Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: A randomized controlled study

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Summary

Background: Empagliflozin is a sodium-glucose-cotransporter-2 inhibitor that improves cardiovascular risk and promotes weight loss in patients with type-2 diabetes. Polycystic ovary syndrome (PCOS) is associated with obesity and increased cardiovascular risk; therefore, empagliflozin may be of benefit for these women. The aim of this study was to compare the effects of empagliflozin vs metformin on anthropometric and body composition, hormonal and metabolic parameters in women with PCOS.

Materials and methods: A randomized open-label study was conducted in women with PCOS who were randomized to either empagliflozin 25 mg (n = 19) or metformin 1500 mg (n = 20) daily for 12 weeks. The main outcomes assessed were changes in anthropometric and body composition, hormonal and metabolic parameters.

Results: Univariate analysis showed significant differences in weight (empagliflozin: −1.4 ± 3.2% vs metformin: 1.2 ± 2.3%; P = 0.006), body mass index (empagliflozin: −1.4 ± 3.2% vs metformin: 1.1 ± 2.2%; P = 0.006), waist circumference (empagliflozin: −1.6 ± 2.8% vs metformin: 0.2 ± 2.1%; P = 0.029) and hip circumference (empagliflozin: −2.0 ± 3.0% vs metformin: 1.1 ± 1.9%; P = 0.001), basal metabolic rate (empagliflozin: −1.8 ± 2.9% vs metformin: 0.1 ± 1.9%, P = 0.024) and fat mass (empagliflozin: −0.7 ± 4.9% vs metformin, 3.2 ± 5.0%; P = 0.023) between the empagliflozin and the metformin groups. These differences were confirmed in linear regression analysis after adjustment for relevant covariates. There were no significant changes in hormonal or metabolic parameters between both groups.

Conclusion: There was a significant improvement in anthropometric parameters and body composition, in overweight and obese women with PCOS after 12 weeks of treatment with empagliflozin compared to metformin, although no changes were seen in hormonal or metabolic parameters.

KEYWORDS
body composition, empagliflozin, hormones, metabolic parameters, polycystic ovary syndrome, SGLT2 inhibitors
Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder featured by hyperandrogenism, menstrual irregularities and polycystic ovaries that affects women of reproductive age.\textsuperscript{1} PCOS is also associated with infertility, obesity, metabolic disturbances and increased cardiovascular risk.\textsuperscript{1,2}

Accordingly, the treatment of PCOS is commonly symptom-based, while the ideal treatment would address both the reproductive and metabolic abnormalities related to PCOS.\textsuperscript{1,3} Hormonal contraceptives alone or combined with anti-androgens have been the cornerstone for managing menstrual disturbances and clinical or biochemical hyperandrogenaemia;\textsuperscript{4} however, some hormonal contraceptives may unfavourably affect the lipid profile in PCOS\textsuperscript{5} and increase the risk of thrombosis and cardiovascular events in the general population.\textsuperscript{5}

Glucose lowering agents including metformin and thiazolidinedione have been shown to be effective in managing the metabolic abnormalities (ie, insulin resistance, hyperinsulinaemia, and diabetes mellitus) and chronic anovulation; however, their use has been inconsistently associated with improvements in weight loss and body composition, menstrual irregularity or clinical symptoms of excess androgens.\textsuperscript{7,8}

Empagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, is a new treatment option for adults with type 2 diabetes;\textsuperscript{9} however, its effects in PCOS have not been previously explored. Its principal action involves inhibition of glucose reabsorption by the kidney, and therefore, glucose excretion via urine. Notably, this action mechanism is insulin-independent; as such it does not increase the risk of hypoglycaemia, making it attractive for use in normoglycaemic individuals.\textsuperscript{10,11} Recent trials have demonstrated that treatment with empagliflozin promotes weight loss,\textsuperscript{12} exerts positive effects on arterial stiffness, vascular resistance and blood pressure and decreases the relative risk for cardiovascular and all-cause mortality in patients with type 2 diabetes.\textsuperscript{10,13} Evidence from preclinical studies suggests that these cardio-protective effects may be due to the reduction in oxidative stress and suppressed markers of inflammation and fibrosis.\textsuperscript{14,15} In humans, the cardiovascular benefits may also be mediated by reductions in HbA1c, insulin resistance, plasma volume, weight/fat mass and inflammation.\textsuperscript{16,17} Given that these pathological features are also common in PCOS\textsuperscript{1,2}; empagliflozin may be of potential benefit for this population.

