

Role of Canagliflozin in treatment of PCOS

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Canagliflozin combined with metformin versus metformin monotherapy for endocrine and metabolic profiles in overweight and obese women with polycystic ovary syndrome:

A single-center, open-labeled prospective randomized controlled trial

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- polycystic ovary syndrome (PCOS) definition and diagnostic criteria
 - ✓ Hyperandrogenism, Ovulatory dysfunction and polycystic ovaries in ultrasonography
- Obesity and Insulin resistance (IR)
- Role of metformin in treatment of PCOS
- SGLT2 inhibitors in PCOS
 - ✓ Canagliflozin/metformin vs metformin

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- Participants
- Ethics
- Inclusion criteria
 - ✓ 18-40 years
 - ✓ Body mass index (BMI) ≥ 24 kg/m²
 - ✓ The phenotype B with HA and oligo/anovulation based on Rotterdam 2003 criteria
 - ✓ A negative serum pregnancy test before enrollment.

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- Exclusion criteria
 - ✓ Pregnancy or breastfeeding
 - ✓ Medication history (OCPs, SGLT-2 inhibitors, GLP 1 receptor agonists, thiazolidinediones, MET, and Chinese herbs)
 - ✓ Comorbidities
 - ✓ Severe hepatic or renal function damage
 - ✓ involvement in other interventional studies
 - ✓ 17a- dihydroxy-progesterone > 2ng/ml
 - ✓ UTI or gastrointestinal problems

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- Study process
 - ✓ CANA/MET group and the MET group
 - ✓ CANA: 100 mg once daily before breakfast
 - ✓ MET: 1000 mg/day (500 mg twice daily with meals) for one week, with the dose increased to 2000 mg/day (1000 mg twice daily with meals)
- Assessments: baseline and 12 weeks post-randomization
 - ✓ Anthropometric indices
- Assessment of menstruation

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- Assessment of biochemical parameters
 - ✓ FSH and LH (mIU/ml)
 - ✓ Total testosterone (TT) (ng/ml)
 - ✓ SHBG(nmol/L)
 - ✓ Free androgen index (FAI)
 - ✓ Androstenedione (AND) (ng/ml)
 - ✓ oral glucose tolerance test (OGTT) (mmol/L)
 - ✓ blood insulin (mU/mL)
 - ✓ Lipid profile

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- The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (FINS) (mU/mL) \times fasting blood glucose (FBG) (mmol/L)/22.5
- The area under the glucose curve (AUCGlu) (mmol/L \cdot min) and insulin (AUCIns) (mU/L \cdot min)

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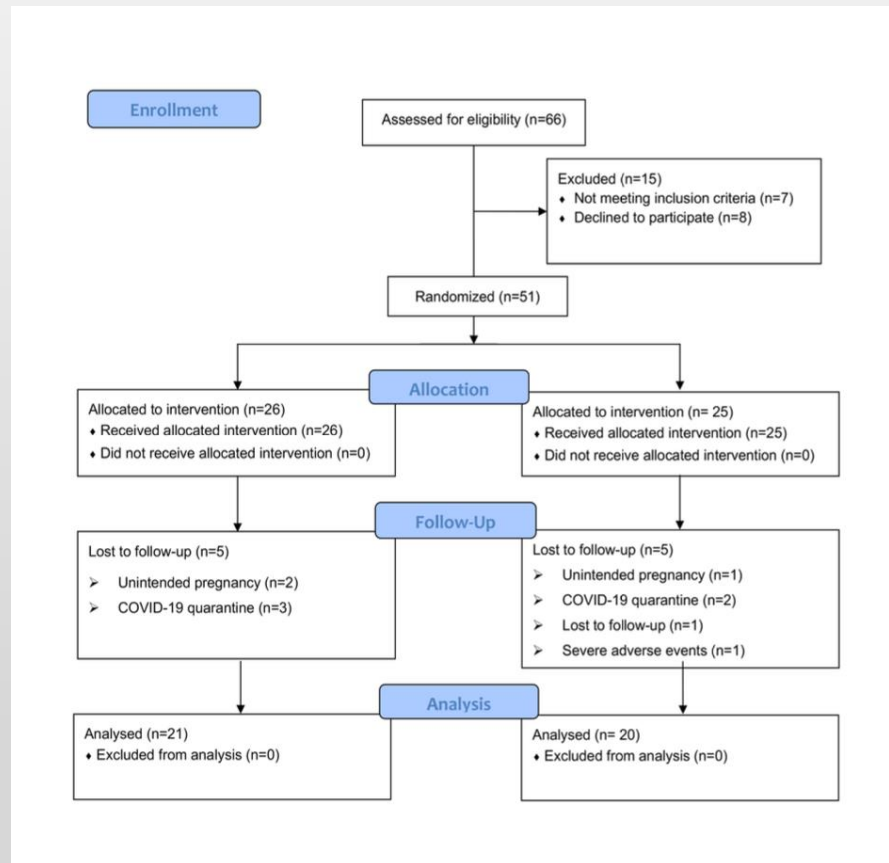
- Sample size estimation
- Statistical analysis

