Original Article

Effect of Half-dose and Standard-dose Conjugated Equine Estrogens Combined with Natural Progesterone or Dydrogesterone on Components of Metabolic Syndrome in Healthy Postmenopausal Women: A Randomized Controlled Trial

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Abstract

Background: Menopausal hormone therapy (MHT) has been proven to have beneficial effects on several components of metabolic syndrome. However, the effects vary according to different regimens, dosages, and duration of MHT. The aim of the study was to evaluate the effect of standard-dose 0.625 mg conjugated equine estrogen (CEE) and half-dose 0.3 mg CEE daily with different progestogens in a continuous sequential regimen on postmenopausal metabolic parameters in generally healthy postmenopausal women.

Methods: A prospective, open-label, randomized controlled clinical trial was conducted between February 2014 and December 2015. Totally 123 Chinese postmenopausal women with climacteric symptoms were included in this study and were randomly assigned to three groups: Group A received CEE 0.3 mg/micronized progesterone (MP) 100 mg daily; Group B received CEE 0.625 mg/MP 100 mg daily; and Group C received CEE 0.625 mg/dydrogesterone 10 mg daily. Drugs were given in a continuous sequential pattern. The duration of treatment was 12 months. Clinical, anthropometrical, and metabolic variables were measured. Data were analyzed according to intention-to-treat analysis, using Student's *t*-test and analysis of variance.

Results: A total of 107 participants completed the 12-month follow-up and were included in the data analysis. At 12 months of treatment, high-density lipoprotein cholesterol and apolipoprotein A significantly increased, and low-density lipoprotein cholesterol, fasting glucose, and glycosylated hemoglobin significantly decreased in Groups B and C, compared with baseline (all $P < 0.05$). Among the three groups, only Group C showed significantly increased triglycerides compared with baseline (1.61 ± 0.80 mmol/L vs. 1.21 ± 0.52 mmol/L, $P = 0.026$). Each group showed a neutral effect on total cholesterol, lipoprotein A, apolipoprotein B, and fasting insulin levels. No cardiovascular and venous thromboembolic events occurred in the three groups.

Conclusions: Among Chinese postmenopausal women, half-dose CEE was not sufficient to induce a favorable lipid and carbohydrate profile compared with standard-dose CEE. Adding natural MP may counterbalance the TG-increasing effect of CEE.

Trial Registration: ClinicalTrials.gov, NCT01698164; https://clinicaltrials.gov/ct2/show/NCT01698164?term=NCT01698164&rank=1.

Key words: Chinese Postmenopausal Women; Conjugated Equine Estrogen; Dydrogesterone; Menopausal Hormone Therapy; Micronized Progesterone

Introduction

Menopause is characterized by a decline of endogenous estrogen that is associated with vasomotor symptoms, vaginal dryness, osteoporosis, and disturbed metabolism. Postmenopausal changes in lipid and glucose metabolism may increase the risk of developing metabolic syndrome (MetS).[1] The concept of MetS was first described in 1988 by Reaven[2] as a constellation of risk factors including visceral adiposity,

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.194646

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Received: 19-08-2016 **Edited by:** Xin Chen

How to cite this article: Xue W, Deng Y, Wang YF, Sun AJ. Effect of Half-dose and Standard-dose Conjugated Equine Estrogens Combined with Natural Progesterone or Dydrogesterone on Components of Metabolic Syndrome in Healthy Postmenopausal Women: A Randomized Controlled Trial. Chin Med J 2016;129:2773-9.

atherogenic dyslipidemia, elevated blood pressure (BP), and insulin resistance (IR) that increase the risk of developing cardiovascular disease (CVD). Menopause is associated with all components of MetS. As the average life expectancy has increased during the past decades, women will spend an increasing duration in menopause. MetS will likely increase dramatically in women around the world.[3]

Menopausal hormone therapy (MHT) was originally prescribed primarily to treat vasomotor symptoms, but had been increasingly viewed as a way to forestall many chronic diseases of aging, including MetS and osteoporosis.[4] Regarding MetS, orally administered conjugated equine estrogens (CEEs) or estradiol alone has been shown to lower low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) and to increase high-density lipoprotein cholesterol (HDL-C); however, CEE and estradiol were also associated with increases in triglycerides (TG).[5] The addition of progestogens may, however, affect some of the beneficial effects of estrogen, which may be dependent on the dosage and structure of the progestogens. Heterogeneity exists in the lipid profile response to MHT, which may be due to the differences in MHT composition, doses, dosing regimen, route of administration, compliance, etc.

