevated HDL cholesterol levels (Fig. 6B).

In comparison with GLP-1 RAs, no significant difference was observed in the post-intervention HDL cholesterol with SGLT2is (WMD: 0; 95% CI −0.03, 0.03).

Triglycerides: Four studies (191 participants) were pooled for the analysis of changes in serum triglycerides (Electronic Supplementary Fig. 30). Compared to metformin, no significant differences were observed in serum triglycerides with SGLT2is/metformin (WMD: −0.22; 95% CI −0.56, 0.12), GLP-1 RAs/metformin (WMD: 0.23; 95% CI −0.75, 1.21) and cyproterone acetate/ethinyl estradiol (WMD: 0.6; 95% CI −0.47, 1.67). Fifteen studies (902 participants) were analyzed for post-interventional triglycerides (Electronic Supplementary Fig. 31). Compared to placebo, SGLT2is/metformin (WMD: −0.37; 95% CI −0.47, −0.27), phentermine/topiramate (WMD: −0.33; 95% CI −0.44, −0.23), GLP-1 RAs/SGLT2is (WMD: −0.3; 95% CI −0.4, −0.2) and GLP-1 RAs (WMD: −0.07; 95% CI −0.12, −0.03) were observed with significantly reduced changes in triglycerides (Fig. 6C).

Compared to GLP-1 RAs, SGLT2is/metformin (WMD: −0.3; 95% CI −0.37, −0.23), phentermine/topiramate (WMD: −0.26; 95% CI −0.34, −0.18) and GLP-1 RAs/SGLT2is (WMD: −0.23; 95% CI −0.3, −0.16) were associated with significantly lower post-intervention triglyceride values.

FFA: Only two studies (90 participants) comparing exenatide/metformin with metformin assessed FFA and no significant differences between the interventions were observed either in the post-interventional values (WMD: −46.75; 95% CI −139.26, 45.75) or change-from-baseline FFA (WMD: −30.78; 95% CI −141.16, 79.6).

HOMA-IR: Seven studies (324 participants) were pooled for the analysis of change-from-baseline HOMA-IR (Electronic Supplementary Fig. 32). No significant differences were observed with SGLT2is/metformin (WMD: −2; 95% CI −4.09, 0.08), metformin (WMD: −1.48; 95% CI −3.18, 0.21), GLP-1 RAs (WMD: 0.01; 95% CI −0.09, 0.1), GLP-1 RAs/metformin (WMD: 0.31; 95% CI −0.93, 1.55) compared to placebo while cyproterone acetate/ethinyl estradiol (WMD: 1.89; 95% CI 0.26, 3.52) was observed with an increased HOMA-IR values. Nineteen studies (1078 participants) reported post-interventional HOMA-IR values (Electronic Supplementary Fig. 33). SGLT2is (WMD: −1.43; 95% CI −1.91, −0.96), SGLT2is/metformin (WMD: −1.33; 95% CI −1.81, −0.86), GLP-1 RAs/SGLT2is (WMD: −1.13; 95% CI −1.59, −0.65), metformin (WMD: −1.09; 95%

CI −1.84, −0.34), GLP-1 RAs (WMD: −1; 95% CI −1.46, −0.55), and phentermine/topiramate (WMD: −0.93; 95% CI −1.41, −0.46) were observed with significantly reduced post-interventional HOMA-IR values compared to placebo.

Compared to GLP-1 RAs, SGLT2is (WMD: −0.43; 95% CI −0.54, −0.32) and SGLT2is/metformin (WMD: −0.33; 95% CI −0.43, −0.23) were observed with significantly reduced post-interventional HOMA-IR values.

Fasting insulin: Six studies (259 participants) were pooled for the analysis of change-from-baseline fasting insulin values (Electronic Supplementary Fig. 34). No significant differences were observed with SGLT2is/metformin (WMD: −4.24; 95% CI −13.57, 5.1), metformin (WMD: −2.67; 95% CI −10.96, 5.63), GLP-1 RAs (WMD: −0.64; 95% CI −6.62, 5.34), GLP-1 Ras/metformin (WMD: 2.76; 95% CI −4.54, 10.06) compared to placebo while an increase was observed with cyproterone acetate/ethinyl estradiol (WMD: 9.18; 95% CI 0.49, 17.87). Fifteen studies (836 participants) were pooled for the analysis of post-interventional fasting insulin levels (Electronic Supplementary Fig. 35). Compared to placebo, no significant differences were observed with SGLT2is/metformin (WMD: −2.93; 95% CI −11.08, 5.21), SGLT2is (WMD: −2.38; 95% CI −15.78, 11.01), GLP-1 RAs (WMD: −1.09; 95% CI −7, 4.83), metformin (WMD: −1.08; 95% CI −7.29, 5.12), GLP-1 RAs/metformin (WMD: 1.15; 95% CI −4.78, 7.09), cyproterone acetate/ethinyl estradiol (WMD: 4.02; 95% CI −3.22, 11.27) and roflumilast (WMD: 5.41; 95% CI −3.53, 14.36) (Fig. 6E).

Compared to GLP-1 RAs, no significant differences were observed with SGLT2is (WMD: −1.3; 95% CI −13.32, 10.72) and SGLT2is/metformin (WMD: −1.85; 95% CI −7.45, 3.75) on the post-interventional fasting insulin levels.