Therefore, the aim of this study was to explore and compare the effects of empagliflozin vs metformin on anthropometric, body composition, hormonal and metabolic parameters in women with PCOS.

2 | MATERIALS AND METHODS

An open-label, randomized, comparative study in women with PCOS was performed in the Academic Diabetes, Endocrinology and Metabolism research centre at Hull Royal Infirmary. All participants were women, aged between 18 and 45 years, had a body mass index (BMI) ≥25 kg/m\textsuperscript{2}, were diagnosed with PCOS based on the Rotterdam criteria [biochemical hyperandrogenism, as indicated by a free androgen index (FAI) >4, and self-reported oligomenorrhea (cycle length >35 days and 9 or fewer periods per year) or amenorrhea (absence of menses for a period ≥3 months)],\textsuperscript{18} Women with differential diagnoses of non-classical 21-hydroxylase deficiency, hyperprolactinaemia, Cushing’s disease and androgen-secret ing tumours were excluded from participation. Additional exclusion criteria included pregnancy or intention to become pregnant, breastfeeding, documented use of oral hormonal contraceptives and hormone-releasing implants, metformin or other insulin-sensitizing medications, clomiphene citrate or oestrogen modulators, gonadotropin-releasing hormone (GnRH) modulators and Minoxidil, diagnosis of diabetes, history or presence of malignant neoplasms within the last 5 years, pancreatitis (acute or chronic), recurrent urinary tract infections or gastrointestinal tract surgery, ongoing, inadequately controlled thyroid disorder and known hypersensitivity to the investigational medicinal products or any of their excipients. All participants provided their written informed consent. This study was approved by the Medicines and Healthcare Products Regulatory Authority (MHRA) (Ref: 21411/0254/001-0001), the Yorkshire & Humber Health Research Authority and Leeds East Research Ethics Committee (REC reference: 17/YH/0118), registered at www.clinicaltrials.gov (NCT03008551) and conducted in accordance with the Declaration of Helsinki and local regulations.

Women with PCOS were randomized on a 1:1 ratio using an online web-based randomization service (https://www.sealedenvelope-lope.com) to receive either empagliflozin 25 mg (Jardiance) or metformin SR (slow release) 1500 mg (Bolamyn) daily for 12 weeks. The dosage of empagliflozin (25 mg) was chosen to get the maximum metabolic response with comparable duration to metformin treatment group. Metformin group received Metformin SR 1500 mg, which is the standard dose commonly used in patients with PCOS in clinical practice.\textsuperscript{19} Metformin SR was preferred over immediate release metformin in view of better gastrointestinal tolerability.\textsuperscript{20} All participants were advised to maintain their usual dietary and lifestyle habits during the study.

Participants attended three visits (visits 1-3). During Visit 1, participants were screened against inclusion and exclusion criteria by medical history and clinical examination, routine blood tests (ie full blood count, liver function tests, urea and electrolytes, clotting screen and a pregnancy test), urine pregnancy test and anthropometric measurements. During Visit 2 (baseline) and Visit 3 (12-week follow-up), participants underwent anthropometric (weight, BMI, waist circumference [WC] and hip circumference [HC]) and body composition assessments and an endothelial function measurement. Blood samples were collected at these time points and analysed for reproductive hormones and cardio-metabolic parameters (fasting glucose, fasting insulin, HOMA-IR, total cholesterol, LDL-C, HDL-C, triglycerides [TG], and hs-CRP).

2.1 | Procedures

Height and weight were recorded with participants wearing light clothing and no shoes using a weighing scale with attached stadiometer.
Three readings were taken at least two minutes apart, and then the average of the readings was obtained. Waist circumference and hip circumference were measured using a tape measure by wrapping it around the patient’s waist at the midway point between the top of the iliac crest and the bottom of the ribs. Basal metabolic rate, total body fat percentage, fat mass, fat free mass, total body impedance and total body water were measured by using a body composition analyser (BC 418 MA; Tanita Corporation Itabashi-ku, Tokyo, Japan). All these measurements were performed at baseline and 12 weeks after the empagliflozin and metformin treatments.