Several large randomized controlled trials have explored the effect of MHT on the components of MetS.[6-10] The durations of the studies were long with a span of 2–5.2 years. They consistently found beneficial effects of MHT on metabolic homeostasis. However, the estrogens used in these studies were all standard-dose CEE or estradiol, and the progestogens were medroxyprogesterone acetate (MPA) or norethisterone acetate, which suppressed the favorable effects of estrogen than natural progesterone. In our study, standard- and half-dose CEEs were chosen to compare their effect on the components of MetS. In addition, we chose natural micronized progesterone (MP) and dydrogesterone, which lack androgenic effect and had less unfavorable effect on metabolic homeostasis, to explore the beneficial effect of CEE on the components of MetS.

Methods

Study design

This was a prospective, open-label, randomized controlled clinical trial conducted at Peking Union Medical College Hospital (PUMCH) in China, between February 2014 and December 2015. Participants were all apparently healthy postmenopausal women with intact uteri seeking treatment for menopausal symptoms. They were aged between 40 and 60 years and experienced spontaneous amenorrhea for ≥6 months and ≤5 years with serum follicle-stimulating hormone levels >40 mU/ml and serum estradiol <30 pg/ml. They were required to have an indication for MHT, which was evaluated by the investigator. No contraindication for MHT was also included in the inclusion criteria. Exclusion criteria were any of the following conditions: a uterine myoma with a diameter >3 cm; endometriosis with obvious symptoms and signs; uncontrolled diabetes and severe hypertension; thromboembolic disease history or inclination for thromboembolic diseases; epilepsy; asthma; hyperprolactinemia; a history of breast cancer among the first-degree relatives; and presence of clinically significant disease. Women who abused alcohol or drugs within 3 months of enrollment and those who smoked above 20 cigarettes per day were also excluded from the study. Other exclusion criteria were use of estrogen/progestin products within 3 months; a endometrial thickness of ≥5 mm even after progestin withdrawal; and allergic to any ingredient of the drug. The study was approved by the Ethics Committee of PUMCH (No. S-648, dated February 20, 2014) and conducted in accordance with the *Declaration of Helsinki* and the International Conference on Harmonization Guideline E6: Good Clinical Practice. All participants provided written informed consent before the study entry.

During consultation, all participants underwent a thorough clinical evaluation, including physical, breast, gynecological examinations, laboratory evaluations, transvaginal ultrasonography, mammography, and dual-energy X-ray absorptiometry (DEXA). All participants were given a number according to their order of inclusion in the study. Randomization process was conducted using IBM SPSS Statistics version 20 (IBM, Armonk, NY, USA) of the study protocol. The women were randomly assigned to three groups: Group A (n = 41) received 0.3 mg CEE (Xinjiang Xinziyuan Pharmaceutical Co., Ltd., China) and 100 mg MP (Zhejiang Xianju Pharmaceutical Co., Ltd., China) daily; Group B (n = 41) received 0.625 mg CEE and 100 mg MP daily; and Group C (n = 41) received 0.625 mg CEE and 10 mg dydrogesterone (Solvay Pharmaceuticals, Inc., France) daily. All drugs were given orally. The CEE was given once daily for consecutive 28 days with progestogen added once daily at the 17th day of CEE use for 12 days. The following cycle would begin without discontinuation of drugs. All drugs were required to be taken before sleep at night to avoid side effects such as dizziness brought by taking progesterone. The participants who received supplementation were instructed to return with capsule containers at each visit to record the medication that was not used and to establish compliance. Duration of the treatment was 12 cycles. The assessments were performed at 0 (baseline) and 12 months. Figure 1 shows flowchart of this study.

