Effect of Menopausal Hormone Therapy on Bone Mineral Density in Chinese Women: A 2-Year, Prospective, Open-Label, Randomized-Controlled Trial

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Background: This study was designed to explore the effect of menopausal hormone therapy (MHT) on bone mineral density (BMD) in Chinese women.

Material/Methods: This was a prospective, open-label, randomized-controlled clinical trial. We randomly assigned 123 postmenopausal women to 3 groups: group A received 0.625 mg conjugated equine estrogen (CEE) plus 100 mg micronized progesterone (MP), group B received 0.3 mg CEE daily plus 100 mg MP, and group C received 0.625 mg CEE daily plus 10 mg dydrogesterone (DHG). All subjects received a 2-year intervention and drugs were given in a continuous sequential pattern.

Results: Ninety-six patients were followed up. At 1 year, groups A and B gained 2.31% and 1.95% BMD, respectively (P<0.01); at 2 years, groups B and C gained 2.37% and 4.15% BMD (P<0.01) respectively. At 2 years, group A gained 3.28% BMD in the femoral neck and 3.77% BMD in Ward’s triangle (P<0.05). At 1 year, group B lost 2.14% BMD in the trochanter and 1.20% BMD in the total hip (P<0.05); at 2 years, group B lost 1.51% BMD in the total hip (P<0.01). ALP, Ca, P, and Ca/Cr levels were all decreased in the 3 groups (P<0.05). The changes in Cr level at 1 and 2 years were not significant when compared with baseline in all groups (P>0.05).

Conclusions: Both lower-dose and standard-dose CEE increased lumbar BMD, sustain femoral neck BMD, and Ward’s triangle BMD, while there was a reduced bone turnover rate. Standard-dose CEE combined with MP can increase BMD at these 2 sites. CEE combined with MP is recommended because it has better clinical benefits.

MeSH Keywords: Bone Density • Hormones • Osteoporosis, Postmenopausal

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Background

With declining levels of estrogen in postmenopausal women, bone absorption is greater than formation, which causes a bone metabolic negative balance. Thus, these women are particularly susceptible to osteoporosis.

In China, postmenopausal osteoporosis is becoming a serious public health issue because of the rapid increase in the average life span. It is a generalized bone disease characterized by low bone mass and deteriorating structure that leads to bone fragility and fractures. Osteoporotic fracture is the most serious outcome of osteoporosis; it may result in permanent disability, admission to institutional care, and even death [1,2].

Many large-scale studies [3,4] found that menopause hormone therapy (MHT) helps to maintain or increase bone mineral density (BMD), prevents postmenopausal osteoporosis, and reduces the risk of osteoporotic fracture. However, different types of estrogen or progestogen, as well as different formulations, doses, timing of initiation, durations of therapy, and patient characteristics, may play different roles in the effects of MHT.

Therefore, a prospective, open-label, randomized-controlled clinical trial was conducted and 123 Chinese postmenopausal women were included in our study. The objective of this study was to evaluate the changes in bone metabolism biomarkers and BMD in the lumbar spine and hip after menopausal hormone therapy (MHT) during follow up. We also discuss which MHT method is most suitable for the prevention of postmenopausal osteoporosis among Chinese postmenopausal women.

Material and Methods

Patients

This was a prospective, open-label, randomized-controlled clinical trial conducted at Peking Union Medical College Hospital in China, between February 2014 and September 2017. We included 123 Chinese postmenopausal women in this study and randomly assigned them to 3 groups according to a random number table. The study was approved by the Ethics Committee of PUMCH (No. S-648, dated February 20, 2014). All participants provided written informed consent before study entry.

To be included in the study, the women had to be early menopausal (defined as going through amenorrhea for longer than 6 months [5,6] and less than 5 years), aged 40–60 years, with serum estradiol <30 pg/ml, follicle stimulating hormone >40 IU/L, with climacteric symptoms, and in good physical and mental health.