Endothelial function was assessed using a plethysmographic device Endo-PAT 2000 (Itamar Medical Ltd, Caesarea, Israel). Participants relaxed for at least 15 minutes in a quiet, controlled temperature (22-24°C) room. Endo-PAT biosensors were placed on the index fingers of both hands. During the measurement, participants were instructed to relax and refrain from talking or making any sudden movements. The probes were inflated, and the signals were recorded on the computer according to manufacturer’s instructions. This measurement consisted of 5 minutes of baseline recording, followed by blood pressure cuff inflation to a supra-systolic level (at least 60 mm Hg above systolic pressure and no less than 200 mm Hg) sustained for 5 minutes and subsequent blood pressure cuff deflation and recording of Endo-PAT readings over a further 5-minute period. Output variables, namely Reactive Hyperaemia Index (RHI), a measure for endothelial function, and Augmentation Index (AI), a measure for arterial stiffness, were assessed using an automated computer software (EndoPAT2000 version 3.3.2; Itamar Medical Ltd). Compliance with the treatments was calculated by counting the returned medications at the end of the 12-week period.

2.2 Blood sampling and biochemical analyses
Following an overnight fast, blood samples were collected both at the baseline and final visit (end of the 12-week period). The fasting venous blood was collected into fluoride oxalate and serum gel tubes. Blood samples were separated by centrifugation at 3500 g for 15 minutes at 5°C, and the aliquots were stored at −80°C within 1 hour of collection.

Serum insulin was assayed using a competitive chemiluminescent immunoassay performed on the manufacturer’s DPC Immulite 2000 analyzer (Euro/DPC, Llanberis, UK), with a coefficient of variation (CV) was 6%, and no stated cross-reactivity with proinsulin. The plasma glucose was measured using a Beckman AU 5800 analyser (Beckman-Coulter, High Wycombe, UK) and according to the manufacturer’s recommended protocol. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and high-sensitivity C-reactive protein (hs-CRP) levels were measured enzymatically using a Beckman AU 5800 analyser (Beckman-Coulter, High Wycombe, UK) with CVs of <4.9%, 0.9%, 1.6% and 8.4%. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. Serum testosterone and androstenedione were quantified using isotop-dilution liquid chromatography tandem mass spectrometry (LC-MS/MS). Sex hormone-binding globulin (SHBG), oestrogen and dehydroepiandrosterone (DHEAS) were measured using a chemiluminescent immunoassay on the Beckman-Coulter UniCel Dxi 800 analyser, applying the manufacturer’s recommended protocol. The free androgen index (FAI) was calculated as: (total testosterone/SHBG) × 100.

2.3 Statistical analysis
There are no previous studies on the effect of empagliflozin or any other SGLT-2 inhibitors on women with PCOS. Sample size was based on an independent t test with an arbitrary level of 5% significance (2-tailed) and power of 80%. Assuming a common standard deviation of 16% for radial augmentation index and a 4% reduction as a significant change, a sample size of 16 patients per group allowed us to detect a between-group mean difference of 4%. To allow for loss-to-follow-up, we aimed to recruit 20 patients per group.

All data were checked for normality according to the Shapiro-Wilk test. Mean differences for all parameters expressed as % change from baseline between women with PCOS in the empagliflozin group and the metformin group were analysed with independent t test or Mann-Whitney U-test for normally and non-normally distributed data, respectively. Mean differences between baseline and 12-week follow-up within each treatment group were analysed with a paired t test or a signed-rank test for normally and non-normally distributed data, respectively. Values are presented as mean SD, if the variables were normally distributed, or median and interquartile range, if the
variables were skewed. All statistical analyses were performed using IBM-SPSS version 24.0 (Chicago, IL) with P-values ≤0.05 considered to be significant. Linear regression analysis using function ln R was used to confirm the findings of univariate analysis after adjustments for confounders. Since this was a randomized controlled trial, we only adjusted for age and age + BMI, where relevant.

