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Efficacy of canagliflozin versus metformin in women with polycystic ovary syndrome: A randomized, open-label, noninferiority trial

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Abstract

Objectives: To determine the safety and efficacy of canagliflozin in comparison to metformin in polycystic ovary syndrome (PCOS) patients with insulin resistance (IR).

Methods: A single-centre, prospective, randomized open-label (ratio 1:1) noninferiority trial was conducted at the Department of Endocrinology, Shanghai Tenth People's Hospital, between July 2019 and April 2021. Women aged 18 to 45 years with PCOS and IR were enrolled and randomly assigned to either 100 mg (n = 33) canagliflozin daily or 1500 to 2000 mg metformin daily (n = 35) for 12 weeks. The primary outcome was changes in homeostatic model assessment (HOMA)-IR after 12 weeks of treatment. The secondary outcomes included changes in anthropometric measurements, menstrual frequency, sex hormone levels, metabolic variables and body fat distribution.

Results: For lowering of HOMA-IR after 12 weeks of treatment, canagliflozin was found to be noninferior to metformin (least-squares mean difference −0.81% [95% confidence interval −2.13 to 0.51]). Both canagliflozin and metformin significantly improved menstrual pattern, reduced body weight and total fat mass, and decreased triglyceride levels. Compared with metformin, canagliflozin had significant advantages in reducing uric acid and dehydroepiandrosterone sulphate levels. Pruritus vulvae (9.09%) and gastrointestinal reaction (55.55%) were the main adverse events in the metformin group and canagliflozin group, respectively.

Conclusion: This study demonstrates that canagliflozin was not inferior to metformin in PCOS patients with IR, which suggests that sodium-glucose cotransporter-2 inhibitors should be considered as effective drugs in the treatment of PCOS patients with IR.

KEYWORDS
polycystic ovary syndrome, insulin resistance, sodium-glucose cotransporter-2 inhibitor, canagliflozin

* Meili Cai, Xiaowen Shao and Feng Xing contributed equally to this study.

1 | INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common reproductive endocrine disease in women of childbearing age, characterized by hyperandrogenism, chronic anovulation, and polycystic ovaries.[1] Often, the disease is associated with insulin resistance (IR) and other metabolic abnormalities, which are risk factors for developing type 2 diabetes mellitus (T2DM), cardiovascular disease and metabolic syndrome in the long term.[2,3] Although treatment of PCOS primarily involves the use of contraceptives containing oestrogen and progesterone, some contraceptives are harmful to lipid profiles and might increase the risk of thrombosis and cardiovascular disease.[4,5]

Insulin resistance affects 50% to 80% of women with PCOS, depending on the population and diagnostic method used,[2,3] and plays an intrinsic role in the pathogenesis of PCOS, independently of obesity.[6,7] Previous studies have demonstrated that IR may bring about hyperandrogenaemia by disrupting the hypothalamic-pituitary-ovarian axis, stimulating the secretion of ovarian androgens, and inhibiting the production of sex hormone-binding globulin (SHBG).[8] Taking insulin-sensitizing drugs, such as metformin and thiazolidinediones, could significantly increase ovulation, and reduce androgen levels in a dose-responsive manner. Thus, targeting IR is an effective strategy for the treatment of PCOS patients.

Canagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor and a low-potency sodium-glucose cotransporter-1 inhibitor, primarily acts on the reabsorption of glucose by the kidneys, which could cause excess glucose to be excreted in the urine, resulting in a decrease in blood sugar.[9] Moreover, SGLT2 inhibitors can also reduce weight, improve IR and glucose metabolism, and protect the cardiovascular system, which might be beneficial to PCOS patients.[10,11] However, limited data are available on the safety and efficacy of SGLT2 inhibitors in PCOS patients.

In the present study, we aimed to determine the safety and efficacy of canagliflozin in PCOS patients and hypothesized that canagliflozin was not inferior to metformin in PCOS patients with IR. This study will provide evidence for SGLT2 inhibitors as promising and effective drugs in the treatment of PCOS.

2 | MATERIALS AND METHODS

2.1 | Research design and patients

A randomized open-label study (ratio 1:1) was conducted in the Department of Endocrinology, Shanghai Tenth People's Hospital between July 2019 and April 2021. A total of 173 female patients were screened in this study; 68 PCOS patients with IR who were aged 18 to 45 years were finally enrolled and randomly assigned to either canagliflozin 100 mg daily (n = 33) or metformin 1500 to 2000 mg daily (n = 35) for 12 weeks (Figure 1). IR was defined as a homeostatic model assessment (HOMA)-IR score ≥ 2.5.[12] Diagnosis of PCOS was