Women were excluded if they had a history or presence of any type of malignancy, cardiovascular disease, severe chronic disease, or endocrine disease, or had been diagnosed with secondary osteoporosis. Women who had ever used estrogen or calcitonin or had used bisphosphonates within the past 6 months were also excluded. Women were excluded if they had any evidence of alcohol or drug abuse.

Medication

Patients in group A received 0.625 mg CEE (Xinjiang Xinziyuan Pharmaceutical Co., China) daily plus 100 mg MP (Zhejiang Xianju Pharmaceutical Co., China) for the last 12 days of each 28-day cycle orally. Patients in group B received 0.3 mg CEE daily plus 100 mg MP for the last 12 days of each 28-day cycle orally. Patients in group C received 0.625 mg CEE daily plus 10 mg DHG (Solvay Pharmaceuticals, Inc., the Netherlands) for the last 12 days of each 28-day cycle orally. The 24 cycles began without discontinuation of drugs.

Curative effect assessment

At baseline, participants were asked about age, menopausal age, and duration of menopause. In addition, anthropometric data, including weight, height, body mass index (BMI=weight/height²), waist circumference, hip circumference, and systolic and diastolic blood pressure, were also measured by the same evaluator.

The BMD of spine (L2–L4) and hip (femoral neck, Ward triangle, trochanter, total hip) were measured by use of a dual-energy X-ray absorptiometry instrument (DXA, Lunar Prodigy, GE®, USA). Bone metabolism markers (alkaline phosphatase (ALP), Ca, P, Cr) were processed by automated analyzer (Beckman Coulter, AU5800® USA). BMD and levels of bone metabolism indexes were measured at 0, 12, and 24 months.

For the safety evaluation, routine blood and urine tests, liver and renal function, blood glucose, and lipid levels were assessed. Pelvic examination, pap smear, transvaginal uterine ultrasonography, and breast examination were conducted annually.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA). The quantitative variables are shown as mean ± standard deviation (SD), and qualitative variables are presented as frequencies and percentages. Repetitive measurement deviation analysis, χ² tests, and Fisher’s exact test were used. Statistical significance was defined as P<0.05.
Results

General Information

A total of 135 women were screened and 123 women were recruited for this study; 12 women were excluded from the analysis because they had an unqualified history or failed to pass the medical examination. Finally, 96 women completed the trial and their data were included in the statistical analysis: there were 33 women in group A, 30 women in group B, and 33 women in group C. There were 27 women who withdrew from the study over a 2-year period: 8 in group A, 11 in group B, and 8 in group C.

The baseline characteristics of the subjects who completed the study are presented in Table 1, showing there were no significant differences among the 3 groups.

Effectiveness evaluation

Changes in lumbar and hip BMD

At baseline, no differences were observed in BMD values between groups. The changes after treatment are shown in Table 2.

BMD of lumbar: At 1 year, groups A and B had gained 2.31% (P<0.01) and 1.95% BMD (P<0.05) respectively; at 2 years, groups B and C had gained 2.37% (P<0.01) and 4.15% BMD (P<0.01) respectively. Other changes compared with baseline were not statistically significant (P all>0.05).

BMD of femoral neck and Ward’s triangle: At 2 years, group A had gained 3.28% BMD in the femoral neck and 3.77% in Ward’s triangle (P<0.05). Other changes compared with baseline were not statistically significant (P>0.05).

BMD of trochanter and total hip: At 1 year, group B had lost 2.14% BMD in the trochanter (P<0.01) and 1.20% in total hip (P<0.05); at 2 years, the BMD in total hip of group B had lost 1.51% (P<0.01). Other changes compared with baseline were not statistically significant (P >0.05).

The differences between 1 year and 2 years were not statistically significant (P>0.05). The differences among treatment groups were not statistically significant (P>0.05).

Changes in bone metabolism biomarkers

At baseline, no significant differences were observed in blood ALP, Ca, P, Cr, or Ca/Cr values between groups.

Levels of bone metabolism biomarkers were significantly decreased after 1-year and 2-year treatment in all groups compared with the baseline (P<0.05). Except the level of Ca at 2 year were higher than 1 year in the 3 groups (P<0.05), there was no significant difference in other bone metabolism biomarkers between 1 year and 2 years (P>0.05). The differences among treatment groups were not statistically significant (P>0.05) (Table 3).