3 | RESULTS

Forty-two participants with PCOS were screened; two participants were excluded from participation because they did not meet inclusion criteria, as such 40 participants were randomized to the two treatment arms (empagliflozin, n = 20 and metformin, n = 20):

TABLE 1 Changes in anthropometric, body composition, hormonal and metabolic parameters following 12 wks of empagliflozin and metformin treatment

| Parameter                     | Empagliflozin (n = 19) | Metformin (n = 20) |
|-------------------------------|------------------------|--------------------|
|                              | Baseline 12 wks % baseline change | Baseline 12 wks % baseline change |
| Weight (kg)                   | 102.3 ± 16.6 101.5 ± 16.3 −1.4 ± 3.2c | 108.8 ± 25.3 110.1 ± 25.7b 1.2 ± 2.3 |
| BMI (kg/m²)                   | 37.1 ± 6.2 36.6 ± 6.0 −1.4 ± 3.2c | 38.7 ± 7.8 39.2 ± 7.9b 1.1 ± 2.2 |
| Waist circumference (cm)      | 101.2 ± 9.7 99.6 ± 9.5b −1.6 ± 2.8c | 106.2 ± 15.7 106.3 ± 15.4 0.2 ± 2.1 |
| Hip circumference (cm)        | 121.6 ± 11.5 119.2 ± 11.4b −2.0 ± 3.2c | 124.1 ± 17.4 125.3 ± 16.7b 1.1 ± 1.9 |
| BMR (kcal)a                   | 1761 ± 205 1728 ± 200b −1.8 ± 2.9c | 1783 (304) 1797 (305) 0.1 ± 1.9 |
| Body fat (%)b                 | 46.7 ± 3.5 47.1 ± 3.4 0.6 (3.2) | 46.8 ± 6.2 47.6 ± 5.9b 1.1 (3.8) |
| Fat mass (kg)c                | 48.9 ± 11.0 48.6 ± 11.0 −0.7 ± 4.9c | 52.3 ± 10.9 53.7 ± 18.3b 3.2 ± 5.0 |
| FFM (kg)d                     | 54.8 ± 5.9 53.7 ± 5.8b −2.0 ± 3.2 | 56.7 ± 7.9 56.5 ± 7.9 −0.3 ± 2.2 |
| TBW (kg)e                     | 40.1 ± 4.3 39.3 ± 4.3b −2.0 ± 3.2 | 41.5 ± 5.8 41.4 ± 5.8 −0.3 ± 2.2 |
| FAI                           | 10.3 ± 3.0 9.4 ± 3.6 −7.0 ± 21.4 | 7.5 (6.4) 8.0 (6.4) −9.7 ± 34.0 |
| Testosterone (nmol/L)         | 1.6 ± 0.4 1.6 ± 0.6 2.6 (37.0) | 1.7 (1.2) 1.5 (1.2) −14.0 (33.6) |
| SHBG (nmol/L)                 | 17.3 ± 6.4 19.2 ± 8.5b 9.9 ± 22.6 | 19.5 (13.5) 19.5 (14.5) 6.4 ± 25.5 |
| Androstenedione (nmol/L)      | 5.7 ± 1.4 5.7 ± 1.9 −2.2 (24.4) | 4.3 (4.4) 5.0 (2.8) 5.6 (59.8) |
| DHEAS (µmol/L)                | 6.1 ± 1.6 6.2 ± 2.1 1.0 ± 20.1 | 5.5 ± 3.3 5.8 ± 3.0 8.1 ± 15.0 |
| Oestradiol (pmol/L)           | 200 (80) 280 (340)b 39.1 (121) | 240 (140) 210 (190) −8.7 (113.1) |
| SBP (mm Hg)                   | 118.1 ± 11.7 117.5 ± 14.2 −0.8 (5.9) | 124.4 ± 15.5 125.9 ± 15.8 1.1 (6.8) |
| DBP (mm Hg)                   | 74.0 (10.0) 73.0 (8.0) −3.1 ± 9.0 | 80.3 ± 10.7 80.7 ± 9.8 0.8 ± 7.1 |
| RHI                           | 1.6 (0.5) 1.5 (0.7) 2.6 (48.1) | 1.7 (0.5) 1.6 (0.7) −1.9 (53.7) |
| AI                            | −3.3 ± 12.0 −3.4 ± 13.3 −570 ± 170 | 0.6 ± 8.1 2.3 ± 10.4 −47.5 ± 146 |
| Fasting glucose (mmol/L)a     | 4.5 (0.6) 4.5 (0.6) −0.8 ± 5.8 | 4.7 (0.5) 4.4 (0.6) −2.3 ± 8.0 |
| Fasting insulin (μIU/ml)       | 12.6 (11.6) 12.7 (14.4) −21.5 (80.1) | 16.6 (11.4) 14.0 (22.7) −14.1 (52.5) |
| HOMA-IRa                      | 2.6 (2.1) 2.4 (2.7) −20.5 (84.6) | 3.7 (2.4) 3.2 (4.9) −18.9 (53.5) |
| TC (mmol/L)                    | 4.8 ± 1.0 4.7 ± 1.1 −1.6 ± 13.7 | 4.7 ± 0.9 4.5 ± 0.9 −2.2 ± 8.5 |
| LDL-C (mmol/L)                | 2.8 ± 1.0 2.7 ± 1.1 2.7 (30.2) | 2.8 (0.6) 2.8 (0.9) −3.4 (9.6) |
| HDL-C (mmol/L)                | 1.1 ± 0.2 1.1 ± 0.2 −0.6 ± 9.2 | 1.2 ± 0.2 1.1 ± 1.9 −3.4 ± 9.6 |
| TG (mmol/L)                   | 1.5 (1.3) 1.4 (0.9) −6.7 (35.8) | 1.1 (0.9) 1.2 (0.7) −9.0 (49.8) |
| hs-CRP (mg/L)                 | 5.4 (6.6) 3.3 (5.9) 9.8 ± 59.1 | 6.1 (9.7) 5.1 (10.9) 8.4 ± 34.0 |