Two-hour insulin: Five studies (218 participants) were pooled for the analysis of change-from-baseline two-hour insulin levels (Electronic Supplementary Fig. 36). Compared to placebo, metformin (WMD: −67.94; 95% CI −127.23, −8.64) and GLP-1 Ras (WMD: −49.72; 95% CI −67.84, −31.6) were observed with reduced two-hour insulin levels. Eleven studies (663 participants) were pooled for the analysis of post-interventional two-hour insulin levels (Electronic Supplementary Fig. 37). No significant differences were observed with metformin (WMD: −47.08; 95% CI −115.17, 21.10), GLP-1 RAs (WMD: −47.05; 95% CI −95.23, 1.12), GLP-1 Ras/metformin (WMD: −33.89; 95% CI −101.23, 33.44) and cyproterone acetate/ethinyl estradiol (WMD: −0.72; 95% CI −78.92, 77.47) (Fig. 6F).

HbA1c: Four studies (200 participants) reported changes in HbA1c of which due to lack of common comparator, only two studies could be pooled (Electronic Supplementary Fig. 38). Compared to metformin, no significant differences were observed in the change-from-baseline HbA1c levels with GLP-1 RAs/metformin (WMD: 0.09; 95% CI −0.04, 0.22) but an increase was observed with cyproterone acetate/ethinyl estradiol (WMD: 0.32; 95% CI 0.04, 0.6). Similarly, three studies (135 participants) reported post-interventional HbA1c values of which two studies could be pooled (Electronic Supplementary Fig. 39). Compared to metformin, no significant differences were observed with either GLP-1 RAs/metformin (WMD: 0.03; 95% CI −0.15, 0.21) or cyproterone acetate/ethinyl estradiol (WMD: −0.01; 95% CI −0.26, 0.24).

Fasting plasma glucose: Seven studies (287 participants) were pooled for the analysis of change-from-baseline fasting plasma glucose (Electronic Supplementary Fig. 40). Compared to placebo, no significant differences were observed with SGLT2is/metformin (WMD: −0.56; 95% CI −1.35, 0.22), metformin (WMD: −0.29; 95% CI −0.99, 0.4), GLP-1 Ras/metformin (WMD: −0.14; 95% CI −0.74, 0.46), and cyproterone acetate/ethinyl estradiol (WMD: 0.02; 95% CI −0.69, 0.73) but an increase was observed with GLP-1 RAs (WMD: 0.46; 95% CI 0.17, 0.75). Seventeen studies (995 participants) were pooled for analysis of post-interventional fasting plasma glucose (Electronic Supplementary Fig. 41). Compared to placebo, SGLT2is/metformin (WMD: −0.42; 95% CI −0.52, −0.31), GLP-1 RAs/SGLT2is (WMD: −0.42; 95% CI −0.52, −0.31), phentermine/topiramate (WMD: −0.22; 95% CI −0.32, −0.11), GLP-1 RAs (WMD: −0.22; 95% CI −0.3, −0.14), and SGLT2is (WMD: −0.12; 95% CI −0.22, −0.01) were observed with significantly reduced post-interventional fasting plasma glucose (Fig. 6G).

Compared to GLP-1 RAs, SGLT2is/metformin (WMD: −0.2; 95% CI −0.25, −0.15) and GLP-1 RAs/SGLT-2is (WMD: −0.2; 95% CI −0.25, −0.15) were observed with significantly lower fasting plasma glucose.

Postprandial plasma glucose: Four studies assessed change-from-baseline postprandial plasma glucose of which three compared GLP-1 RAs/metformin with metformin and one GLP-1 RAs with placebo and mixed treatment comparison pooled estimates were not generated due to the lack of a common comparator. Nine studies (536 participants) reported post-interventional plasma glucose (Electronic Supplementary Fig. 42). Compared to placebo, GLP-1 RAs/metformin (WMD: −1.08; 95% CI −2.02, −0.14) and GLP-1 RAs (WMD: −0.98; 95% CI −1.79, −0.17) were reported with significantly lower postprandial plasma glucose (Fig. 6H).

hsCRP: Seven studies (452 participants) were pooled for the analysis of post-interventional hsCRP levels (Electronic Supplementary Fig. 43). Compared to

metformin, no significant differences were observed with SGLT2is (WMD: −1.8; 95% CI −7.26, 3.66), and GLP-1 RAs (WMD: 0.2; 95% CI −1.04, 1.44) while an increase was observed with GLP-1 RAs/metformin (WMD: 1.44; 95% CI 0.19, 2.7) and cyproterone acetate/ethinyl estradiol (WMD: 2.28; 95% CI 0.7, 3.86) (Fig. 6I).

Compared to GLP-1 RAs, no significant difference was observed in the post-interventional hsCRP levels with SGLT2is (WMD: −1.69; 95% CI −7.24, 3.87).

ISSI: Two studies (998 participants) were pooled for the estimation of post-interventional ISSI values (Electronic Supplementary Fig. 44). Compared to metformin, GLP-1 RAs (WMD: 163; 95% CI 93.74, 232.26) and GLP-1 RAs/metformin (WMD: 284; 95% CI 213.99, 354.01) were observed with significantly higher ISSI values (Fig. 6J).

Compared to GLP-1 RAs, no significant difference was observed with SGLT2is (WMD: −160; 95% CI −205.56, 114.44) but SGLT2is/metformin (WMD: −76; 95% CI −120, −31.91) was observed with significantly reduced ISSI values.

ISOGTT: Three studies (259 participants) were pooled for the analysis of post-interventional ISOGTT values (Electronic Supplementary Fig. 45). Compared to placebo, GLP-1 RAs (WMD: 0.7; 95% CI 0.46, 0.94) and metformin (WMD: 0.89; 95% CI 0.6, 1.17) were associated with significantly higher ISOGTT values.