Assessments

The anthropometric data included weight, height, body mass index (BMI = weight/height^2), and waist and hip circumference. Waist circumference (WC) was measured at the midpoint between the lowest rib and the top of the iliac crest. The hip circumference was measured at the maximum circumference over the buttocks. These measurements for the anthropometric data and BPs were performed by a single evaluator. DEXA instrument (Lunar Prodigy, GE®, USA) was used to measure body composition, and the examination

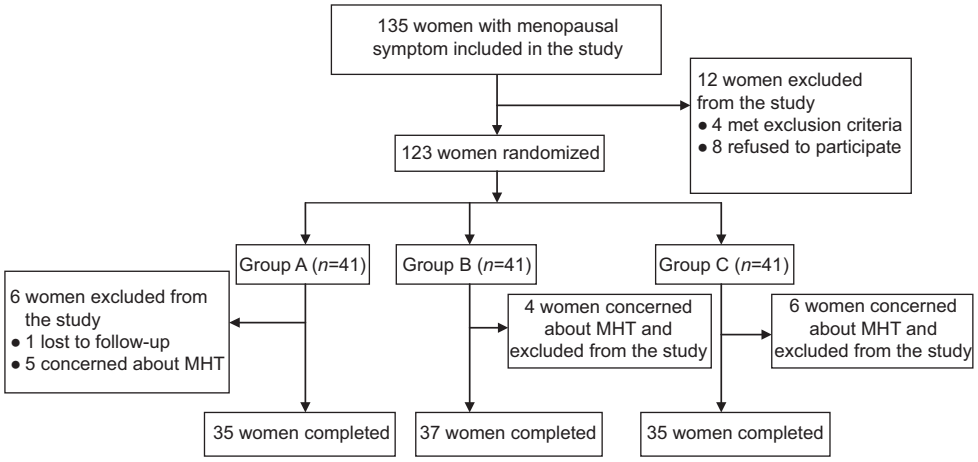

Figure 1: Flow diagram of this study. Group A: Received CEE 0.3 mg + MP 100 mg daily; Group B: Received CEE 0.625 mg + MP 100 mg daily; Group C: Received CEE 0.625 mg + dydrogesterone 10 mg daily. MHT: Menopausal hormone therapy; CEE: Conjugated equine estrogen; MP: Micronized progesterone.

was performed by a single examiner. Blood samples were collected from each participant after 12 h of fasting at baseline and at 12 months. After centrifugation to remove the clot, sera underwent biochemical analysis immediately. Lipid parameters and fasting glucose were processed by an automated analyzer, AU5800® (Beckman Coulter, USA). Insulin was quantified using the ADVIA Centaur XP® (Siemens®, Germany), which uses chemiluminescent immunoassay. To evaluate IR, we used a method that was based on statistical measurement of two plasma components: insulin and fasting glucose. Homeostasis model assessment-IR (HOMA-IR) was calculated using the following formula: insulin (mU/ml) × fasting glucose (mg/L)/405. IR was defined as HOMA-IR >2.7.[11]

Statistical analysis

Data were analyzed according to intention-to-treat analysis, including all participants in each group. The quantitative variables were shown as mean ± standard deviation (SD), and qualitative variables were presented as frequencies and percentages. In case of quantitative variables, Student's *t*-test was used. In case of quantitative variables where data were not normally distributed, Kruskal-Wallis test and Wilcoxon Mann-Whitney test were used. Analysis of variance was used to explore the effect of drugs across various groups in case of continuous variables. A $P < 0.05$ was considered statistically significant. Analyses were performed using the IBM SPSS statistics version 20 (IBM, Armonk, NY, USA).

Results

Baseline characteristics of all participants

Of all women screened, 123 women were randomized. During 12 months of follow-up, no one was withdrawn due to intolerable side effects, but 15 women were withdrawn due to concerns about MHT and one due to lost to follow-up. Finally, 107 participants completed the 12-month follow-up and were included in the data analysis. They were treated with CEE 0.3 mg/MP 100 mg (n = 35, Group A), CEE 0.625 mg/MP 100 mg (n = 37, Group B), or CEE 0.625 mg/dydrogesterone 10 mg (n = 35, Group C). The overall rate of discontinuation among the three groups was similar (14.6%, 9.8%, and 14.6%, respectively). A comparison of baseline characteristics of postmenopausal women among the three groups is presented in Table 1. No significant difference was found among and between groups for all variables (all $P > 0.05$).