Data are presented as mean ± SD if normally distributed or as median (interquartile range), if skewed.

AI, augmentation index; BMI, body mass index; BMR, basal metabolic rate; DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulphate; FAI, free androgen index; FFM, fat free mass; HDL, high-density lipoproteins; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoproteins; RHI, reactive hyperaemic index; SBP, systolic blood pressure in; SHBG, sex hormone-binding globulin; TBW, total body water; TC, total cholesterol; TG, triglycerides.

a Data available for 18 participants in the empagliflozin group.

*b P < 0.05, significant difference from baseline within treatment group.

**P < 0.05, significant difference from metformin group.
During the intervention phase of the study, one participant in the empagliflozin group was lost to follow-up. Finally, 19 participants in the empagliflozin group (age: 26.0 [8.0] years, BMI: 37.1 ± 6.2 kg/m²) and 20 participants in the metformin group (age: 31.5 [20.0] years, BMI: 38.7 ± 7.8 kg/m²) completed the trial, and their data were included in the final analysis (Figure 1). The baseline characteristics of both groups are presented in Table 1 and Table S1. Compliance was over 90% in both groups. There were no adverse events or serious adverse events in the metformin group. In the empagliflozin group, two patients reported adverse events (headache and dizziness, n = 1; mild rash, n = 1), which were, however, unrelated to the study drug.

### 3.1 Anthropometric and body composition parameters

In the empagliflozin group, waist circumference ($P = 0.024$), hip circumference ($P = 0.013$), BMR ($P = 0.016$), fat free mass (FFM) ($P = 0.013$) and total body water ($P = 0.014$) at 12 weeks decreased significantly compared to baseline, but no changes were seen in total mass ($P = 0.079$) or BMI ($P = 0.069$; Table 1). In the metformin group, body mass ($P = 0.019$), BMI ($P = 0.024$) and hip circumference ($P = 0.031$), total fat percentage ($P = 0.015$) or fat mass ($P = 0.005$) significantly increased after 12 weeks of treatment (Table 1).