Adiponectin: Two studies (107 participants) were pooled for the analysis of serum adiponectin (Electronic Supplementary Fig. 46). Compared to placebo, metformin (WMD: 1.9; 95% CI 0.23, 3.57) and GLP-1 RAs/metformin (WMD: 2.2; 95% CI 0.54, 3.86) were associated with an elevated adiponectin level.

Apolipoproteins A and B1, and Lp (a): Two each assessed apolipoproteins A and B1 and one study assessed Lp (a) levels due to which pooled analyses could not be performed.

Grading the strength of evidence

The strength of evidence is very low limited mainly by the precision of estimates, risk of bias and potential publication bias of the included studies (Electronic Supplementary Table 3).

Assessment of clinical trials registered in clinicaltrials.gov

The search strategy led to 934 registered clinical trials of which 32 met the criteria relating to either GLP-1 RAs or SGLT2is in PCOS management (Electronic Supplementary Table 2). The studies range from phase I to IV, with sample sizes varying from 30 to 890 participants, predominantly involving adult populations. Primary outcomes frequently focus on weight loss, metabolic parameters (including insulin resistance), and reproductive function (menstrual cyclicity, ovulation, and pregnancy rates). The most studied GLP-1 RAs include semaglutide, liraglutide, and exenatide, while dapagliflozin, empagliflozin, and canagliflozin are the main SGLT2is under investigation. Most trials combine these agents with metformin and feature treatment durations ranging from 3 to 14 months. The studies are predominantly open-label, randomized trials conducted across multiple countries including China, USA, UK, Egypt, and Slovenia. Secondary outcomes commonly assess changes in hormonal parameters (androgens, FSH, LH), metabolic markers (glucose, insulin, lipids), body composition, and quality of life measures. Several trials also intend to evaluate pregnancy outcomes and safety parameters, reflecting the comprehensive approach to understanding these agents'effects in PCOS management.

Assessment of GLP-1 RAs and SGLT2is in PCOS animal models

A summary (Table 2) of evidence relating to the use of SGLT2is and GLP-1 RAs in animal models of PCOS revealed that majority of the studies used rat models (primarily Sprague Dawley and Wistar rats) followed by C57BL/6 J mice. PCOS was induced through various methods: dihydrotestosterone pellet implantation, DHEA subcutaneous injection, letrozole administration, estradiol valerate injection, and estradiol intramuscular injection. The studies identified the following effects relating to the therapeutic effects of GLP-1 RAs in PCOS animal models: metabolic effects (reduced body weight, improved insulin sensitivity, decreased HOMA-IR, and improved glucose tolerance), hormonal regulation (decreased testosterone, LH/FSH ratio, and increased SHBG) and ovarian effects (reduced cystic follicles, increased corpus luteum formation, and restored regular estrous cycles). The following molecular pathways were explored and identified for GLP-1 RAs effects: increased expression of adenosine mono phosphate-activated protein kinase alpha subunit (AMPK-α), Silent information regulator 1 (SIRT1) and ferredoxin-reducing (FDX) proteins; enhanced phosphatidylinositol 3-kinase/protein kinase B (PI3 K/AKT) signaling in ovarian cells; reduced inflammatory markers [IL-6, TNF-α, toll-like receptor-4 (TLR4), nuclear factor kappa B (NF-κB)]; increased anti-inflammatory markers (IL-10); modified steroidogenic enzyme expression [steroidogenic acute regulatory protein (STAR), CYP17 A1)]; and improved adipokine profile.

For SGLT2is, the following effects were observed in the animal models: metabolic improvements (reduced body weight, improved glucose metabolism, and insulin sensitivity), hormonal effects (decreased testosterone, LH, FSH, and increased estradiol), reduced visceral fat accumulation, and ovarian effects (decreased cystic follicles,

Table 2 Summaries of preclinical studies exploring SGLT-2is and GLP-1 RAs in animal models of PCOS

Study ID	Animal model	Intervention	Control	Key findings of interest
Hoang 2015 [57]	Prepubertal female Sprague Dawley rats implanted SC with DHT pellet	Liraglutide 0.2 mg/kg twice daily SC for 4 weeks (n = 15)	Saline injections twice daily for 4 weeks (n = 16)	• Significant reduction in body weight (Intervention: 276.25 ± 2.7 g; and control: 294.75 ± 3.2 g), abdominal adipose tissue mass, blood glucose, glucose surge with OGTT, total cholesterol, SBP, night-time DBP, and MAP with liraglutide compared to saline • No significant changes were observed in daytime DBP
Koksal 2020 [58]	21-day-old Sprague Dawley rats with DHEA SC injection	Exendin-4 10 µg/kg/day IP alone (n = 9) and with stress (n = 10) for 4 weeks	Stress (n = 10) No intervention (n = 10) for 4 weeks	• Significant reductions in body weight (Intervention: 179.3 ± 6.3 g; intervention with stress: 193.9 ± 3 g; and no intervention: 207 ± 9.3 g), LH/FSH (Intervention: 1.43 ± 0.1; intervention with stress: 1.5 ± 0.2; and no intervention: 2.36 ± 0.3), and HOMA-IR (Intervention: 1.37 ± 0.12; intervention with stress: 1.87 ± 0.35; and no intervention: 2.08 ± 0.31) • All animals in all these groups completed estrous cycles by 10 th day
Liu 2024 [59]	Female C57BL/6 J mice injected SC with DHEA	Semaglutide 0.42 mg/kg/week (n = 6) and 0.84 mg/kg/week (n = 6) for 28 days	No treatment for 28 days	• Significant reductions in body weight, insulin resistance, testosterone • Significant increase in estrogen and progesterone levels, and increased STAR and CYP17 A1 in ovaries • Improved the expression of pAMPK and SIRT1 and inhibited the expression of pIκBα and nuclear factor- κB