Lipid and carbohydrate parameters

The comparison of lipid and carbohydrate parameters between baseline and 12 months after treatment is presented in Table 2. The Groups B and C (receiving standard-dose CEE) showed a significant increase in HDL-C level at 12 months after treatment ($P = 0.033$ in Group B; $P = 0.006$ in Group C) while HDL-C level in Group A (the half-dose CEE) did not significantly changed ($P = 0.519$), compared with baseline. The mean increases of HDL-C levels in Groups B and C were similar ($P = 0.679$) and were significantly more than that in Group A ($P = 0.012$ and $P = 0.024$, respectively). The LDL-C levels were decreased at 12 months after treatment in Groups B and C by 9.6% and 12.9%, respectively, compared with baseline ($P = 0.039$ in Group B; $P = 0.029$ in Group C), without significant difference between the two groups ($P = 0.524$). In Group A, no significant change was observed in LDL-C level compared with baseline ($P = 0.426$). The change of LDL-C level in Group B and Group C was significantly higher than that in Group A ($P = 0.026$ and $P = 0.014$, respectively). TC levels in each group were all decreased but without significant difference compared with baseline (all $P > 0.05$).

Triglyceride level in Group C increased significantly by 33.1% at 12-month treatment compared with baseline ($P = 0.026$), and the significant difference was found in triglyceride level at 12 months after treatment between Groups A and C ($P < 0.001$); although triglyceride level in Group B also increased by 30.0% at 12 months after treatment compared with baseline, but the difference was not

Table 1: Baseline characteristics of postmenopausal women among the three groups in this study

Characteristics	Group A (n = 35)	Group B (n = 37)	Group C (n = 35)	F	P
Age (years)	53.7 ± 4.2	53.1 ± 3.1	53.4 ± 4.5	0.277	0.827
Age at menopause (years)	49.4 ± 3.7	49.3 ± 2.8	49.4 ± 4.0	0.095	0.980
Length of menopause (years)	4.4 ± 1.5	3.9 ± 1.3	4.0 ± 1.3	0.941	0.394
Systolic BP (mmHg)	117.2 ± 13.4	111.3 ± 9.6	110.1 ± 11.3	2.549	0.085
Diastolic BP (mmHg)	73.6 ± 8.6	69.1 ± 7.8	69.3 ± 7.9	2.604	0.081
BMI (kg/m^2)	23.6 ± 3.1	22.8 ± 3.0	23.6 ± 2.3	0.721	0.484
WC (cm)	78.9 ± 8.4	75.9 ± 7.1	77.5 ± 7.5	0.941	0.395
Waist-hip ratio	0.77 ± 0.05	0.75 ± 0.06	0.79 ± 0.05	0.935	0.390
TFM (g)	17,441 ± 1779	18,215 ± 2238	17,608 ± 1641	0.337	0.715
TC (mmol/L)	5.22 ± 0.77	5.26 ± 0.63	5.30 ± 1.36	0.975	0.377
Triglycerides (mmol/L)	1.43 ± 0.73	1.20 ± 0.73	1.21 ± 0.52	0.652	0.570
HDL-C (mmol/L)	1.52 ± 0.28	1.48 ± 0.32	1.42 ± 0.35	0.785	0.468
LDL-C (mmol/L)	3.24 ± 0.80	3.33 ± 0.69	3.49 ± 1.20	0.562	0.572
Apolipoprotein A (g/L)	1.51 ± 0.12	1.49 ± 0.14	1.44 ± 0.17	2.347	0.115
Apolipoprotein B (g/L)	0.98 ± 0.22	1.00 ± 0.15	0.98 ± 0.17	0.574	0.566
Fasting glucose (mmol/L)	5.10 ± 0.37	5.65 ± 0.90	5.44 ± 0.67	2.824	0.078
HbA1c (%)	5.56 ± 0.32	5.69 ± 0.68	5.61 ± 0.40	0.244	0.812
Insulin (mU/ml)	7.96 ± 4.41	8.49 ± 3.05	9.49 ± 4.63	1.012	0.320
HOMA-IR	1.97 ± 0.93	2.17 ± 0.98	2.37 ± 1.35	0.560	0.573