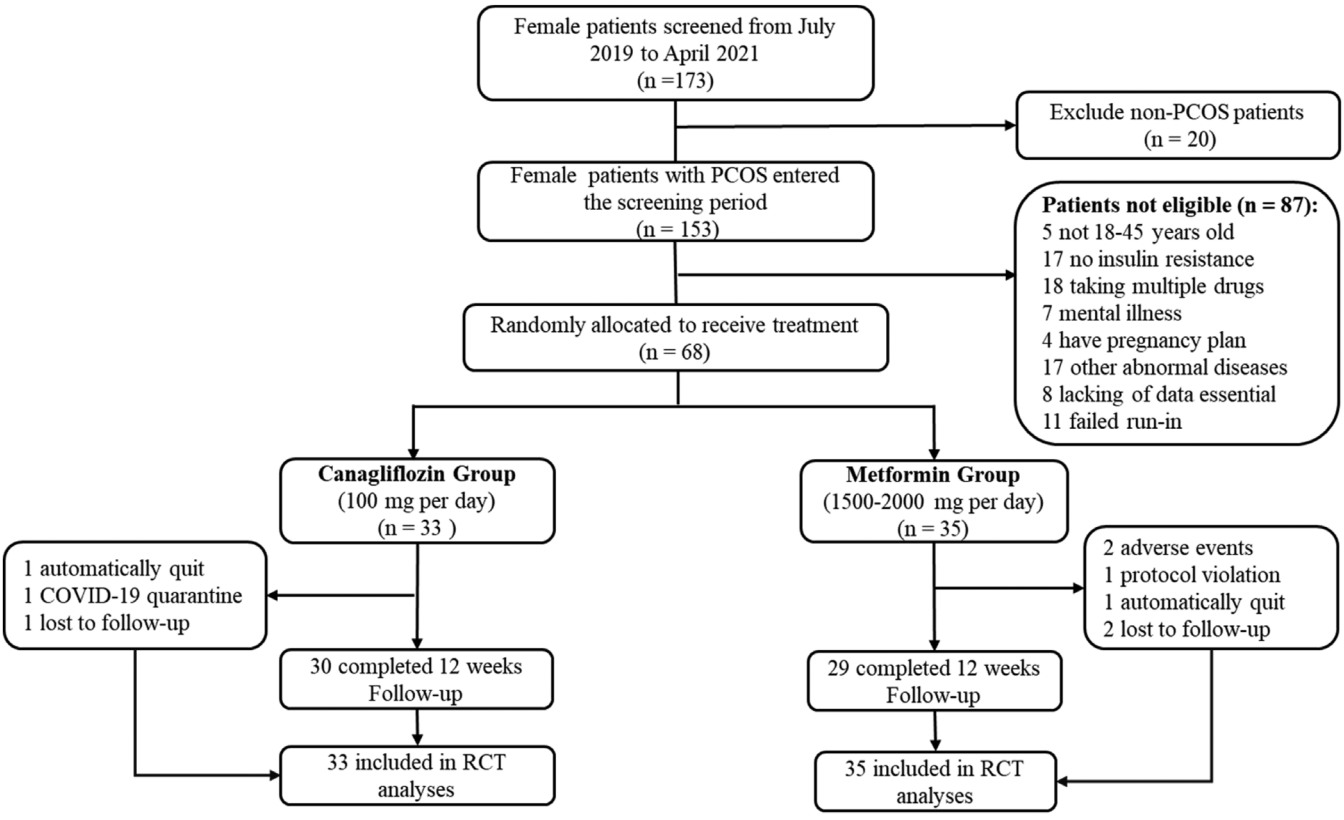


FIGURE 1 Flow diagram of this randomized, open label, non-inferiority trial. PCOS, polycystic ovary syndrome; RCT, randomized controlled trial

based on the Rotterdam diagnosis criteria (2003).[13] Exclusion criteria for PCOS patients were as follows: younger than 18 years or older than 45 years; mental illness that rendered the individual unable to provide informed consent; severe hepatic and renal dysfunction and/or heart failure; taking/having taken traditional Chinese medicine, contraceptives, SGLT2 inhibitors, metformin, glucagon-like peptide-1 or pioglitazone in the previous 3 months; current or recent participation in another clinical trial; and strong fertility needs within half a year of the study period. Key withdrawal criteria included allergic reaction or intolerance to study drugs, inability to continue according to protocol requirements, unwillingness to complete the study, or pregnancy. This study was approved by the Ethics Committee of Shanghai Tenth People's Hospital (approval number SHSY-IEC-4.1/20-263/01). Written informed consent was obtained from all participants and the clinical trial registration number was NCT04700839.

2.2 | Randomization and intervention procedures

Eligible participants were randomized, in a 1:1 ratio, to either a canagliflozin or a metformin group, using blocked randomization (block size: 6). Sequentially numbered, sealed, opaque envelopes were used for allocation concealment. Within 2 weeks prior to the initial treatment, medical history and anthropometric measurements were taken and laboratory and auxiliary examinations performed by trained specialists.