Table 2 (continued)

Study ID	Animal model	Intervention	Control	Key findings of interest
Saad 2020 [60]	Rat by letrozole oral route	Liraglutide 200 µg/kg/day for 30 days IP (n = 14)	Vehicle of liraglutide injection for 30 days (n = 14)	• Significant reductions in NICD (40%) and Hes-1 (39.8%) proteins, *JNK* (46%) and *Presenelin-1* (64.5%) gene expressions, and Aβ secretase (38%), γ secretase (39%), AchE (66%) were observed with liraglutide compared to control group in hippocampus • Significant reductions of serum testosterone (65%) and insulin (71%) were observed with liraglutide compared to control group • Significant improvement in memory was observed with liraglutide • Liraglutide treatment resulted in change of menstrual cycle of rats to estrous phase unlike control group that had proestrus phase • Liraglutide treatment resulted in the presence of normal histological structure in different stages of follicular maturation with detection of multiple corpus luteum formation at the cortex

Table 2 (continued)

Study ID	Animal model	Intervention	Control	Key findings of interest
Singh 2019 [61]	Pre-pubertal female Parkes strain mice induced by DHEA (In vivo) and 3T3-L1 pre-adipocytes (In vitro)	In vivo: Liraglutide (at 100 and 200 µg/kg/day) twice daily for 14 days In vitro: Liraglutide added to the culture medium at 10 and 100 nM concentrations	Vehicle (sesame oil and ethanol) daily	• Liraglutide resulted in 76% up-regulation in adiponectin and 55% down-regulation in ICAM-1, promote adipogenesis, triggers glucose uptake, increased expression of PPAR-γ and C/EBPα in pre-adipocytes compared to control • Liraglutide significantly decreased body mass, serum glucose, triglycerides, testosterone, adiponectin and estradiol • Liraglutide increased the numbers of healthy follicles and decreased the numbers of cystic follicles, and oocytes and corpora lutea were normal and healthy • Liraglutide (100 µg/kg/day) showed acyclic estrous cycle that was long followed by normal cycle while high dose (200 µg/kg/day) were observed with short acyclic period with two normal cycles • Liraglutide (100 µg/kg/day) showed moderate GLTU4 protein while high dose (200 µg/kg/day) was observed with absent GLUT4 protein • Liraglutide increased expression of PI3 K and Akt in thecal and granulosa cells of ovary compared to control group
Sun 2016 [62]	Female Sprague Dawley rats induced by DHEA SC injection	Exenatide (10 µg/kg/d) SC (n = 10) for 4 weeks	Metformin (265 mg/kg/d) (n = 10) and saline (n = 10) for 4 weeks	• Exenatide and metformin resulted in significant reduction of body weight • Exenatide and metformin significantly decreased testosterone, LH, LH/FSH ratio, fasting insulin, fasting glucose while increased FSH and SHBG compared to control group • Exenatide only slightly decreased HOMA-IR while metformin significantly reduced it • Exenatide significantly reduced LDL, Lp-a and TC but not TG and HDL compared to control group • Exenatide and metformin significantly reduced IL-6, PEDF and visfatin compared to control group but not TNF-α

Table 2 (continued)

Study ID	Animal model	Intervention	Control	Key findings of interest
Tao 2015 [63]	Female Sprague Dawley rats induced by DHEA by SC injection	Exenatide (10 µg/kg/d) SC (n = 10)	Metformin (300 mg/kg/d) (n = 10) and control group (n = 10)	• Exenatide and metformin significantly increased the expression of SIRT1 compared to control group
Tao 2019 [64]	Female Sprague Dawley rats induced by DHEA by SC injection	Exenatide (10 µg/kg/d) SC (n = 11) for 4 weeks	Metformin (300 mg/kg/d) (n = 11) and sterile water group (n = 10) for 4 weeks	• Exenatide significantly reduced body weight, and testosterone • Exenatide significantly improved insulin sensitivity and HOMA-IR • Exenatide significantly increased the expression of AMPKα and SIRT1 proteins
Torres Fernandez 2019 [65]	Female Sprague Dawley rats induced by SC by DHT and were evaluated at 17 months for postmenopausal PCOS	Liraglutide (0.3 mg/kg/day) SC for 21 days	Saline for 21 days	• Liraglutide significantly reduced food intake, body weight and abdominal circumference • Liraglutide significantly reduced HOMA-IR, leptin, total cholesterol, LDL, HDL and TG compared to control group • Liraglutide did not affect plasma DHT levels, angiotensinogen mRNA expression in renal cortex and medulla • Liraglutide significantly lowered mRNA expression of renin, ACE, mineralocorticoid receptor and AT1R • Liraglutide decreased MAP and increased heart rate
Vatankhah 2024 [66]	Wistar female rats induced by intramuscular estradiol	Exenatide (50 and 100 µg/kg/day) for 30 days	Control group received vehicle for 30 days	• Exenatide at both doses significantly decreased the mRNA expression of adiponectin compared to control group
Wu 2021 [67]	Female Sprague Dawley rats induced by DHEA by SC injection	Dulaglutide (50, 150 and 400 µg/kg/day) SC once a week for 3 weeks (n = 10 each)	Normal saline once a week for 3 weeks (n = 10)	• Dulaglutide (150 and 400 µg/kg/day) were associated with significant reduction in body weight, cystic follicles in ovaries and significant increase in corpus luteum • Dulaglutide at all doses significantly reduced ovarian insulin content, serum testosterone, and preantral follicles, and increase in SHBG • No significant differences were observed with HOMA-IR, blood glucose and fasting insulin compared to control