**FIGURE 2** Percentage changes from baseline in anthropometric and body composition parameters after 12 wks with empagliflozin and metformin treatment. *$P < 0.05$; BMI, body mass index; BMR, basic metabolic rate; FFM, fat free mass; HC, hip circumference; TBW, total body water; WC, waist circumference. Body composition data (BMR, body fat %, fat mass, FFM and TBW) are presented for 18 participants in the empagliflozin group with available data.
When data were expressed as percentage change from baseline in each group, significant differences in weight (empagliflozin: -1.4 ± 3.2% vs metformin: 1.2 ± 2.3%; \( P = 0.006 \)), BMI (empagliflozin: -1.4 ± 3.2% vs metformin: 1.1 ± 2.2%; \( P = 0.007 \)), waist (empagliflozin: -1.6 ± 2.8% vs metformin: 0.2 ± 2.1%; \( P = 0.029 \)) and hip circumference (empagliflozin: -2.0 ± 3.0% vs metformin: 1.1 ± 1.9%; \( P = 0.001 \)) were seen between the treatment groups. Similarly, the percentage changes from baseline in BMR (empagliflozin: -1.8 ± 2.9% vs metformin: 0.1 ± 1.9%; \( P = 0.024 \)) and fat mass (empagliflozin: -0.7 ± 4.9% vs metformin, 3.2 ± 5.0%; \( P = 0.023 \)) were significantly different between the empagliflozin and metformin groups (Table 1, Figure 2). The proportion of women with PCOS who experienced (a) a decrease >5%, (b) an increase >5%, or (c) a change ≤5% from baseline in anthropometric and body composition parameters are presented in Table S2.

3.2 | Hormonal and metabolic parameters

In the empagliflozin group, significant increases in SHBG (\( P = 0.049 \)) and oestradiol levels (\( P = 0.032 \)) were seen after 12 weeks of treatment (Table 1). There were no other hormonal changes for either group (Table 1). No differences were seen in percentage change from baseline for any of the hormone parameters between groups (Table 1, Figure 2).

There were no changes following 12 weeks of treatment in blood pressure, endothelial function (RHI, AI), insulin sensitivity (insulin, fasting glucose, HOMA-IR), fasting lipid profile or hs-CRP in either treatment arm (Table 1). Between groups, comparisons did not reveal any differences in percentage changes from baseline for any of these metabolic parameters (Table 1, Figure 2).

3.3 | Regression analysis modelling

Table 2 shows the results of the linear regression analysis modelling percentage changes from baseline in anthropometric characteristics, hormonal and metabolic parameters as function of metformin or empagliflozin treatment. The results confirm statistically significant reduction in weight, BMI, WC, HC, fat mass and BMR in those randomized to empagliflozin group as compared to those in metformin group.

4 | DISCUSSION

In this first study on the comparative effects of the SGLT2 inhibitor, empagliflozin and metformin in overweight and obese women with PCOS, we demonstrated that treatment with empagliflozin over a 12-week period, resulted in significant reductions in weight, BMI, waist and hip circumference, total body fat mass and BMR, compared to treatment with metformin, but did not differentially affect hormonal or metabolic parameters.

Obesity is prevalent among women with PCOS and has been associated directly and/or indirectly with negative metabolic, cardiovascular, endocrine, reproductive and mental health outcomes.\(^1\) Weight reduction exerts positive effects on PCOS-related outcomes; therefore, it is a primary goal of the management of the condition.\(^3\) In the present study, women with PCOS in the empagliflozin group had a mean weight loss of 1.5 kg, which is similar to the weight loss reported in previous short-term trials.\(^12\) Mechanistically, initial weight loss in empagliflozin studies is attributed to the calorie loss (approximately 200-300 kcal/d) associated with glucose excretion, but also to the mild diuretic effects of the drug.\(^9\)\(^12\) Conversely, the steady-state weight loss associated with SGLT2 inhibitors treatment may result from fat loss.\(^22\)\(^23\) In animal models, SGLT2 inhibitors have been shown to cause reduction in body weight and fat mass by enhancing lipolysis, fatty acid oxidation and adipose tissue browning.\(^14\)\(^24\) These findings coincide with the alterations seen in substrate utilization from carbohydrates to lipids and potentially, ketone bodies.\(^9\)\(^25\) Reductions in other measures of adiposity including waist and hip circumference, visceral and subcutaneous fat depots or indices, which may better reflect risk for metabolic disturbances and cardiovascular disease, have also been demonstrated in patients with type 2 diabetes following treatment with SGLT2 inhibitors.\(^22\)\(^23\) With these findings being in agreement with the improvements in waist and hip circumference seen in our women with PCOS assigned to receive empagliflozin.