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- **Participants**
 - ✓ fifty-one PCOS patients who met the inclusion criteria were enrolled in the study, including 21 in the CANA/MET group and 20 in the MET group
- **Baseline information**
- **Assessment of anthropometric parameters**

Patient selection flow diagram



Baseline information

TABLE 1 Demographic data and baseline characteristics of patients.

| | CANA/MET (N = 21) | MET (N = 20) | P value |
|--------------------------|--------------------|---------------------|---------|
| Age (years) | 26.38 ± 5.89 | 525 ± 4.36 | 0.6118 |
| Height (m) | 1.62 ± 0.04 | 1.63 ± 0.05 | 0.4495 |
| Body weight (kg) | 81.23 ± 9.83 | 74.78 ± 8.91 | 0.2365 |
| BMI (kg/m ²) | 31.11 ± 3.02 | 29.33 ± 3.19 | 0.1024 |
| FSH (mIU/mL) | 6.58 ± 1.54 | 6.05 ± 1.60 | 0.2800 |
| LH (mIU/mL) | 10.85 (6.36-16.22) | 11.63 (9.69-16.87) | 0.4304 |
| TT (ng/mL) | 0.95 (0.78-1.08) | 0.89 (0.74-1.09) | 0.7616 |
| FAI (%) | 28.62 ± 16.4 | 19.26 ± 9.46 | 0.0738 |
| SHBG (nmol/L) | 13.60 (8.55-20.15) | 18.45 (13.13-21.98) | 0.1626 |
| AND (ng/ml) | 3.57 ± 1.29 | 4.48 ± 1.42 | 0.0715 |
| FBG (mmol/L) | 5.70 (5.27-6.02) | 5.30 (5.16-5.80) | 0.1625 |
| FINS (mU/L) | 21.5 (14.35-24.20) | 16.70 (14.58-24.33) | 0.5919 |
| AUCGlu (mmol/L*min) | 1086 ± 208.7 | 985.3 ± 160.7 | 0.0915 |
| AUCIns (mU/L*min) | 14808 ± 6668 | 13867 ± 7201 | 0.6664 |
| AUCIns/AUCGlu | 13.97 ± 6.83 | 13.90 ± 6.55 | 0.9728 |
| HOMA-IR | 5.70 (3.38-6.08) | 4.25 (3.26-6.44) | 0.6515 |
| TG (mmol/L) | 1.54 (1.09-2.01) | 1.49 (1.07-1.74) | 0.6668 |
| TC (mmol/L) | 4.90 ± 0.93 | 4.74 ± 0.63 | 0.5353 |
| LDL-C (mmol/L) | 3.06 ± 0.97 | 3.01 ± 0.54 | 0.8401 |
| Apo A1 (g/L) | 1.16 ± 0.15 | 1.25 ± 0.20 | 0.1516 |
| Apo B (g/L) | 0.98 ± 0.26 | 0.88 ± 0.18 | 0.2032 |
| Apo B/A1 | 0.85 ± 0.23 | 0.72 ± 0.18 | 0.0732 |

CANA, canagliflozin; MET, metformin; BMI, body mass index; FSH, follicle stimulating hormone; LH, luteinizing hormone; TT, total testosterone; FAI, free androgen index; SHBG, sex hormone-binding globulin; AND, androstenedione; FBG, fasting blood glucose; FINS, fasting insulin; AUCGlu, area under the glucose curve; AUCIns, area under the insulin curve; HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo A1, Apolipoprotein A1; Apo B, Apolipoprotein B.

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- Assessment of menstruation and gonadal parameters
 - ✓ no significant difference between the two interventions regarding menstrual cycle improvement
 - ✓ There was a clinically significant decrease in TT in the CANA/ MET group compared to MET
 - ✓ Both groups showed no significant changes in FSH, LH, or AND levels after treatment
- Glucose homeostasis assessment
- Assessment of lipid homeostasis
- AE assessment

Assessments

TABLE 2 Information of 12-weeks post treatment and changes in endocrine and metabolic profile.