Osteoporotic fracture

No osteoporotic fractures were found during the 2-year follow-up.

Table 1. Baseline characteristics of the subjects who completed the study.

|                          | Group A      | Group B      | Group C      | F value | P value |
|--------------------------|--------------|--------------|--------------|---------|---------|
| age (y)                  | 52.76±2.96   | 53.35±4.24   | 52.96±4.28   | 0.187   | 0.83    |
| Menopause age (y)        | 49.49±2.65   | 49.63±3.85   | 49.71±3.99   | 0.031   | 0.969   |
| Menopausal duration (y)  | 3.27±1.31    | 3.71±1.44    | 3.75±1.24    | 1.232   | 0.297   |
| Height (cm)              | 158.89±4.66  | 160.65±4.30  | 160.65±4.60  | 1.549   | 0.218   |
| Weight (Kg)              | 58.37±8.92   | 61.25±7.59   | 60.50±6.52   | 1.162   | 0.317   |
| BMI (Kg/m²)              | 23.05±2.96   | 23.81±3.51   | 23.43±2.19   | 0.518   | 0.598   |
| WC (cm)                  | 77.30±7.30   | 79.30±8.03   | 77.45±6.95   | 0.718   | 0.491   |
| HC (cm)                  | 94.60±5.28   | 96.70±6.96   | 96.18±4.37   | 1.148   | 0.322   |
| Waist-to-hip ratio       | 0.82±0.06    | 0.82±0.04    | 0.80±0.05    | 0.77    | 0.466   |
| Systolic BP (mmHg)       | 111.67±10.41 | 114.52±14.34 | 110.03±11.16 | 1.118   | 0.332   |
| Diastolic BP (mmHg)      | 68.63±7.18   | 73.06±8.84   | 69.03±7.84   | 2.997   | 0.055   |
| TN (mm)                  | 0.38±0.08    | 0.38±0.08    | 0.40±0.07    | 0.727   | 0.486   |

WC – waist circumference; HC – hip circumference; thickness of endometrium.
### Table 2. Changes in lumbar and hip BMD (g/cm²).

|                      | Group A          | Group B          | Group C          |
|----------------------|------------------|------------------|------------------|
|                      | Baseline         | 1 year           | 2 year           |
| Lumbar 2–4           | 1.147±0.150      | 1.146±0.176      | 1.151±0.137      |
|                      | 1.171±0.144*     | 1.166±0.164*     | 1.172±0.137      |
|                      | 1.167±0.139      | 1.170±0.163*     | 1.195±0.137*     |
| Femoral neck         | 0.879±0.127      | 0.878±0.127      | 0.901±0.145      |
|                      | 0.898±0.155      | 0.891±0.126      | 0.911±0.112      |
|                      | 0.905±0.124*     | 0.888±0.112      | 0.915±0.137      |
| Ward’s triangle      | 0.719±0.131      | 0.716±0.143      | 0.731±0.122      |
|                      | 0.725±0.143      | 0.703±0.130      | 0.735±0.106      |
|                      | 0.745±0.135**    | 0.723±0.127      | 0.748±0.121      |
| Trochanter           | 0.743±0.120      | 0.763±0.113      | 0.749±0.088      |
|                      | 0.745±0.118      | 0.746±0.111*     | 0.745±0.086      |
|                      | 0.750±0.118      | 0.756±0.106*     | 0.756±0.090      |
|                      | 0.95±0.137       | 0.949±0.128      | 0.95±0.116       |
| Total hip            | 0.95±0.135       | 0.936±0.122*     | 0.946±0.100      |
|                      | 0.945±0.130      | 0.932±0.113*     | 0.96±0.126       |

* 1-year or 2-year vs. baseline P<0.05; * 1-year vs. 2-year P<0.05.