Data are given as mean ± SD. Group A: Received CEE 0.3 mg + MP 100 mg daily; Group B: Received CEE 0.625 mg + MP 100 mg daily; Group C: Received CEE 0.625 mg + dydrogesterone 10 mg daily. CEE: Conjugated equine estrogen; MP: Micronized progesterone; HOMA-IR: Homeostasis model assessment-insulin resistance; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; HbA1c: Glycosylated hemoglobin; SD: Standard deviation; WC: Waist circumference; BP: Blood pressure; TC: Total cholesterol; TFM: Total fat mass; BMI: Body mass index.

significant (P = 0.140). Moreover, the elevations in Groups B and C were also comparable (P = 0.342).

The levels of apolipoprotein A at 12 months after treatment in Groups B and C significantly increased by 9.4% and 13.2% compared with baseline and were significantly more than that of Group A (P = 0.005 and P = 0.002, respectively). Apolipoprotein B levels of the three groups did not change significantly at 12 months after treatment compared with baseline and were comparable among the three groups (all P > 0.05).

The levels of fasting glucose decreased significantly in both Group B (by 12.0%, P = 0.003) and Group C (by 9.7%, P = 0.006) at 12 months after treatment compared with baseline, and no significant difference was found between these two groups (P = 0.573). In Group A, the level of fasting glucose increased slightly compared with baseline, but without a significant difference (P = 0.103). Compared with baseline, levels of glycosylated hemoglobin (HbA1c) decreased significantly in Groups B and C (P = 0.037 and P = 0.012, respectively) and increased slightly in Group A (P = 0.645) at 12 months after treatment. The levels of fasting insulin in three groups did not reach significance at 12 months after treatment compared with baseline and were comparable among the three groups (all P > 0.05), as was also the case in HOMA-IR.

Body composition and blood pressure

After 12-month treatment, no significant increases in BMI were found in any of the three groups compared with baseline, so as to WC and total fat mass. Waist-hip ratio decreased significantly in Group C at 12 months after treatment compared with baseline (P = 0.004), but there were no significant differences in waist-hip ratio at 12 months between Group C and other two groups (all P > 0.05). There were no significant differences in systolic BP among the three groups. A significant decrease in diastolic BP compared with baseline was found in Group A [P = 0.007; Table 3].

Discussion

Our study demonstrated that the effect of standard-dose CEE supplementation was better than that of half-dose CEE on the parameters of MetS components among generally healthy postmenopausal women in China. Adding natural MP will not increase triglyceride levels compared with adding dydrogesterone after 12-month continuous sequential MHT. The CEE 0.625 mg/MP 100 mg and CEE 0.625 mg/dydrogesterone 10 mg resulted in improvements of HDL-C, LDL-C, apolipoprotein A, fasting glucose, and HbA1c levels, compared with CEE 0.3 mg/MP 100 mg at 12 months of treatment. However, CEE 0.625 mg/dydrogesterone 10 mg increased the triglyceride levels compared with the other two groups. All the three groups had neutral effects on TC, apolipoprotein B, and fasting insulin levels.

The alterations of lipid profile during perimenopause and after menopause are toward a more atherogenic direction, with increased levels of LDL-C and TG and decreased levels of HDL-C although the mechanisms behind these changes are unknown. All large randomized controlled trials for MHT using CEE, including postmenopausal estrogen/progestin interventions (PEPI), Heart and Estrogen/Progestin Replacement Study (HERS), and

Table 2: Lipid and carbohydrate parameters at baseline and 12 months after treatment in the three groups