After the randomization, the participants were treated with canagliflozin or metformin for 12 weeks. The dose of canagliflozin was 100 mg per day before breakfast. Metformin was started at 500 mg twice per day, after breakfast and after dinner for the first week. If tolerated, the dose was increased to 1500 mg daily in the second week, and the recommended maximum dose was 2000 mg daily in the following weeks. All participants received counselling and education on healthy lifestyle, before randomization and periodically throughout the study. The participants were advised to use adequate contraception while receiving canagliflozin.

Outpatient follow-ups were conducted on the first day of treatment and at weeks 4, 8 and 12. Body weight, height, waist circumference, hip circumference, menstrual frequency and Ferriman-Gallwey score were recorded at all visits. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated as follows: BMI = (body weight [kg])/(height [m^2]) and WHR = (waist circumference [cm]/(hip circumference [cm]). Hirsutism was evaluated with the Ferriman-Gallwey score in each of nine locations of the body (including upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, upper arms, and thighs).[14] The number of menstrual cycles per year was defined as the number of menstruations during the last 12 months.

Blood samples were obtained from all patients the morning after at least 10 hours of overnight fasting, at baseline and at 12 weeks. Fasting plasma glucose (FPG), fasting serum insulin (FINS), glycated haemoglobin (HbA1c), creatinine, uric acid (UA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, electrolytes, and sex hormone-binding globulin (SHBG) were measured. Postprandial plasma glucose and postprandial insulin (PINS) measurements were performed using a 75-g oral glucose tolerance test, followed by examination at 120 minutes.[15] Luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, and free testosterone were obtained from Roche Diagnostics GmbH (Mannheim, Germany). The following characteristics were obtained using the associated equations: HOMA-IR = (FBG [mmol/L] × FINS [mU/L])/22.5; and HOMA-insulin sensitivity index = ln 22.5/(FPG [mmol/L] × FINS [mU/L]).[16,17]

Dual-energy X-ray absorptiometry (APEX 4.5.0.2, Hologic Inc., Marlborough, Massachusetts) was used to assess body composition of all patients at baseline and at 12 weeks. Whole-body measurements obtained included total fat mass, total lean mass, percent of total fat mass, android fat mass and visceral adipose tissue (VAT) mass. The abdominal subcutaneous adipose tissue (SAT) mass was calculated as android fat mass minus VAT mass.[18]

2.3 | Endpoints and assessments

The primary endpoint was change from baseline in HOMA-IR at week 12. The secondary endpoints included changes from baseline in anthropometric, hormonal and metabolic variables, and body fat distribution at week 12. Overall safety and tolerability were assessed based on adverse event (AE) reports, safety laboratory tests, vital sign measurements and physical examinations. The incidence rates of documented hypoglycaemia, gastrointestinal symptoms, urinary tract infections, genital mycotic infections, osmotic diuresis-related AEs and volume-related AEs were also assessed.

2.4 | Sample size estimation and statistical analysis

The sample size was calculated using the online calculator provided by the Massachusetts General Hospital Mallinckrodt General Clinical Research Center (http://hedwig.mgh.harvard.edu/sample_size/size.html). Based on previous literature, the mean reduction in HOMA-IR with metformin treatment in obese PCOS patients with hyperinsulinaemia was 2.9.[19] Noninferiority was considered if the upper bound of the 95% confidence interval (CI) for between-treatment difference (canagliflozin minus metformin) in HOMA-IR was less than 0.6 from baseline to week 12. Operating on the assumption that mean difference = 0.3, standard deviation = 1.2, alpha = 0.05, beta = 0.80, noninferiority margin = 0.6, and drop-out rate = 0.2, the sample size required for each study group was 30.

The intention-to-treat population was used to analyse the safety of canagliflozin versus metformin and the per-protocol population was used to analyse the efficacy of canagliflozin versus metformin. All statistical analyses were performed using SPSS version 25.0. We calculated least squares means and 95% CIs for mean differences between the two treatment groups. We used an analysis of covariance model, with treatment as a fixed effect and the corresponding baseline value as a covariate, to assess primary and continuous

secondary endpoints. Category variables and proportions of participants with AEs between groups were analysed using χ^2 tests or Fisher's exact test, where appropriate. A value of $P < 0.05$ was considered statistically significant.

3 | RESULTS

A total of 59 subjects (canagliflozin group: n = 30; metformin group; n = 29) completed the follow-up. The dropout rate was 17.1 % (6/35) for the metformin group and 9.09% (3/33) for the canagliflozin group (Figure 1). The majority of patients (30/35) in the metformin group reached the recommended maximum dose (2000 mg). Five out of the 35 patients in this group received a daily dose of 1500 mg and three of these patients were lost to follow-up during the trial. Demographic and baseline characteristics of the canagliflozin and metformin groups are shown in Table 1.

After 12 weeks of treatment, both canagliflozin and metformin reduced HOMA-IR (Figure 2). The least squares mean change in HOMA-IR from baseline to week 12 was −2.04 (95% CI −2.89 to −1.18) for the canagliflozin group and −1.23 (95% CI −2.15 to −0.30) for the metformin group. The upper bound of the 95% CI (0.51) was within the inferiority margin of 0.6 at week 12. In the per-protocol analysis, canagliflozin was found to be noninferior to metformin for lowering HOMA-IR. In accordance with this, HOMA-insulin sensitivity index was substantially improved from baseline to week 12 in the two groups (Figure 3).

