The effects of different dosages of oestrogen on the bone mineral density of postmenopausal Hong Kong Chinese women: randomised controlled trial

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Objective. To determine the effects of different dosages of conjugated equine oestrogen on the bone mineral density of postmenopausal Hong Kong Chinese women.
Design. A 1-year three-arm randomised controlled trial.
Setting. Out-patient setting at a government hospital in Hong Kong.
Participants. One hundred and five women aged 45 years or older, in whom menopause had occurred not more than 2 years previously.
Intervention. Women were assigned randomly to treatment with conjugated equine oestrogen 0.625 mg/d or 0.3 mg/d, or no oestrogen.
Main outcome measure. Bone mineral density.
Results. Women who were assigned to the control group showed a significant reduction in bone mineral density in both the femoral neck and the lumbar spine (3.6%; P=0.001 and 4.0%; P<0.001, respectively). Those who received oestrogen 0.3 mg/d showed a significant reduction (3.9%; P=0.01) and a non-significant reduction (2.2%; P=0.14) in their lumbar spine and femoral neck bone mineral densities, respectively. In contrast, there was little change in the spinal and femoral neck bone mineral densities in women who received oestrogen 0.625 mg/d.
Conclusion. The minimum effective dosage of conjugated equine oestrogen to prevent osteoporosis in postmenopausal Hong Kong Chinese women is 0.625 mg/d. The bone mineral density, however, was maintained but not increased.

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Key words: Bone density; Estrogen replacement therapy; Hong Kong; Osteoporosis, postmenopausal

Introduction

Osteoporotic fractures are a major public health problem. Although ageing is associated with a gradual loss of bone mineral density (BMD), menopause accelerates the rate at which bone is lost.[1] The mainstay of prevention of postmenopausal osteoporosis is oestrogen treatment.[2] Western studies have shown that oestrogen replacement therapy increases bone mineral density (BMD) and reduces the frequency of hip fractures in postmenopausal women.[3-6]

Osteoporosis and hip fractures become more common in the Chinese population as the population ages.[7] But we have few data on the effects of oestrogen on BMD in postmenopausal Chinese women. Whether the results of studies in western populations can be extrapolated to the Chinese population is open to question because there are many differences in the epidemiological factors between the two groups. The incidence of hip fracture in the local population[8] and in other Asian populations[9] has been found to be lower than that in the United States. Differences in bone density,[10,11] body size,[10,11] diet,[10] exercise,[10] and use of drugs[10] have been observed between American Caucasians and American Japanese, and between Japan-born and United States–born Japanese.

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It is important to know if there are any differences in the effects of oestrogen on BMD between Chinese and western populations. The first question is whether oestrogen can increase BMD in Chinese women as it does in Caucasian women, or else maintain or reduce bone loss after menopause has occurred. The second question concerns the minimum effective dose of oestrogen. Although the common consensus is that the minimum effective dose of conjugated equine oestrogen (CEO) to prevent osteoporosis is 0.625 mg,[12,13] some menopausal women are still taking long-term CEO 0.3 mg. They either cannot tolerate a higher dose of CEO or cannot continue treatment with CEO 0.3 mg that has been given initially to relieve vasomotor symptoms. A dose of CEO 0.3 mg has thus been assumed to be adequate to prevent bone loss in Chinese women. Only one study, which was a retrospective study of a western population, has shown that CEO 0.3 mg is associated with a reduction in the frequency of menopausal fractures.[14]

We conducted a randomised controlled trial to test two hypotheses: (1) that CEO 0.625 mg/d can increase BMD; and (2) that CEO 0.3 mg/d can prevent bone loss in Chinese women after menopause has occurred.

Methods

Approval of the research protocol was given by the Ethics Committee of the Hospital Authority of Hong Kong. The study was a 1-year prospective randomised controlled trial. The principal outcome measure was bone mineral density.

Study participants

One hundred and five women were recruited from the gynaecological out-patient clinics of the Queen Elizabeth Hospital between April 1995 and November 1997. Participants were Hong Kong Chinese women aged 45 years or older, in whom menopause (natural or surgical) had occurred not more than 2 years previously. The exclusion criteria were as follows: a history of breast cancer, endometrial cancer, chronic liver disease, undiagnosed vaginal bleeding, osteoporotic fracture, oestrogen treatment within 3 months of the study, diseases that involved malabsorption of calcium, and drug treatment that included corticosteroids, fluoride, vitamin D, or rifampicin.

General and pelvic examination were performed to exclude unexpected medical problems. If the last menstrual period had occurred within the previous 12 months, blood tests were performed to determine the levels of follicle-stimulating hormone and luteinizing hormone to confirm the menopausal state.

The following patient information was recorded at the time of recruitment: age; number of months after natural or surgical menopause; ethnic group; height; weight; smoking habit; alcohol consumption; physical activity; and calcium intake.