In the present study, the metformin group experienced modest increases in body weight. Studies on the effect of metformin on body weight in women with PCOS have yielded mixed results.\(^8\)\(^26\)\(^27\) While some studies have suggested that metformin therapy may result in weight reduction, some randomized controlled trials have failed to confirm this. For example, a large, randomized, double-blind, placebo-controlled trial evaluated the combined effects of lifestyle modification and metformin (850 mg twice daily), by studying 143 anovulatory

| TABLE 2 | Linear regression analysis modelling percentage (%) changes in key anthropometric characteristics, hormonal and metabolic parameters as function of metformin or empagliflozin |
|---|---|---|
| Beta | SE | P-value |
| % change in BMI\(^a\) | -2.27 | 0.95 | 0.02 |
| % change in weight\(^a\) | -2.28 | 0.96 | 0.02 |
| % change in fat mass\(^a\) | -3.43 | 1.74 | 0.05 |
| % change in WC\(^a\) | -1.76 | 0.85 | 0.04 |
| % change in HC\(^a\) | -2.87 | 0.88 | 0.002 |
| % change in BMI\(^b\) | -1.73 | 0.86 | 0.05 |
| % change in FAI\(^b\) | 5.42 | 11.97 | 0.65 |
| % change in SHBG\(^b\) | 5.89 | 8.69 | 0.5 |
| % change in TC\(^b\) | 2.78 | 3.85 | 0.47 |
| % change in fasting glucose\(^a\) | 1.12 | 2.48 | 0.65 |

BMI, body mass index; BMR, basal metabolic rate; FAI, free androgen index; FFM, fat free mass; HC, HIP circumference; SHBH, sex hormone-binding globulin; TC, total cholesterol; WC, waist circumference. Metformin group used as reference group.

\(^\text{a}\)Adjusted for age.

\(^\text{b}\)Adjusted for age and BMI.
women in the UK with a mean BMI of 38 kg/m² and showed that it is no different than placebo in terms of weight reduction. However, women in this study were not required to have clinical and biochemical evidence of hyperandrogenemia—an essential component of the diagnosis of PCOS. Conversely, a Finnish multicentre randomized study compared metformin with placebo in 320 women with PCOS and the authors reported significantly higher live birth rates in the metformin group (41.9% vs 28.8%; P = 0.014) and maximal effect was seen in obese women with PCOS. A recent Cochrane review explored the effect of metformin on PCOS (40 studies, total n = 3848 women) failed to provide any conclusive evidence against or for metformin in women with PCOS. These mixed results in the literature with regards to metformin treatment indicate that there are subtypes of PCOS which might respond beneficially to PCOS. Our study is not powered to assess the phenotypic heterogeneity in PCOS with regards to response to metformin—and highlights the need to study this with large scale studies looking at the effect of metformin on PCOS subtypes.