As shown in Table 2, the canagliflozin and the metformin groups showed a similar decrease in body weight, BMI, waist circumference and hip circumference. Canagliflozin, but not metformin, appeared to significantly change HbA1c, FPG, FINS and PINS levels, from baseline. However, there were no significant differences in reduction of these endpoints, from baseline to week 12, between the two groups. The patients in the canagliflozin group had greater reductions in UA levels from baseline to week 12 than those in the metformin group. Compared with metformin, the difference in least squares mean changes was −74.95 mmol/L (95% CI −95.30 to −54.59) for canagliflozin. Both the canagliflozin and the metformin group had a similar decrease in serum triglyceride levels. Although canagliflozin was associated with an increase in LDL cholesterol, no difference in LDL cholesterol from baseline to week 12 was found between the canagliflozin and metformin groups.

At week 12, the number of menstrual cycles per year was increased compared with baseline in both the canagliflozin and the metformin group. A significant difference between the canagliflozin and the metformin group was observed in reduction of dehydroepiandrosterone sulphate (DHEAS). Compared with metformin, difference in least squares mean changes was −68.96 ug/dL (95% CI −123.36 to −11.55) for canagliflozin. However, there was no difference in changes in LH, FSH, testosterone, free testosterone, androstenedione and SHBG levels or in Ferriman-Gallwey score between the two groups from baseline to week 12. In terms of body fat distribution, the two groups had a similar decrease in percentage of total body fat, total fat mass, VAT mass and SAT mass (Table 2).

During the treatment period, the rate of AEs in the canagliflozin and metformin groups was 15.15% (5/33) and 50.55% (20/35), respectively. AE-related discontinuation rates were 2.94% (2/68) across both groups. Metformin was associated with a higher frequency of gastrointestinal symptoms than canagliflozin. Canagliflozin was associated with higher incidences of pruritus vulvae and osmotic diuresis-related AEs than metformin. Three patients had, generally mild, pruritus vulvae at approximately weeks 11 to 12. After the treatment was stopped, the adverse reactions resolved within a few days. One patient had osmotic diuresis-related AEs (increased urinary frequency). No urinary tract and genital mycotic infections or volume-related AEs were observed in the canagliflozin group. There were no differences in serum ALT, AST or creatinine levels between the canagliflozin and metformin groups (Table 3).

4 | DISCUSSION

Growing evidence indicates that PCOS patients generally have IR and that insulin sensitizers play an important role in the treatment of PCOS.[20,21] SGLT inhibitors, a new class of antidiabetic drug, could ameliorate IR and improve insulin sensitivity in T2DM patients.[11,22] However, limited data are available on the efficacy of SGLT2 inhibitors in the treatment of PCOS patients with IR. To the best of our knowledge, the present study is the first head-to-head comparison of the efficacy and safety of canagliflozin and metformin in PCOS patients with IR.

In the present study, we demonstrated that both canagliflozin and metformin can significantly improve HOMA-IR in PCOS patients with IR. The change in HOMA-IR with metformin treatment was generally in line with previous studies.[23,24] Our data indicated that canagliflozin was noninferior to metformin in terms of HOMA-IR reduction after 12 weeks of treatment. Javed et al[25] have shown that empagliflozin did not differ from metformin treatment in terms of reduction in HOMA-IR. The two drugs have different underlying mechanisms: metformin inhibits gluconeogenesis from liver glycogen in PCOS patients and increases the absorption and utilization of glucose by surrounding tissues,[26] whereas canagliflozin acts by inhibiting renal glucose reabsorption, inducing urinary glucose excretion, and delaying the rate of appearance of oral glucose.[9,27]

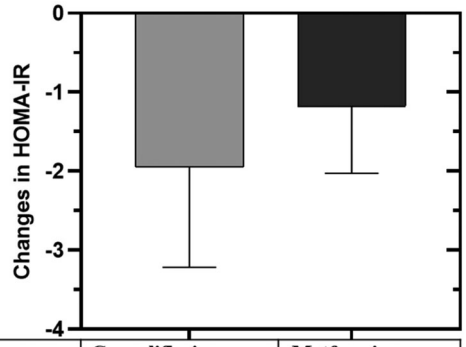
Furthermore, the present study showed that both canagliflozin and metformin monotherapy were associated with reductions in body weight and BMI, as well as waist circumference and hip circumference, in PCOS patients with IR. These findings are consistent with previous studies, which showed that taking metformin can reduce BMI in PCOS patients.[23,24] Moreover, many studies have reported that canagliflozin could achieve weight loss in T2DM by inhibiting renal glucose reabsorption, and enhancing lipolysis, fatty acid oxidation, and adipose tissue browning.[28,29] The present study data indicate that canagliflozin has the same effects on body weight in PCOS patients with IR. Consistent with previous studies, weight loss in the canagliflozin group was primarily attributable to loss of fat mass rather than lean mass.[30,31] Notably, the mean weight loss of the PCOS