Parameters	Baseline	12 months after treatment	Absolute change	Statistical values	*P*
TC (mmol/L)					
Group A	5.22 ± 0.77	5.19 ± 1.05	−0.03 (−2.5)	−0.112*	0.906
Group B	5.26 ± 0.63	5.22 ± 0.89	−0.04 (−2.2)	−0.194*	0.848
Group C	5.30 ± 1.36	5.28 ± 0.77	−0.02 (−3.0)	−0.060*	0.953
Triglycerides (mmol/L)					
Group A	1.43 ± 0.73	1.40 ± 0.98	−0.03 (−2.1)	−0.112*	0.912
Group B	1.20 ± 0.73	1.56 ± 0.97	0.36 (30.0)	1.529*	0.140
Group C	1.21 ± 0.52	1.61 ± 0.80	0.40 (33.1)	2.387*	0.026
HDL-C (mmol/L)					
Group A	1.52 ± 0.28	1.56 ± 0.24	0.04 (2.6)	0.654*	0.519
Group B	1.48 ± 0.32	1.66 ± 0.32	0.18 (12.2)	2.263*	0.033
Group C	1.42 ± 0.35	1.65 ± 0.35	0.23 (16.2)	3.0278	0.006
LDL-C (mmol/L)					
Group A	3.24 ± 0.80	3.08 ± 0.70	−0.16 (−4.9)	−0.811*	0.426
Group B	3.33 ± 0.69	3.01 ± 0.75	−0.32 (−9.6)	−2.215*	0.039
Group C	3.49 ± 1.20	3.04 ± 0.77	−0.45 (−12.9)	−2.308*	0.029
Apolipoprotein A (g/L)					
Group A	1.51 ± 0.12	1.52 ± 0.17	0.01 (0.7)	0.440*	0.664
Group B	1.49 ± 0.14	1.63 ± 0.20	0.14 (9.4)	3.030*	0.006
Group C	1.44 ± 0.17	1.63 ± 0.18	0.19 (13.2)	5.529*	<0.001
Apolipoprotein B (g/L)					
Group A	0.98 ± 0.22	1.11 ± 0.41	0.13 (13.3)	2.583*	0.162
Group B	1.00 ± 0.15	0.97 ± 0.20	−0.03 (−3.0)	−0.404*	0.690
Group C	0.98 ± 0.17	0.98 ± 0.18	0 (0.0)	0.008*	0.994
Fasting glucose (mmol/L)					
Group A	5.10 ± 0.37	5.36 ± 0.67	0.26 (5.1)	1.698*	0.103
Group B	5.65 ± 0.90	4.97 ± 0.60	−0.68 (−12.0)	−3.323*	0.003
Group C	5.44 ± 0.67	4.91 ± 0.85	−0.53 (−9.7)	−3.027*	0.006
HbA1c (%)					
Group A	5.56 ± 0.32	5.61 ± 0.39	0.05 (0.9)	0.467*	0.645
Group B	5.69 ± 0.68	5.35 ± 0.40	−0.34 (−5.1)	−2.220*	0.037
Group C	5.61 ± 0.40	5.35 ± 0.43	−0.26 (−4.6)	−2.731*	0.012
Insulin (mU/ml)					
Group A	7.96 ± 4.41	8.97 ± 4.24	1.01 (12.7)	0.862*	0.399
Group B	8.49 ± 3.05	7.37 ± 4.21	−1.12 (−13.2)	−1.109*	0.279
Group C	9.49 ± 4.63	8.60 ± 4.10	−0.89 (−9.4)	−0.773*	0.448
HOME-IR					
Group A	1.97 ± 0.93	2.23 ± 1.06	0.26 (13.2)	0.918†	0.378
Group B	2.17 ± 0.98	1.66 ± 1.06	−0.51 (−23.5)	−1.988†	0.072
Group C	2.37 ± 1.35	1.96 ± 1.16	−0.41 (17.3)	−1.244†	0.226

Data are given as mean ± SD, or different value (%). *Student's *t*-test; †Kruskal-Wallis test and Wilcoxon Mann-Whitney test. Group A (n = 35): Received CEE 0.3 mg + MP 100 mg daily; Group B (n = 37): Received CEE 0.625 mg + MP 100 mg daily; Group C (n = 35): Received CEE 0.625 mg + dydrogesterone 10 mg daily. CEE: Conjugated equine estrogen; MP: Micronized progesterone; HOMA-IR: Homeostasis model assessment-insulin resistance; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; HbA1c: Glycosylated hemoglobin; SD: Standard deviation; TC: Total cholesterol.