Table 2 (continued)

Study ID	Animal model	Intervention	Control	Key findings of interest
Xing 2021 [68]	Female Sprague Dawley rats induced by oral letrozole	Exenatide (10 µg/kg/d) SC (n = 6) for 3 weeks	Metformin (300 mg/kg/day) (n = 6) and saline (n = 6) for 3 weeks	• Metformin and exenatide significantly reduced body weight, blood glucose, insulin, HOMA-IR, testosterone, FAI and cystic ovarian follicles • Metformin and exenatide significantly increased the expression of PI3 K and AKT, granular thecal cells in ovaries • 83.3% of rats in the exenatide-treated group and 67.7% of those in the metformin-treated group recovered their regular estrous cycle • Exenatide and metformin significantly reduced liver expression of triglycerides, SHBG and NHF-4α
Xiong 2024 [69]	Female C57BL/6 J mice induced by DHEA	Liraglutide (0.3 mg/kg/day) IP for 4 weeks	Semaglutide (0.1 mg/kg/three times a week) IP for 4 weeks	• Liraglutide and semaglutide changed the abnormal microbiota (increasing the ratio of Bacillota to Bacteroidota, reducing the specific bacteria enriched in the PCOS group and enriching the relative abundance of Lactobacillaceae and other probiotics) compared to control group • Semaglutide altered the gut microbiota composition mainly through enriching the relative abundance of the phylum Campylobacterota, the family Helicobacteraceae, the genus Helicobacter, and the species Alistipes muris

Table 2 (continued)

Study ID	Animal model	Intervention	Control	Key findings of interest
Zhang 2023 [70]	Female C57BL/6 J mice induced by DHEA	Liraglutide (0.3 mg/kg/day) and semaglutide (0.1 mg/kg/three times weekly) for 4 weeks	Normal saline for 4 weeks	• Liraglutide and semaglutide increased the quantity of corpus luteum, decreased the quantity of cystic follicles, reduced mRNA of STAR, CYP11 A1, CYP17 A1, HSD3B, and HSD17B and iNOS while increasing CYP19 A1 and ARG1 • Liraglutide and semaglutide significantly reduced IL-1b, IL-6, TNF, Ccl2 while increased IL10 expressions • Liraglutide and semaglutide decreased serum IL-6, TLR4, NF-κB, increased IL-10 • Liraglutide and semaglutide significantly decreased the Cleaved-Caspase 3 protein levels • Liraglutide and semaglutide significantly reduced serum testosterone and FAI without altering SHBG, and reduced LH levels and LH/FSH ratio • Liraglutide and semaglutide also reduced macrophage infiltration in the ovaries • Liraglutide and semaglutide significantly increased the expressions of uncoupling protein1,deiodinase, iodothyronine, type II deiodinase, and peroxisome proliferative activated receptor, gamma,coactivator 1 alpha
Yuan 2022 [71]	Female Sprague Dawley rats induced by DHEA by SC injection	Exenatide 10 µg/kg/day for 4 weeks	Metformin 300 mg/kg/day for 4 weeks to one group and normal diet to another group	• Exenatide and metformin significantly increased the GIR, GRd, HGP, BMP-9 and suppression of HGP • Exenatide and metformin significantly increased the number of granulosa cells in ovaries

Table 2 (continued)

Study ID	Animal model	Intervention	Control	Key findings of interest
Mahmoud 2023 [72]	Female Wistar rats induced by letrozole	Empagliflozin 10 mg/kg/day orally for 28 days to one group; Empagliflozin 10 mg/kg/day with metformin 300 mg/kg/day orally for 28 days and Metformin 300 mg/kg/day orally for 28 days to another group	Distilled water (control group) to one group and PCOS was not induced in another control group	• Empagliflozin, metformin and their combination resulted in elevated insulin, glucose levels, and the HOMA-IR and reduced total cholesterol, LDL, triglycerides and elevated HDL • Empagliflozin, metformin and their combination resulted in significant lowering of testosterone, LH and FSH, and elevated estradiol • Empagliflozin, metformin and their combination significantly lowered IL-6 and TNF-α • Empagliflozin, metformin and their combination showed a significant improvement in the relative expression of AMPKα and lowered SIRT1 expression in ovarian tissue • Empagliflozin, metformin and their combination resulted in reduction in the size and number of ovarian cystic follicles with increase in the granulosa cell layer thickness. The combination treatment led to restoration of the follicular growth and maturation into different stages with significant increase in the number of the mature ovarian follicles and corpora lutea

Table 2 (continued)