TABLE 1 Comparison of anthropometric, body composition, hormonal and metabolic variables at baseline

	Canagliflozin group, Mean (95% CI) (n = 33)	Metformin group, Mean (95% CI) (n = 35)
Age (years)	28.58 (26.72 to 30.43)	27.83 (25.97 to 29.68)
Ferriman-Gallwey score	6.20 (4.62 to 7.77)	7.40 (5.91 to 8.89)
Weight (kg)	72.94 (67.89 to 77.99)	73.34 (68.40 to 78.28)
BMI (kg/m^2)	27.26 (25.55 to 28.99)	27.95 (26.22 to 29.69)
Waist circumference (cm)	92.87 (88.00 to 97.75)	92.26 (87.54 to 96.99)
Hip circumference (cm)	101.96 (98.43 to 105.49)	104.21 (100.99 to 107.43)
Waist-hip ratio	0.91 (0.88 to 0.93)	0.88 (0.86 to 0.91)
Menstrual cycles (no./year)	6.17 (4.83 to 7.51)	7.76 (6.25 to 9.27)
Ferriman-Gallwey score	6.38 (4.69 to 8.07)	7.55 (5.84 to 9.27)
HbA1c (%)	5.60 (5.37 to 5.83)	5.53 (5.39 to 5.68)
HOMA-IR	5.33 (3.92 to 6.73)	4.61 (3.42 to 5.80)
HOMA-ISI	−1.42 (−1.68 to −1.16)	−1.31 (−1.54 to −1.08)
FBG (mmol/L)	5.18 (4.99 to 5.38)	5.17 (5.00 to 5.34)
PBG (mmol/L)	7.29 (6.48 to 8.09)	7.67 (6.81 to 8.53)
FINS (mU/L)	22.58 (16.99 to 28.17)	19.57 (15.02 to 24.11)
PINS (mU/L)	158.36 (113.20 to 203.51)	149.19 (104.33 to 194.05)
ALT (U/L)	34.82 (20.89 to 48.76)	37.45 (20.76 to 54.15)
AST (U/L)	26.66 (18.66 to 34.66)	26.26 (20.05 to 32.47)
Creatinine (umol/L)	59.98 (56.41 to 63.56)	56.45 (53.59 to 59.31)
Uric acid (umol/L)	381.60 (356.00 to 407.19)	326.30 (295.16 to 357.44)
Total cholesterol (mmol/L)	4.87 (4.58 to 5.16)	4.37 (4.09 to 4.65)
Triglycerides (mmol/L)	1.75 (1.37 to 2.14)	1.41 (1.16 to 1.66)
LDL cholesterol (mmol/L)	3.04 (2.66 to 3.43)	2.64 (2.43 to 2.85)
HDL cholesterol (mmol/L)	1.33 (1.12 to 1.54)	1.17 (1.09 to 1.25)
LH (IU/L)	9.85 (7.97 to 11.73)	13.63 (9.79 to 1.47)
FSH (IU/L)	5.35 (4.64 to 6.05)	5.54 (4.79 to 6.29)
Total testosterone (ng/mL)	1.78 (1.52 to 2.05)	1.70 (1.43 to 1.96)
Free testosterone (pg/mL)	2.40 (1.92 to 2.88)	2.05 (1.47 to 2.63)
Androstenedione (ng/mL)	4.17 (3.53 to 4.81)	4.43 (3.75 to 5.11)
DHEAS (ug/dL)	261.80 (217.77 to 305.83)	242.87 (191.69 to 294.04)
SHBG (nmol/L)	33.76 (21.64 to 45.89)	40.39 (25.26 to 55.52)
Total body fat (%)	40.34 (38.73 to 41.94)	40.81 (39.19 to 42.43)
Total body lean (%)	56.43 (54.94 to 57.91)	55.69 (54.19 to 57.20)
Total fat mass (kg)	28.83 (25.72 to 31.95)	29.75 (26.58 to 32.92)
Total lean mass (kg)	39.83 (37.14 to 42.53)	39.77 (37.30 to 42.24)
SAT mass (kg)	1.69 (1.43 to 1.95)	1.75 (1.48 to 2.03)
VAT mass (kg)	0.64 (0.51 to 0.77)	0.65 (0.52 to 0.79)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; DHEAS, dehydroepiandrosterone sulphate; FBG, fasting blood glucose; FINS, fasting serum insulin; FSH, follicle-stimulating hormone; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-ISI, homeostatic model assessment insulin sensitivity index; HOMA-IR, homeostatic model assessment insulin resistance; LDL, low-density lipoprotein; LH, luteinizing hormone; PBG, postprandial blood glucose; PINS, postprandial insulin; SAT, abdominal subcutaneous adipose tissue; SHBG, sex hormone-binding globulin; VAT, visceral adipose tissue.