Women's Health Initiative (WHI) trials, confirmed that MHT produced a reduction in LDL-C, an increase in HDL-C, and an increase in TG compared with placebo.[10,12,13] In the PEPI trial, the greatest increase in HDL-C was seen with oral administration of CEE alone and the HDL-C increase was attenuated in women treated with a combination of CEE and progestin (least with micronized progestin and most with MPA).[10] CEE 0.625 mg/d plus cyclic MP 200 mg/d 12 d/months for 3 years increased HDL-C by 0.11 mmol/L. The HERS trial (CEE 0.625 mg/MPA 2.5 mg) found a mean LDL-C decreased by 11%, mean HDL-C increased by 6%, and mean TG levels increased by 7%. Our study found that a 12-month continuous sequential oral intake of 0.625 mg CEE combined with 100 mg MP or 10 mg dydrogesterone daily could increase HDL-C by 12.2–16.2% and decrease LDL-C by 9.6–12.9%. Half-dosage CEE seemed not to make any improvement in lipid profile. Compared with other major trials, the better improvement of LDL-C and HDL-C in our trial attributable to the progestin part was MP and dydrogesterone or racial differences. Another interesting issue

Table 3: Body composition parameters and BP at baseline and 12 months after treatment in the three groups

Parameters	Baseline	12 months after treatment	Absolute change	Statistical values	*P*
BMI (kg/m^2)					
Group A	23.6 ± 3.1	23.8 ± 3.2	0.2 (0.8)	0.167	0.866
Group B	22.8 ± 3.0	22.8 ± 2.8	0 (0.0)	0.316	0.758
Group C	23.6 ± 2.3	23.5 ± 2.3	0.1 (0.4)	0.098	0.923
WC (cm)					
Group A	78.9 ± 8.4	81.4 ± 6.3	2.5 (3.2)	0.997	0.319
Group B	75.9 ± 7.1	79.6 ± 8.2	3.7 (4.9)	0.605	0.579
Group C	77.5 ± 7.5	80.1 ± 7.1	2.6 (3.4)	0.167	0.878
Waist-hip ratio					
Group A	0.77 ± 0.05	0.75 ± 0.05	−0.02 (−2.6)	−1.307	0.194
Group B	0.75 ± 0.06	0.72 ± 0.05	−0.03 (−4.0)	−1.978	0.067
Group C	0.79 ± 0.05	0.76 ± 0.04	−0.03 (−3.8)	−3.212	0.004
TFM (g)					
Group A	17,441 ± 1779	18,209 ± 1885	768 (4.4)	1.529	0.140
Group B	18,215 ± 2238	17,167 ± 1883	−1048 (−5.8)	−1.817	0.092
Group C	17,608 ± 1641	18,270 ± 2115	662 (3.8)	1.244	0.223
Systolic BP (mmHg)					
Group A	117.2 ± 13.4	119.0 ± 10.4	1.8 (1.5)	0.928	0.366
Group B	111.3 ± 9.6	111.7 ± 12.4	0.4 (0.4)	0.135	0.894
Group C	110.1 ± 11.3	109.3 ± 12.4	−0.8 (0.7)	0.322	0.750
Diastolic BP (mmHg)					
Group A	73.6 ± 8.6	67.2 ± 6.5	−6.4 (8.7)	−2.926	0.007
Group B	69.1 ± 7.8	70.7 ± 8.3	1.6 (2.3)	0.645	0.525
Group C	69.3 ± 7.9	66.1 ± 7.6	−3.2 (4.5)	−1.536	0.133

Data are given as mean ± SD, or different value (%). Group A (n = 35): Received CEE 0.3 mg + MP 100 mg daily; Group B (n = 37): Received CEE 0.625 mg + MP 100 mg daily; Group C (n = 35): Received CEE 0.625 mg + dydrogesterone 10 mg daily. CEE: Conjugated equine estrogen; MP: Micronized progesterone; BMI: Body mass index; WC: Waist circumference; BP: Blood pressure; TFM: Total fat mass; SD: Standard deviation.

found in our trial was that adding MP to standard-dosage CEE seemed not to improve triglyceride levels (P = 0.140) although this might due to small sample size of our trial.