Women with PCOS experience higher prevalence of insulin resistance, type 2 diabetes mellitus, dyslipidaemia, endothelial dysfunction and atherosclerosis compared to age-matched women without PCOS. Such metabolic disturbances are characterized by chronic low-grade inflammation and vascular impairments which increase cardiovascular risk. The effects of SGLT-2 inhibitors on glycaemic control have been evaluated as the primary outcome in the majority of the studies investigating this new class of glucose lowering agents in type 2 diabetes. A meta-analysis of 13 randomized trials on the efficacy of SGLT-2 inhibitors compared to placebo demonstrated improvements in glycaemic control in type 2 diabetes patients, as evidenced by reductions in HbA1c (−0.49% and −0.50% after one and 2 years of treatment) and fasting plasma glucose levels (−0.81 and −0.76 mmol/L after 1 and 2 years of treatment). Similar results were shown in a meta-analysis (10 studies, total n = 6203 participants) on the efficacy and safety of empagliflozin only. In addition to glycaemic control, use of SGLT-2 inhibitors results in a reduction in TG levels and increases in HDL-cholesterol levels, but also LDL-cholesterol levels, possibly due to the shifted metabolism favouring lipid utilization. In contrast to these beneficial effects on glycaemic control and less pronounced lipids effects of SGLT-2 inhibitors reported in type 2 diabetes, we did not observe significant changes in fasting glucose, insulin fasting lipids or hs-CRP at 3 months after empagliflozin treatment compared to baseline or any differences between our treatment groups. These results may be related to the short duration of the study or to the baseline characteristics of our participants with PCOS, who were young and did not have diabetes.

Further evidence from studies in patients with type 2 diabetes suggest that empagliflozin, and other SGLT2 inhibitors such as canagliflozin and dapagliflozin cause reductions in blood pressure, as a result of their natriuretic effects or due to the intensification of anti-hypertensive therapy. No such blood pressure changes were demonstrated in our women with PCOS, though these subjects were normotensive and changes may not have been expected. Similarly, measures of endothelial function (RHI) or arterial stiffness (AI) were not altered compared to baseline in either treatment groups. Empagliflozin has been shown to improve endothelial dysfunction in preclinical studies in diabetic rat models, but human data are scarce. A recent 16-week study demonstrated that dapagliflozin add-on therapy to metformin improved endothelial function, as evaluated by flow-mediated dilation, in patients with inadequately controlled early-stage type 2 diabetes mellitus. Although there are no comparative data from studies that have investigated the effects of SGLT-2 inhibitors in women with PCOS, the results of our 12-week intervention contrast those of a longer study which demonstrated that metformin treatment for 6 months improved or even normalized abnormal flow-mediated dilation on the brachial artery and improved plasma endothelin-1 levels in women with PCOS. The discrepancies in these results may be at least partially explained by differences in study duration and the use of different endothelial function measures.

There were significant increases in the SHBG and oestradiol levels in the empagliflozin group, but no significant reductions were seen in FAI and serum total testosterone levels. The % changes from baseline in hormonal levels did not differ to metformin. Metformin use in women with PCOS has been associated with improvements in hormonal levels. A recent meta-analysis demonstrated that metformin treatment resulted in small improvements in serum testosterone, but no changes in free testosterone, FAI, SHBG, DHEAS LH, FSH, LH/FSH ratio, oestradiol or progesterone compared to placebo in women with PCOS. Metformin may also have some beneficial effects on ovulation and menstrual frequency. Given the short follow-up of the present study, we did not assess these parameters, which is a limitation of the present study.

5 | CONCLUSIONS

Empagliflozin treatment over a 12-week period had beneficial effects on weight, BMI, waist and hip circumference and total body fat in overweight and obese women with PCOS compared to metformin, but no differences were seen in hormonal and metabolic parameters including insulin resistance and androgen levels. Placebo-controlled and comparative treatment randomized controlled trials of longer-term duration are needed to confirm these findings and provide further insights into the effects of empagliflozin on PCOS-related outcomes in women with PCOS with different PCOS phenotypes and PCOS-related complications (eg with/without diabetes), before empagliflozin gains a therapeutic place in PCOS. Lifestyle interventions (preferably multicomponent including diet, exercise and behavioural strategies) should still be considered the first line of treatment for overweight/obese women with PCOS for reductions in body weight, central obesity and insulin resistance.

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CONFLICT OF INTEREST
The authors report no conflict of interest in this work.

AUTHOR CONTRIBUTIONS
ZJ, ESK, SLA, TS participated in study conception and design. ZJ, TS performed the acquisition of data. ZJ, MP, HD, UQ, JA, AYK, ASR, ESK, SLA and TS participated in analysis and/or interpretation of data. ZJ and MP drafted the paper; all authors reviewed and approved the final manuscript. TS is the guarantor of the study.

DATA AVAILABILITY
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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