patients, in either the canagliflozin or the metformin group, seemed to be higher than in previous short-term trials,[32-34] which might be explained by the fact that the patients in the present study received education on healthy lifestyle and took part in regular exercise and had a balanced diet throughout the study. Although the changes in HbA1c, FPG, FINS and PINS levels from baseline to week 12 were more substantial in the canagliflozin group, there were no significant differences in the reductions in these variables between the two



Week 12 HOMA-IR	Canagliflozin group (n=30)	Metformin group (n=29)
Baseline HOMA-IR (95% CI)	5.46 (3.93 to 6.99)	4.84 (3.43 to 6.26)
Change from baseline LS mean (95% CI)	-2.05 (-2.92 to -1.18)	-1.20 (-2.15 to -0.26)
Treatment difference (Canagliflozin-Metformin) LS mean (95% CI)	-0.85 (-2.19 to 0.49)	

FIGURE 2 Changes from baseline in homeostatic model assessment of insulin resistance (HOMA-IR) at week 12. The model was assessed based on the per-protocol population, after adjusting for the possible confounders at baseline. CI, confidence interval; LS, least squares

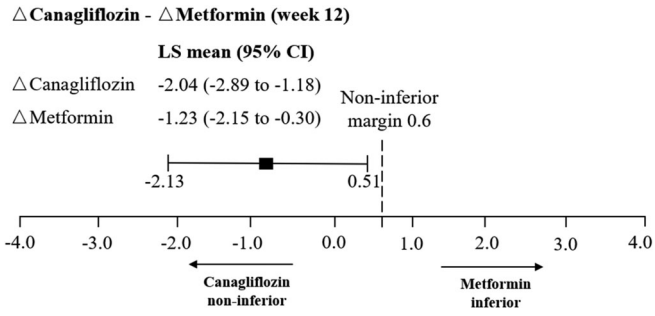


FIGURE 3 Primary outcome according to treatment group. △ indicates the changes in indicators in polycystic ovary syndrome patients before and after treatment. △Canagliflozin – △Metformin represents the difference in the primary outcome of homeostatic model assessment of insulin resistance reduction between canagliflozin group and metformin group at 12 weeks. CI, confidence interval; LS, least squares

groups, which suggest that the contribution of the differences of these variables to the primary study endpoint was limited.

In the present study, the canagliflozin group showed a greater reduction in UA levels than the metformin group, which is also consistent with previous studies.[35,36] The underlying mechanism might be associated with renal SLC2A9 transporter, which is known to exchange glucose for UA.[35,37] Thus, higher glucose concentrations in the urine could cause an increase in the exchange of glucose for UA in the apical membrane of tubular cells. Increasing evidence has shown that serum UA levels are considerably higher in patients with PCOS than in patients without PCOS and that hyperuricaemia can exacerbate insulin resistance.[38] Therefore, the decrease in UA level caused by canagliflozin in the present study may be beneficial to PCOS patients with hyperuricaemia. Studies with a larger sample size and longer duration are needed to investigate this.

It is well documented that menstrual disorders are the main clinical features of PCOS.[1] After 12 weeks of treatment, menstrual cycle status was improved, compared with baseline, in both the canagliflozin and metformin groups. The beneficial effect of metformin in improving menstrual patterns in the present study is in concordance with previous studies.[21,39] Further, our results suggest that canagliflozin could also be efficacious in improving menstrual patterns. In addition, there was a prominent decrease in DHEAS levels in the canagliflozin group. Previous studies have shown that approximately 40% to 60% of patients with PCOS have adrenal hyperandrogenism, characterized by increased DHEAS levels.[40] Therefore, our finding of decreased DHEAS levels in the canagliflozin group may be beneficial to PCOS patients with adrenal hyperandrogenism. The underlying mechanism of this decrease in DHEAS level by canagliflozin is unclear and may be associated with the decrease in UA level brought about by canagliflozin. It was reported that dehydroepiandrosterone (DHEA) might increase sodium reabsorption and reduce water excretion by activating mineralocorticoid receptors and inhibiting glucocorticoid receptors,[41] thereby reducing renal UA excretion and increasing serum UA levels. However, given that DHEA plays a protective role in obesity and has anti-atherosclerotic effects in the general population,[42] further studies are needed to clarify the impact of canagliflozin on DHEAS levels in patients with PCOS.

No significant reductions were seen in serum LH, FSH, total testosterone, free testosterone, androstenedione or Ferriman-Gallwey score in either of the two groups. These findings are in line with some studies,[43,44] but differ from other studies showing that metformin reduced total testosterone level.[24,45] The discrepancies in these findings might be attributable to differences in study populations, study durations, and drug dosages.