Our findings were consistent with the results of large randomized controlled trials and observational studies of MHT on apparently healthy postmenopausal women, which found decreased fasting glucose levels[10,14-16] and hemoglobin A1C levels,[17-19] but this only referred to standard-dosage CEE, not half-dosage CEE. In the PEPI trial, 875 younger postmenopausal women (45–64 years of age) were followed up for 3 years and a statistically significant decrease of 2–3% in fasting glucose level (P < 0.03) was found.[10] Our study found no significant change in fasting glucose in women taking 0.3 mg CEE daily continuously with sequential natural MP 100 mg daily for 12 days, but found a significant decrease in fasting glucose level for those who take 0.625 mg CEE daily (12% when MP added, P = 0.003; 9.7% when dydrogesterone added, P = 0.006). No significant difference was found in fasting glucose level after 12 months of treatment between Group B and Group C (P = 0.573). This suggested that the treatment benefit on fasting glucose level might be attributable to the estrogen component, but did not change when progestin was added.

Several studies have reported favorable effects of MHT on BMI, abdominal fat, and waist-hip ratio. Our study demonstrated that 12-month continuous sequential supplement of CEE 0.3 mg/MP 100 mg, CEE 0.625 mg/MP 100 mg, or CEE 0.625 mg/dydrogesterone 10 mg did not alter BMI, WC, and total fat mass (TFM). However, CEE 0.625 mg/dydrogesterone 10 mg could reduce waist-hip ratio slightly but significantly by 3.8% (P = 0.004). The WHI trial (CEE 0.625 mg/MPA 2.5 mg) showed a statistically significant decrease in BMI (−0.19 ± 0.04, P < 0.01) and WC (0.77 ± 0.10 cm, P < 0.01) during the 1st year of treatment.[20] The HERS (HERS; CE 0.625 mg/MPA 2.5 mg) also found that women receiving MHT experienced slight but significant weight loss (−0.5 kg), decreased BMI (−0.2 kg/m^2), and decreased abdominal obesity (waist hip ratio: −0.01; WC: −0.8 cm) during follow-up, compared with placebo.[8] All women in the PEPI trial (CEE 0.625 mg/d + MPA 2.5 mg or MP 200 mg) gained weight, but the mean increase from baseline was smaller among women assigned to unopposed CEE at 3 years of follow-up.[10] The half-dose CEE group reduced diastolic pressure significantly by 8.7%. This might be due to the reduced protective effect of half-dose CEE compared with standard-dose CEE on elasticity of the vascular wall. And, this was supported by a pile of basic researches.[21-24]

MHT affects many metabolic processes that have a potential influence on CVD risk. The randomized controlled trials provided evidence that MHT products may differ substantially with regard to their impact on the components of

MetS parameters, which depend on the estrogen and progestin used, as well as regimen, dosage, and routes of administration. The favorable effects of MHT on the components of MetS parameters may be in a CEE dose-dependent manner, which explained why standard-dosage CEE was effective in improving serum lipid and sugar parameters while half-dosage CEE was not in our trial. Adding MP or dydrogesterone has similar effects on biochemical markers of MetS, but adding 100 mg MP daily sequentially for 10 days may not improve TG level. Larger sample size is needed to further prove this phenomenon. Our study will follow the participants for the extended 12 months to further discover the 24-month effects of the three MHT regimens on MetS parameters.

In conclusion, among Chinese postmenopausal women, half-dose CEE was not sufficient to induce a favorable lipid and carbohydrate profile compared with standard-dose CEE. Adding natural MP may counterbalance the TG-increasing effect of CEE.

Financial support and sponsorship

This study was supported by a grant from National "Twelfth Five-Year" Plan for Science and Technology Support (No. 2014BAI10B10-1).

Conflicts of interest

There are no conflicts of interest.

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