Study ID	Animal model	Intervention	Control	Key findings of interest
Rakic 2024 [73]	Wistar rats induced PCOS by estradiol valerate	Empagliflozin at doses of 5, 15 and 45 mg/kg to each group and metformin 500 mg/kg to another group for 28 days	Distilled water for 28 days	• Empagliflozin (15 and 45 mg/kg) and metformin significantly reduced body weight • Empagliflozin and metformin treatment resulted in resumption of regular estrous cycle • Empagliflozin and metformin significantly improved blood glucose and SBP while only empagliflozin (15 mg/kg) significantly reduced DBP • Empagliflozin and metformin treatment lowered hydrogen peroxide while all except empagliflozin (5 mg/kg) significantly reduced malondialdehyde • Empagliflozin (45 mg/kg) and metformin significantly increased SOD activity • Empagliflozin and metformin significantly increased catalase • Empagliflozin (15 and 45 mg/kg) and metformin significantly increased GSH, lowered estradiol, progesterone and lowered testosterone • Only metformin significantly lowered LH and FSH • Empagliflozin (15 and 45 mg/kg) and metformin significantly increased the number of corpora lutea and all treatments were observed with reduced number of cystic follicles • Empagliflozin increased the number of secondary follicles and reduced the numbers of atretic follicles • Empagliflozin and metformin also reduced the visceral fat area and diameter

Table 2 (continued)

Study ID	Animal model	Intervention	Control	Key findings of interest
Ji 2024 [74]	Female Sprague–Dawley rats induced PCOS by DHEA	Liraglutide (210 μg/kg/day) SC to one group and combined liraglutide and metformin to another group	Metformin (210 mg/kg/day) to one group and soybean oil injection to another group	• Liraglutide, metformin and their combination increased the expression of FDX1, and lowered expressions of CYP11 A1 and CYP19 A1 • Liraglutide, metformin and their combination restored estrous cycle, an increase in the number of ovarian corpus luteum and number of normal follicles, a decrease in the number of empty and atretic follicles • Liraglutide, metformin and their combination lowered LH/FSH levels,

SC: Subcutaneous; DHT; dihydrotestosterone; OGTT: oral glucose tolerance test; SBP: systolic blood pressure; MAP: mean arterial pressure; DBP: diastolic blood pressure; DHEA: dehydroepiandrosterone; IP: intraperitoneally; HOMA-IR: Homeostatic model assessment for insulin resistance; CYP: Cytochrome P450; STAR: Steroidogenic acute regulatory protein; NICD: Notch intracellular signaling domain protein; Hes-1: Hairy/enhancer of split-1 protein; JNK: c-Jun N-terminal kinase; AchE: Acetylcholinesterase; ICAM-1: intercellular adhesion molecule-1; GLUT4: Glucose transporter 4; PI3 K: phosphatidylinositol 3-kinase; AKT: Protein kinase B; LH: luteinizing hormone; FSH: follicle-stimulating hormone; SHBG: sex hormone binding globulin; LDL: low-density lipoprotein; Lp-a: lipoprotein a; TC: Total cholesterol; HDL: High density lipoprotein; IL-6: Interleukin 6; PEDF: Pigment epithelium-derived factor; TNF-α: Tumor necrosis factor alpha; SIRT1: Silent information regulator 1 protein; AMPKα: AMP-activated protein kinase alpha subunit; ACE: Angiotensin converting enzyme; MAP: Mean arterial pressure; AT1R: Angiotensin II receptor type 1; FAI: Free androgen index; HNF-α: Hypoxic necrosis factor alpha; HSD3B: hydroxy-delta-5-steroid dehydrogenase 3 beta; HSD17B: hydroxysteroid 17-beta; IL: interleukins; Ccl2: Chemokine (C–C motif) ligand 2; iNOS:; inhibitory nitric oxide synthase; and ARG1: arginase 1; SOD: Superoxide dismutase; GSH: Glutathione; GIR: Glucose infusion rate; GRd: Glucose disappearance rate; HGP: Hepatic glucose production; BMP-9: Bone morphogenic protein 9; and FDX1: Ferridoxin-reducing protein

increased corpus luteum formation, and improved follicular development). The following molecular pathways were explored and identified for SGLT2is efficacy in PCOS animal models: enhanced AMPKα expression; reduced inflammatory markers (IL-6, TNF-α); reduced expression of endothelial adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin, and improved oxidative stress markers (increased superoxide dismutase, catalase, and reduced glutathione).

Discussion

Key findings

This comprehensive meta-analysis, including 27 RCTs, reveals that both GLP-1 RAs and SGLT2is demonstrate significant efficacy in managing PCOS, particularly in improving anthropometric and metabolic parameters. GLP-1 RAs (alone and in combination with metformin) were observed to improve menstrual frequencies. GLP-1 RAs showed significant reductions in all anthropometric parameters, while SGLT2is was observed to improve WHR and AGF ratio (in addition to reduced body weight observed with SGLT2is/metformin combination). Reductions in WHR and AGF were better with SGLT2is compared to GLP-1 RAs. The combination of GLP-1 RAs and SGLT2is was observed to have superior efficacy in reducing body weight, percent fat mass, and AGF ratio compared to GLP-1 RAs alone. Regarding hormonal parameters, GLP-1 RAs were observed with significant improvement in FAI, free testosterone, androstenedione, and SHBG levels. SGLT2is was observed with significant improvements in FAI and total testosterone, outperforming GLP-1 RAs in reducing these parameters. The combination of GLP-1 RAs and metformin significantly improved total testosterone, androstenedione, luteinizing hormone, and estradiol levels. Regarding metabolic parameters, GLP-1 RAs significantly improved triglycerides, markers of insulin resistance (HOMA-IR, two-hour insulin, ISSI and ISOGTT), and fasting and postprandial plasma glucose. SGLT2is was associated with significant improvements in HOMA-IR and fasting plasma glucose, and in combination with metformin, SGLT2is significantly improved triglycerides. SGLT2is outperformed GLP-1 RAs in reducing LDL cholesterol and HOMA-IR, while GLP-1 RAs were observed with higher ISSI values compared to SGLT2is/metformin. The combination of SGLT2is and GLP-1 RAs was better than GLP-1 RAs in reducing triglycerides and fasting plasma glucose. However, the strength of evidence for these findings was either low or very low. Assessment of ongoing clinical trials registered on ClinicalTrials.gov revealed that a considerable number are focusing on clinical parameters, including pregnancy outcomes, and most are in combination with metformin. Systematic assessment of animal studies revealed a potential association of several molecular pathways, including AMPK-α, SIRT1, FDX, PI3 K/AKT, endothelial adhesion molecules (VCAM, ICAM, and E-selectin), STAR, and CYP17 A1, with the therapeutic effects of GLP-1 RAs and SGLT2is in PCOS. Both drug classes were associated with significant improvements in ovarian morphology in animal studies.