In terms of AEs, canagliflozin was generally well tolerated in PCOS patients with IR. After 12 weeks of treatment, there were no genital mycotic infections or urinary tract infections in the canagliflozin group. The frequency of pruritus vulvae with canagliflozin osmotic diuresis-related AEs was increased compared with metformin, which is consistent with previous reports.[46,47] In the present study, the incidence of AEs with metformin treatment was much higher than that in other trials, but is consistent with a previous study on elderly Chinese people with diabetes, which showed that 196 patients (54.3% of the study population) experienced at least one AE.[48] This phenomenon of high AE incidence in the present study may be explained by the all-female study population and the presence of comprehensive records (including temporary response) and information bias, since this study was open-label. All AEs in this study were generally self-limiting and mild.

The present study has several limitations. First, sex hormones were not measured during the menstrual period, which might have introduced a measurement bias. Second, we did not assess changes in

TABLE 2 Secondary endpoints after treatment at 12 weeks

	Canagliflozin group, LS mean (95% CI) (n = 30)	Metformin group, LS mean (95% CI) (n = 29)	Treatment difference (Canagliflozin-metformin), LS mean (95% CI)	*P values*
Weight (kg)	−2.82 (−3.97 to −1.66)	−2.68 (−3.93 to −1.43)	−0.14 (−1.91 to 1.63)	0.876
BMI (kg/m^2)	−1.04 (−1.56 to −0.53)	−0.90 (−1.46 to −0.35)	−0.14 (−0.93 to 0.65)	0.727
Waist circumference (cm)	−4.05 (−6.18 to −1.91)	−3.27 (−5.54 to −0.99)	−0.78 (−4.01 to 2.45)	0.629
Hip circumference (cm)	−2.62 (−4.02 to −1.21)	−2.93 (−4.42 to −1.44)	0.31 (−1.81 to 2.43)	0.767
Waist-hip ratio	−0.02 (−0.04 to 0.00)	−0.01 (−0.03 to 0.01)	−0.01 (−0.04 to 0.02)	0.513
Menstrual cycles (no./year)	1.34 (0.66 to 2.02)	1.37 (0.63 to 2.11)	−0.03 (−1.08 to 1.02)	0.950
Ferriman-Gallwey score	−0.26 (−0.68 to 0.15)	−0.20 (−0.67 to 0.26)	−0.06 (−0.72 to 0.59)	0.844
HbA1c (%)	−0.26 (−0.43 to −0.09)	−0.08 (−0.27 to 0.11)	−0.18 (−0.44 to 0.09)	0.181
HOMA-ISI	0.42 (0.23 to 0.62)	0.29 (0.08 to 0.50)	0.13 (−0.17 to 0.43)	0.382
FBG (ng/mL)	−0.23 (−0.40 to −0.06)	−0.23 (−0.41 to −0.05)	−0.00 (−0.26 to 0.26)	0.995
PBG (ng/mL)	−1.26 (−2.07 to −0.45)	0.26 (−1.24 to 0.72)	−1.00 (−2.37 to 0.37)	0.147
FINS (ng/mL)	−7.70 (−11.46 to −3.94)	−3.97 (−7.97 to 0.03)	−3.73 (−9.47 to 2.00)	0.196
PINS (ng/mL)	−81.43 (−122.71 to −40.14)	−40.12 (−88.20 to 7.95)	−41.90 (−108.00 to 25.40)	0.218
ALT (U/L)	−13.99 (−29.88 to 1.91)	−8.43 (−25.40 to 8.53)	−5.55 (−30.03 to 18.92)	0.650
AST (U/L)	−9.25 (−15.46 to −3.04)	−3.64 (−10.42 to −3.14)	−5.61 (−15.24 to 4.02)	0.247
Creatinine (umol/L)	1.14 (−1.38 to 3.67)	1.32 (−1.39 to 4.02)	−0.18 (−4.06 to 3.71)	0.928
Uric acid (umol/L)	−74.95 (−95.30 to −54.59)	−2.52 (−23.74 to 18.69)	−72.42 (−102.86 to −41.99)	**<0.001***
Total cholesterol (mmol/L)	0.17 (−0.05 to 0.39)	−0.00 (−0.23 to 0.24)	0.17 (−0.17 to 0.50)	0.329
Triglycerides (mmol/L)	−0.36 (−0.54 to −0.17)	−0.23 (−0.44 to −0.03)	−0.12 (−0.41 to 0.17)	0.393
LDL cholesterol (mmol/L)	0.22 (0.06 to 0.51)	−0.03 (−0.28 to 0.34)	0.19 (−0.24 to 0.63)	0.378
HDL cholesterol (mmol/L)	0.02 (−0.17 to 0.13)	0.13 (−0.04 to 0.30)	−0.15 (−0.39 to 0.09)	0.211
LH (IU/L)	0.53 (−2.75 to 3.80)	−1.84 (−5.41 to 1.72)	2.37 (−2.69 to 7.42)	0.351
FSH (IU/L)	−0.09 (−1.13 to 0.94)	−0.12 (−1.23 to 0.98)	0.03 (−1.55 to 1.61)	0.971
Testosterone (ng/mL)	−0.15 (−0.38 to 0.08)	−0.00 (−0.25 to 0.24)	−0.15 (−0.50 to 0.21)	0.411
Free testosterone (pg/mL)	0.30 (−0.30 to 0.89)	0.30 (−0.44 to 1.04)	−0.01 (−1.02 to 1.01)	0.991
Androstenedione (ng/mL)	−0.48 (−1.04 to 0.09)	0.04 (−0.49 to 0.56)	−0.51 (−1.32 to 0.29)	0.199
DHEAS (ug/dL)	−68.96 (−126.36 to −11.55)	36.52 (−16.31 to 89.35)	−105.47 (−186.42 to −24.53)	**0.013***
SHBG (nmol/L)	−4.82 (−19.40 to 9.75)	−13.58 (−31.21 to 4.05)	8.7 (−15.94 to 33.46)	0.472
Total body fat (%)	−1.58 (−2.63 to −0.53)	−1.97 (−3.34 to −0.60)	0.39 (−1.36 to 2.14)	0.652
Total body lean (%)	1.10 (−0.68 to 2.88)	1.31 (−0.92 to 3.53)	−0.21 (−3.09 to 2.68)	0.884
Total fat mass (kg)	−2.51 (−3.48 to −1.54)	−2.53 (−3.79 to −1.27)	0.01 (−1.59 to 1.62)	0.986
Total lean mass (kg)	−1.30 (−3.14 to 0.54)	−0.76 (−3.05 to 1.54)	−0.54 (−3.52 to 2.44)	0.713
SAT mass (kg)	−0.20 (−0.30 to −0.09)	−0.20 (−0.33 to −0.07)	0.00 (−0.17 to 0.17)	0.966
VAT mass (kg)	−0.08 (−0.12 to −0.03)	−0.12 (−0.18 to −0.06)	0.04 (−0.03 to 0.11)	0.260