### Table 3. Changes in bone metabolism biomarkers.

|                      | Group A          | Group B          | Group C          |
|----------------------|------------------|------------------|------------------|
|                      | Baseline         | 1 year           | 2 year           |
| ALP (IU/L)           | 77.21±19.75      | 60.07±14.58*     | 62.40±18.17*     |
|                      | 60.07±14.53*     | 61.73±18.33*     | 61.42±14.87*     |
|                      | 62.40±18.17*     | 63.12±16.96*     | 64.74±19.87*     |
| Ca (mmol/L)          | 2.38±0.09        | 2.37±0.11        | 2.40±0.09        |
|                      | 2.38±0.07*       | 2.61±0.07*       | 2.26±0.09*       |
|                      | 2.30±0.08**      | 2.31±0.07**      | 2.32±0.13**      |
| P (mmol/L)           | 1.24±0.11        | 1.24±0.14        | 1.25±0.10        |
|                      | 1.11±0.14*       | 1.15±0.14*       | 1.14±0.15*       |
|                      | 1.10±0.11*       | 1.18±0.17        | 1.21±0.59        |
| Cr (µmol/L)          | 60.25±6.71       | 58.76±8.76       | 60.07±7.47       |
|                      | 60.40±6.00       | 61.39±7.75       | 62.00±7.93       |
|                      | 61.47±9.39       | 60.6±6.98        | 61.45±8.01       |
| Ca/Cr                | 0.040±0.0056     | 0.041±0.0082     | 0.04±0.0054      |
|                      | 0.038±0.0049*    | 0.038±0.0058*    | 0.037±0.0047*    |
|                      | 0.038±0.0054*    | 0.038±0.0051*    | 0.038±0.0058*    |

* 1-year or 2-year vs. baseline P<0.05; * 1-year vs. 2-year P<0.05.
Safety evaluation

All the 3 groups could sustain or improve blood glucose and lipid metabolism in postmenopausal women, but the effects of group A and C were better than in group B. The thickness of endometrium and grade of breast density showed no obvious differences among the 3 groups. The incidence of uterine bleeding and breast tenderness were lower in group B.

Discussion

The rapid loss of bone mass after menopause is mainly due to the decrease in estrogen level, and bone resorption is greater than bone formation, so the bone remodeling is unbalanced. The clinical manifestations and treatments of postmenopausal osteoporosis are significantly different from other types of osteoporosis. The loss of bone mass in the first 10 years after menopause accounts for 2/3 of the total loss, especially in the period 1 to 3 years after menopause.

Bone loss in the 1st year is 3–10%. In the 2nd to 3rd year, bone loss is 6–14% [7]. The risk of fracture doubles with every 10% reduction in BMD [8]. In recent years, many large clinical studies proved that MHT can increase BMD and prevent osteoporosis, and the 2017 position statement of the North America Menopause Society (NAMS) states that MHT is the first-line therapy for women to prevent postmenopausal osteoporosis [9].

The main purpose of this study was to compare the effect of lower-dose and standard-dose CEE combined with MP and DHG on bone density and bone metabolism. In the Women's Health, Osteoporosis, Progestin, and Estrogen trial (HOPE) [3], lower-dose CEE (0.3 mg/d and 0.45 mg/d) with or without medroxyprogesterone acetate (MPA) increased spine BMD, and Ran et al. [10] found similar results. In our study, at 1-year visit, groups A and B had gained 2.31% (P<0.01) and 1.95% BMD (P<0.05) respectively; at 2-year visit, groups B and C had gained 2.37% (P<0.01) and 4.15% BMD (P<0.01), respectively. Other changes compared with baseline were not statistically significant (P >0.05). The results suggested that both lower-dose and standard-dose CEE could sustain BMD of the 2 sites and prevent bone loss.

Research showed that lower-dose estrogen can increase BMD, but the effect was lower than in the higher-dose group [12]. At 2-year visit in our study, group A had gained 3.28% BMD in the femoral neck and 3.77% in Ward’s triangle BMD (P<0.05). The differences between group A and B might be caused by different doses of CEE, and the difference between group A and C might be caused by different types of progesterone. However, the differences were not statistically significant, and firm conclusions should only be drawn after studies with larger samples.