Comparison with existing literature

This network meta-analysis has identified that GLP-1 RAs, SGLT2is, and their combination (also individually with metformin) were associated with significant improvements in various metabolic, hormonal, and anthropometric parameters in PCOS. Amongst similar reviews, Kesavan et al. [75] observed in six clinical trials that the GLP-1 RA exenatide was significantly associated with a reduction in BMI and testosterone compared to metformin. Austregésilo de Athayde De Hollanda Morais et al. [76] reported in four trials (176 participants) that the GLP-1 RAs semaglutide and liraglutide were associated with significant reductions in waist circumference, BMI, triglycerides, and total testosterone. Regarding SGLT2is, only one meta-analysis exists for their indication in PCOS. Sinha et al. [16] pooled data from four trials (158 participants) and observed a reduction in body weight, fasting plasma glucose, and insulin resistance. All these previous meta-analyses were limited by a small number of study participants and only compared the interventions to placebo or metformin, without a comprehensive inclusion of clinical outcomes. In contrast, the present meta-analysis is the first to directly compare the effects of GLP-1 RAs and SGLT2is, both alone and in combination with metformin, on a wide range of outcomes in PCOS. The results of our meta-analysis are in concordance with the previous reviews regarding the anthropometric, metabolic, and hormonal outcomes. Additionally, the present meta-analysis included both change-from-baseline values and post-interventional values, which was not the case in previous meta-analyses, leading to their smaller sample sizes. Furthermore, we also explored the effects of GLP-1 RAs on clinical outcomes, which was limited in previous reviews. The only other meta-analysis that examined the effect of GLP-1 RAs on clinical parameters was Ye et al. [77], who included nine clinical trials (785 participants) and observed a significant reduction in BMI, insulin resistance, and improvement in pregnancy and ovulation rates. However, the authors included unpublished data from gray literature in Chinese, which is not accessible to individuals outside China. The only other meta-analysis comparing all the key outcome measures in PCOS was by Kamrul-Hasan

et al. [78] that assessed the effects of SGLT2is in PCOS. The published study and our meta-analysis share several similarities in their findings regarding the effects of SGLT2is and GLP-1 RAs on metabolic and hormonal parameters in patients with PCOS. Both studies observed that SGLT2is improve insulin resistance, as evidenced by reductions in HOMA-IR and fasting plasma glucose, and noted favorable changes in body composition, including reductions in body weight and fat distribution. Additionally, both studies reported that combining SGLT2is with other therapies (metformin or GLP-1 RAs) enhances efficacy, with the published study highlighting benefits in metabolic parameters with SGLT2i-GLP1RA combinations and our study further demonstrating superior reductions in fat mass and triglycerides with this combination. However, key differences emerge in the scope and specific outcomes. While the published study focused primarily on SGLT2is and reported improvements in DHEAS and menstrual irregularity, our meta-analysis included a broader range of interventions (GLP-1 RAs alone and in combination) and found more pronounced hormonal benefits, such as significant reductions in FAI and testosterone with SGLT2is, outperforming GLP-1 RAs in these aspects. Our study also highlighted that GLP-1 RAs alone improved menstrual frequency and androgen-related markers more than SGLT2is, whereas the published study did not extensively compare GLP-1 RAs but primarily included only studies that have assessed SGLT2is. Secondly, the published study assessed only change-from-baseline values while we evaluated both the change-from-baseline and post-interventional values. Additionally, our findings emphasized that SGLT2is were more effective than GLP-1 RAs in reducing LDL cholesterol and HOMA-IR, while GLP-1 RAs had stronger effects on postprandial glucose and triglycerides. These differences suggest that while both drug classes are beneficial, their comparative advantages depend on the specific clinical outcomes of interest.

The present study is the first to compare SGLT2is and GLP-1 RAs through a common comparator (placebo/metformin) for PCOS. The only other network meta-analysis in PCOS treatment was from Peng et al. [79], which compared metformin, clomifene citrate, and pioglitazone, but did not include emerging drug therapies such as GLP-1 RAs and SGLT2is. The results from the present meta-analysis provide evidence for trialing GLP-1 RAs and SGLT2is for improving therapeutic outcomes in PCOS. This recommendation is also supported by the findings from the preclinical studies included in this review, which demonstrate that both GLP-1 RAs and SGLT2is work through multiple complementary mechanisms, affecting metabolic, hormonal, and inflammatory pathways in PCOS. The studies suggest these agents may provide therapeutic benefits beyond their primary metabolic effects, directly influencing ovarian function and steroidogenesis through various molecular pathways.