| | CANA/MET (N = 21) | | MET (N = 20) | | P value (Change) |
|---|--------------------------------|------------------------|----------------------------------|-----------------------|------------------|
| | 12 weeks | Change from baseline | 12 weeks | Change from baseline | |
| Anthropometric characteristics | | | | | |
| Body weight (kg) | 75.40 ± 8.68 ^d | -6.66 ± 4.24 | 72.49 ± 9.97 ^d | -5.85 ± 3.32 | 0.5386 |
| BMI (kg/m ²) | 28.62 ± 2.91 ^d | -2.49 ± 1.55 | 27.14 ± 3.50 ^d | -2.20 ± 1.30 | 0.5441 |
| Gonadal hormones | | | | | |
| FSH (mIU/mL) | 5.84 ± 2.24 | -0.75 ± 2.51 | 5.36 ± 1.94 | -0.68 ± 2.17 | 0.9309 |
| LH (mIU/mL) | 8.59 (3.96-12.16) | -1.91 (-7.40 to 2.49) | 10.27 (8.22-13.61) | 0.42 (-7.10 to 4.19) | 0.1990 |
| TT (ng/mL) | 0.53 (0.45-0.84) ^d | -0.33 ± 0.23 | 0.71 (0.55-0.91) ^a | -0.18 ± 0.18 | 0.0233 |
| FAI (%) | 19.15 ± 13.19 ^a | -9.47 ± 11.65 | 14.14 ± 12.57 | -5.11 ± 7.40 | 0.1631 |
| SHBG (nmol/L) | 13.6 (9.55-24.10) | 0.10(-3.45 to 5.30) | 22.35(14.78-26.70) ^a | 2.95 (-2.15-10.30) | 0.4579 |
| AND (ng/ml) | 3.22 ± 1.35 | -0.36 ± 1.17 | 3.79 ± 2.21 | -0.39 ± 1.58 | 0.9555 |
| Glucose and lipid-related parameters | | | | | |
| FBG (mmol/L) | 5.20 (4.88-5.35) ^c | -0.33 (-0.95 to -0.05) | 5.30 (4.96-5.42) | -0.11(-0.49 to 0.1) | 0.1711 |
| FINS (mU/L) | 12.0 (8.20-20.15) ^c | -7 (-10.4 to -2) | 14.70 (10.80-20.40) ^b | -4.2 (-9.8 to -0.7) | 0.4565 |
| AUCGlu (mmol/L*min) | 928.3 ± 124.5 ^b | -158 ± 225.4 | 988.5 ± 129.0 | 2.63 ± 180.7 | 0.0182 |
| AUCIns (mU/L*min) | 10543 ± 6888 ^b | -4264 ± 5627 | 11691 ± 5212 | -2640 ± 6108 | 0.3869 |
| AUCIns/AUCGlu | 11.12 ± 7.12 ^a | -2.86 ± 5.71 | 11.76 ± 4.64 ^a | 0.51 ± 0.61 | 0.0164 |
| HOMA-IR | 3.14 (1.91-4.71) ^c | -1.83 (-3.01 to -0.96) | 3.51 (2.36-4.71) ^b | -1.29 (-2.9 to -0.05) | 0.4015 |
| TG (mmol/L) | 1.20 (0.84-1.63) ^a | -0.27 ± 0.51 | 1.43 (1.03-2.06) | -0.05 ± 0.59 | 0.2011 |
| TC (mmol/L) | 4.54 ± 0.80 ^a | -0.22 ± 0.43 | 4.54 ± 0.52 | -0.27 ± 0.48 | 0.7954 |
| LDL-C (mmol/L) | 2.83 ± 0.70 | -0.12 ± 0.49 | 2.83 ± 0.49 | -0.19 ± 0.50 | 0.6894 |
| Apo A1 (g/L) | 1.20 ± 0.21 | -0.02 ± 0.33 | 1.25 ± 0.26 | -0.02 ± 0.16 | 0.9465 |
| Apo B (g/L) | 0.92 ± 0.26 | -0.05 ± 0.13 | 0.90 ± 0.13 | 0.01 ± 0.17 | 0.2887 |
| Apo B/A1 | 0.78 ± 0.23 ^a | -0.08 ± 0.14 | 0.74 ± 0.16 | 0.02 ± 0.22 | 0.1450 |

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Adverse events (AE)

TABLE 3 AEs of two treatment groups.

| | CANA/MET (N = 26) | MET (N = 25) |
|-----------------------|-------------------|--------------|
| Patients with AEs | | |
| Severe AEs | | |
| Vaginal bleeding | 0 | 1 |
| Mild and moderate AEs | | |
| Nausea | 11 | 14 |
| Abdominal discomfort | 1 | 4 |
| Abdominal pain | 2 | 1 |
| Bloating | 0 | 1 |
| Diarrhea | 4 | 8 |
| Loss of appetite | 2 | 4 |
| Anorexia | 1 | 0 |
| Acid reflux | 1 | 1 |
| Headache | 1 | 0 |
| Dizziness | 3 | 0 |
| Asthenia | 1 | 0 |
| Bitter mouth | 0 | 1 |

CANA, canagliflozin; MET, metformin; AEs, adverse events.

- Our results supported MET as conventional therapy for PCOS
- CANA/ MET might be more beneficial
- mean weight loss
- There was an improvement in menstrual cycle frequency in the CANA/MET and MET groups, with no significant difference
- CANA/ MET may be superior to MET in the reduction of TT in women with PCOS

- CANA/MET and MET could reduce FINS and HOMA-IR, with no significant difference
- the serum TG levels decreased significantly in the CANA/MET group
- The LDL-C levels in the CANA/MET group were not altered from baseline
- the Apo B/A1 ratio declined after CANA and MET combination therapy
- CANA vs DAPA
- we found that CANA/ MET may be more beneficial in improving TT

In overweight and obese women with PCOS, CANA and MET combination therapy may be similar to MET monotherapy in improving menstrual frequency, weight control, hyperandrogenemia, and relieving insulin resistance.

CANA/MET may have more benefits in reducing TT, AUCGlu, and the AUCIns/AUCGlu ratio within three months than MET monotherapy.

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Questions? **our attention**

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