At 1-year visit, group B had lost 2.14% BMD in the trochanter (P<0.01) and 1.20% in total hip (P<0.05); at 2-year visit, group B had lost 1.51% BMD in total hip (P<0.01). Other changes compared with baseline were not statistically significant (P >0.05). The results suggest that lower-dose CEE can increase lumbar BMD but cannot prevent trochanter and total hip bone loss. The reasons may include the following. Firstly, the effects of estrogen on BMD were site-specific and were greater in the spine than in the hip. These results were expected, since the spine has a higher remodeling rate than the hip [13]; thus, they may be more responsive to estrogen, which alters the resorption-formation balance. Secondly, it has been hypothesized that the differential distributions of cortical and trabecular bone in the spine and hip are associated with differential rates of loss and gain of BMD at those sites [14], but the standard-dose groups sustained the BMD of trochanter and total hip in our study. This indicates that these 2 sites may not be sensitive to CEE, and a larger dose was needed to prevent bone loss.

The PEPI trial (a 3-year study) showed that between 70% and 90% of the increase in BMD of participants in active regimens occurred during the first 12 months, with the remaining 10% to 30% increase occurred during the final 24 months. In our study, the differences in BMD in all groups between 1-year visit and 2-year visit were not statistically significant (P>0.05), which indicates that the increase in BMD mainly occurred in the first 12 months, then the level was sustained in the following months.

There are many biomarkers reflecting bone transformation; we chose the most frequently and routinely examined biomarkers used in clinical laboratory tests – alkaline phosphatase (ALP), calcium (Ca), phosphorus (P), creatinine (Cr), and ratio of calcium to creatinine (Ca/Cr) – to reflect the bone metabolic process, and this would make clinical work easier.
Mukaiyama et al. [15] found that, in postmenopausal women, elevated ALP in serum was associated with aging and was mainly caused by high bone turnover. Therefore, ALP may be used as a bone formation marker and can be used to diagnose osteoporosis.

In a 3-year study, SUN Aijun [16] et al. found that either 0.75 mg or 1.5 mg 17β-estradiol with MP or MPA was effective in preventing early bone loss in postmenopausal women. The ALP level decreased after MHT, and the drop rate was 20–36% in the 1 year and then maintained at a low level. In our study, ALP level also decreased, and drop rates were 18.4–24.1% at 1 year (P<0.001) and 16.5–19.9% at 2 year (P<0.001). The results indicated that both lower-dose and standard-dose CEE can reduce the bone formation rate. The differences in ALP in all groups between 1 year and 2 years were not statistically significant (P>0.05), which suggests that the level of ALP tend to be stable after treatment for 1 year, consistent with previous studies.

Ca and P are the most abundant inorganic elements in the human body and are important components of inorganic salt in bone. Bone mineral is formed by the 1: 2 combination of Ca and P [17]. Marenzana [18] et al. reported that serum Ca level is an important indicator for evaluating bone metabolism in the body.

Seventy-five years ago, Albright described for the first time a connection between osteoporosis and estrogen loss. He went on to show that estrogen treatment (ET) leads to positive Ca and P balance as well as prevention of vertebral damage in postmenopausal osteoporosis [19]. Although prior clinical studies demonstrate that ET prevents postmenopausal bone loss and ET has important effects on calcium and phosphorus homeostasis, the biological basis of these actions is poorly understood.

In the Multi-Ethnic Study of Atherosclerosis (MESA) [20], the results showed that women who used ET had lower serum Ca [–13 mg/dl, (95% CI –0.17, –0.10), P<0.001] and lower Feca [–0.15%, (95% CI –0.21, –0.09), P<0.001]. P was lower [–0.19 mg/dL (95% CI –0.23, –0.15), P<0.001] and Fephos [0.56% (95% CI 0.16, 0.96), P=0.007] was higher in women on ET. The results suggest that these associations are attributable to increased Ca intake into bone and increased urinary P excretion.