Given the potential cost implications, GLP-1 RAs and SGLT2is could be considered as second-line options in case of failure of first-line drugs (metformin, pioglitazone, and clomifene citrate), as the latter are likely to be much cheaper. Although in some outcomes, GLP-1 RAs and SGLT2is outperformed metformin, considering the low strength of evidence, we would recommend GLP-1 RAs and SGLT2is as second-line drugs for PCOS. Combinations of GLP-1 RAs and SGLT2is with metformin were observed to have better therapeutic effects compared to individual drug classes. Therefore, in patients with an insufficient response to metformin, it is preferred to use these drug classes as add-on to metformin, rather than shifting to GLP-1 RAs/SGLT2is alone. Further, between GLP-1 RAs and SGLT2is, studies indicate better cardiovascular and renal protection with SGLT2is, but reduced thromboembolic events favor GLP-1 RAs [80, 81]. Given the increased cardiovascular and renal risk associated with PCOS [82], the combination of SGLT2is and GLP-1 RAs may provide superior outcomes, as supported by population-based data [83]. However, more evidence is required to draw robust conclusions on the optimal combination therapy in PCOS.

Strengths, limitations and way forward

This is the first systematic review and meta-analysis that comprehensively compares the therapeutic effects of GLP-1 RAs and SGLT2is, as well as their combinations, on anthropometric, metabolic, hormonal, and clinical parameters in PCOS. Through network meta-analysis, we were able to compare the effect estimates between GLP-1 RAs and SGLT2is on most outcomes, despite the absence of head-to-head clinical trials. This approach is particularly advantageous as it can provide the necessary effect estimates without the need for several years and resources to obtain them through real-world data in PCOS. Furthermore, we comprehensively reviewed the registered ongoing clinical trials and animal studies that have explored the potential molecular mechanistic pathways related to the therapeutic effects of SGLT2is and GLP-1 RAs in PCOS. This provides valuable insights into the current research landscape and the underlying mechanisms that may contribute to the observed clinical benefits.

The study is limited by the small number of studies evaluating clinical outcomes, with none for SGLT2is. This

precluded the ability to perform intra-class comparisons. Additionally, the dose–effect relationship was not assessed, and the follow-up duration of the included studies was relatively short, with most lasting up to 14 months.

Going forward, several key considerations should be addressed to further expand our understanding and optimize the use of GLP-1 RAs and SGLT2is in PCOS: Longer-term studies: The current trials have relatively short durations, necessitating the need for longer-term studies to assess the sustained efficacy and safety of these interventions in PCOS. Standardization of outcome measures and reporting: Outcome measures and reporting methods should be standardized across studies to facilitate better comparison and interpretation of the results. This should include the incorporation of pregnancy outcomes and patient-oriented outcomes, such as quality-of-life measures, to better inform clinical decision-making. Inclusion of diverse populations: Future studies should aim to include more diverse populations, particularly in terms of age and ethnic groups, to ensure the generalizability of the findings. Head-to-head trials of treatment combinations: More head-to-head trials comparing different drug combinations would help establish optimal treatment algorithms in PCOS, which is characterized by a multi-system abnormality affecting multiple systems. Cost-effectiveness evaluation: Given the relatively recent development and potential higher cost of GLP-1 RAs and SGLT2is compared to traditional treatments, such as metformin, evaluating the cost-effectiveness of various treatment options is crucial for prioritizing in healthcare settings. Predictive biomarkers: Further evidence should emerge in identifying predictive biomarkers that could help identify which patients are most likely to benefit from GLP-1 RAs and SGLT2is, and their combination, in the management of PCOS.

By addressing these limitations and incorporating the suggested directions for future research, the scientific community can build upon the findings of this comprehensive meta-analysis to inform and optimize the clinical management of PCOS using GLP-1 RAs and SGLT2is, ultimately improving the health outcomes for individuals affected by this complex and multifaceted condition.

Conclusion

This systematic review and meta-analysis demonstrated that both GLP-1 RAs and SGLT2is effectively reduce BMI and body weight in PCOS patients. SGLT2is showed superior outcomes in waist-to-hip ratio, hormonal parameters (FAI and testosterone levels), HOMA-IR, and fasting glucose levels. GLP-1 RAs demonstrated consistent benefits in weight reduction and glycemic control. The combination therapy exhibited enhanced efficacy compared to monotherapy across multiple parameters, suggesting complementary mechanisms of action. These findings support the therapeutic potential of both drug classes, individually or combined, in PCOS management, providing a foundation for more personalized treatment approaches.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01730-8.

Supplementary material 1

Acknowledgements
We wish to sincerely acknowledge Claude-Instant for improving the language clarity and grammar in this manuscript.

Author contributions
KS: Conceived the idea; KS and GS: Data curation, analysis and interpretation; KS: Wrote the first draft of the manuscript; and KS and GS: Involved in critical revisions and final acceptance of the manuscript. The authors confirm that we have substantially contributed to the conception and design of the review article and interpreting the relevant literature and have been involved in writing the review article and revising it for intellectual content.

Funding
This paper was not funded.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pharmacology & Therapeutics, College of Medicine & Health Sciences, Arabian Gulf University, Manama, Kingdom of Bahrain. [2]Bahrain Defence Force Royal Medical Services, Riffa, Kingdom of Bahrain.

Received: 10 February 2025 Accepted: 6 May 2025
Published online: 24 May 2025

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