Note: All were adjusted for the possible confounders (HOMA-IR, number of menstruations per year at baseline, triglycerides and uric acid). Bold values indicates statistical significance.

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; DHEAS, dehydroepiandrosterone sulphate; FBG, fasting blood glucose; FINS, fasting serum insulin; FSH, follicle-stimulating hormone; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-ISI, homeostatic model assessment insulin sensitivity index; LDL, low-density lipoprotein; LH, luteinizing hormone; LS, least squares; PBG, postprandial blood glucose; PINS, postprandial insulin; SAT, abdominal subcutaneous adipose tissue; SHBG, sex hormone-binding globulin; VAT, visceral adipose tissue.

*$P < 0.05$.

blood pressure, whereas a previous study showed that no blood pressure changes were demonstrated in PCOS patients taking empagliflozin.[24] Third, given that this study was designed as a single-centre, open-label study, and not a multicentre, blinded study, our findings, particularly those pertaining to the multiple secondary outcomes investigated, might be attributable to chance. However, the

TABLE 3 Adverse events and safety data during 12 weeks in two treatment groups

Event	Canagliflozin group (n = 33), n (%)	Metformin group (n = 35), n (%)
Headache	0 (0)	3 (8.57)
Gastrointestinal symptoms	1 (3.03)	20 (55.55)
Nausea	1 (3.03)	13 (37.14)
Diarrhoea	0 (0)	14 (38.89)
Loss of appetite	0 (0)	13 (37.14)
Vomiting	0 (0)	4 (11.11)
Abdominal pain	0 (0)	2 (5.56)
Stomach pain	0 (0)	1 (2.86)
Hypoglycemia	0 (0)	0 (0)
Osmotic diuresis-related AEs	1 (3.03)	0 (0)
Volume-related AEs	0 (0)	0 (0)
Urinary tract infections	0 (0)	0 (0)
Pruritus vulvae	3 (9.09)	0 (0)
Genital mycotic infections	0 (0)	0 (0)
Severe hypersensitivity reaction	0 (0)	0 (0)

Abbreviation: AE, adverse event.

present study still has great value in exploring the safety and efficacy of canagliflozin in PCOS patients. It should also be noted that canagliflozin is not recommended for patients contemplating pregnancy.

In conclusion, in the present study, canagliflozin was well tolerated and had similar efficacy to that of metformin for HOMA-IR reduction, weight loss and menstrual pattern improvement in Chinese PCOS patients with IR. In addition, compared with metformin, canagliflozin had the certain advantage of reducing UA and DHEAS levels, which suggests that SGLT2 inhibitors should be considered as effective drugs in the treatment of PCOS patients with IR.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Meili Cai, Xiaowen Shao and Feng Xing: follow-up of PCOS patients, statistical analysis and interpretation of the data. Diliqingna Dilimulati and Yuqin Zhang: acquisition of the data. Shen Qu and Manna Zhang: conception, design and edit. All authors: checking and interpretation of the data, drafting of the manuscript, reviewing or approving the final manuscript.

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article.

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