In our study, levels of Ca decreased both at 1 year and 2 years in group ABC (P all<0.001). At 1 year, the drop rates were 4.2%, 4.6%, and 5.8% respectively, suggesting that both lower-dose and standard-dose CEE can reduce bone resorption and lower bone turnover rate, perhaps through the mechanism described above. The level of Ca decreased at 2 years compared with baseline, but increased compared with 1 year (P<0.05), perhaps because endogenous estrogen levels were further reduced, so bone destruction and bone resorption were accelerated.

Levels of P decreased at 1 year in group ABC (P<0.001), and the drop rates were 10.5%, 7.3%, and 9.6%, respectively. The results indicated that both lower-dose and standard-dose CEE can lower the bone turnover rate. At 2 years, only group A had a statistically significant decline compared with baseline (P<0.001). The differences of P values in all groups between 1 year and 2 years were not statistically significant (P all>0.05).

Creatinine is produced from creatine metabolism, so it can reflect the level of creatine to some extent. Studies [21–23] have reported that creatine is closely related to lean mass and BMD. Therefore, regardless of whether the serum creatinine level is elevated or decreased, it warrants attention.

Serum creatinine levels increase when kidney function is impaired. Kaygusuz et al. [24] found that MHT was associated with statistically significant increases in glomerular filtration rate (p<0.01), while serum urea, creatinine, uric acid, urine protein, urinary creatinine, and urinary protein/creatinine ratio did not change significantly. MHT may protect the kidneys against adverse effects of aging.

In our study, the changes in Cr level at 1 year and 2 years were not significant in any of the 3 groups (P>0.05), suggesting that the serum creatinine level was stable, and MHT had no adverse effect on renal function.

The increased level of Ca in fasting morning urine was mainly from bone mass, indicating increased bone absorption. This method is the cheapest but the least sensitive, and is easily disturbed by diet. It is meaningful only when bone absorption increases significantly. In addition, the sampling is very troublesome [25].

So, in our study, Ca/Cr was tested in blood. The ratio was decreased compared with baseline both at 1 year and 2 years in all groups (P all<0.05). The results also indicate that both lower-dose and standard-dose CEE can lower the bone turnover rate.

Generally speaking, it takes 1 to 3 years for the changes of BMD to be detected in DXA, but bone metabolism biomarkers can rapidly reflect the therapeutic effect within days to 3 months after the initial treatment [26]. BMD combined with bone metabolism biomarkers can monitor of therapeutic effect of osteoporosis drugs and can assess fracture risk.

It must be mentioned that hormone therapy inevitably has some adverse effects. Zhang et al. found that low-dose HT is safer than standard-dose therapy in regard to risks of development of endometrial hyperplasia and carcinoma in postmenopausal women [27], and it was reported that tibolone causes significantly less breast tenderness and mastalgia than EPT in women [28]. The rate of vaginal bleeding was low following
low-dose oral EPT compared to that after standard-dose therapy in women [29,30]. Some RCTs have shown that low- or ultralow-dose HT is effective for the relief of menopausal symptoms and maintaining bone mass with fewer adverse effects in postmenopausal Chinese women. Isik Kaban et al. [31] suggested that pomegranate itself or its formulation extracts may support or be an alternative to the primary treatment modalities in the preservation of bone density and the treatment of vaginal epithelial atrophy in menopause. Phytoestrogen preparations are generally considered to be a safe alternative to HT [32]. Therefore, it is recommended that the lowest effective dose of HT or alternative methods should be used and individualized in postmenopausal women. This may induce fewer adverse effects and be safer and more economical for postmenopausal women.

Conclusions

Both lower-dose and standard-dose CEE increased the lumbar BMD and sustained BMD of the femoral neck and Ward’s triangle, and the standard-dose CEE combined with micronized progesterone increased BMD of these 2 sites. Lower-dose CEE could not prevent bone loss in the trochanter and total hip, whereas the standard-dose CEE could do so.

In conclusion, among Chinese postmenopausal women, standard-dose CEE induced a more favorable profile of BMD in the lumbar and hip, and standard-dose CEE combined with micronized progesterone had more clinical benefits, so this formulation is recommended.

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Conflict of interest

None.

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