Randomisation, treatment, and follow-up

After giving informed consent, eligible women were allocated at random to one of the following three groups: the CEO 0.625 mg/d group, CEO 0.3 mg/d group, and control group. Allocation instructions were contained in consecutively numbered, opaque, sealed envelopes.

Women who were allocated to the CEO 0.625 mg/d and CEO 0.3 mg/d groups were advised to take their medications daily. Medroxyprogesterone acetate 5 mg/d was added to the regimen in the first 12 days of each month if the uterus was present. For the control group, no hormones were given. Calcium supplementation was not prescribed for any of the three groups.

Women were followed up in the gynaecological clinics 3 months, 6 months, and 1 year after the first visit. At each visit, side effects of the medications, adherence to assigned medication, development of any medical illnesses, and use of other medications was recorded. Physical examination included blood pressure measurement and pelvic examination. Drug compliance was encouraged, and research assistants telephoned women who had defaulted follow-up visits.

Main outcome measures

The main outcome measures were the BMDs (expressed in g/cm^2) of the femoral neck, and the second to fourth lumbar vertebrae. These BMDs were measured at the time of recruitment and after 12 months by using dual energy X-ray absorptiometry at the Department of Nuclear Medicine at the Queen Elizabeth Hospital. Whether the participants were taking hormones was unknown to the staff (who were blinded) at the Department of Nuclear Medicine Department.

Fasting serum cholesterol and triglyceride concentrations were measured at the time of recruitment and after 12 months.

Sample size calculation

According to the study conducted by Jensen et al,[15] the mean difference in the BMD of the lumbar spine between women taking CEO 0.625 mg and that of controls was 3.6 g/cm^2 (standard deviation [SD],

6.7 g/cm^2). The sample size was calculated according to a statistical table for the design of clinical trials.[16] To have at least an 80% chance of finding significant results at the probability level P<0.05 using a one-tailed test, 42 subjects were required in each of the three arms of the study; hence, the total sample size of the study was 126. A one-tailed test was chosen because nearly all previous studies have shown that the minimum effective dose of CEO is 0.625 mg.[12,13]

Statistical analysis

The Student's *t* test and odds ratios with 95% confidence intervals were used for continuous data and categorical data, respectively. The Student's *t* test was used because the sample size of each group was more than 30 and a Normal distribution of the continuous data was assumed. The actual and percentage changes in women's BMD from their baseline were calculated. The Statistical Package for Social Science/PC (Windows version 6.1; SPSS Asia Pacific Pte. Ltd., Chicago, US) was used for statistical analysis of the data.

Results

The study was terminated prematurely, after significant results were obtained. The total drop-out rate was 12.4%. Five women in the CEO 0.625 mg/d group, six women in the CEO 0.3 mg/d group, and two women in the control group dropped out from the study. Among those who dropped out, two women in the CEO 0.625 mg/d group and two women in the CEO 0.3 mg/d group said they were afraid of side effects of hormone replacement therapy. One woman in the CEO 0.625 mg/d group, four women in the CEO 0.3 mg/d group, and two women in the control group defaulted follow-up for unknown reasons. In the CEO 0.625 mg/d group, one woman did not comply with treatment and one woman withdrew from the study; both felt that they did not need hormone treatment. Results were analysed according to the allocation at randomisation despite non-compliance. Data of two women who were initially assigned to the control group and who subsequently took CEO 0.625 mg/d after 3 months to treat vasomotor symptoms, were analysed within the control group.

The characteristics of women at the time of study entry were similar between the three groups (Table 1). The mean age was 48.1 (2.8, SD) years and the mean duration since menopause was 6.8 (6.7) months. The majority of participants did not smoke or drink. The average daily duration of exercise and calcium intake were 6.5 (6.4) minutes and 600.4 (467.8) mg, respectively.

Bone mineral density

The mean femoral neck and spinal BMDs at baseline were 0.850 (0.110) g/cm^2 and 1.100 (0.160) g/cm^2, respectively. There were no significant differences in BMD between the three groups at baseline (Tables 2 and 3). Women who were assigned to the control group had a significant reduction in BMD at both the femoral neck and spine after 1 year (0.031 [0.009] g/cm^2; P=0.001 and 0.046 [0.010] g/cm^2; P<0.001, respectively). Women assigned to the CEO 0.3 mg/d group showed a significant reduction in spinal BMD (0.043 [0.016] g/cm^2; P=0.01) and a non-significant reduction in femoral neck BMD (0.018 [0.012] g/cm^2; P=0.14). In contrast, BMDs at both the femoral neck and spine of women who were assigned to the CEO 0.625 mg/d group were maintained after 1 year (0.002 [0.010] g/cm^2; P=0.87 and -0.007 [0.012] g/cm^2; P=0.55, respectively).

In the CEO 0.3 mg/d group, women who took oestrogen alone had a significant reduction in spinal BMD (0.042 [0.018] g/cm^2; P=0.03) while women who took oestrogen and progestogen did not. In both 0.625 mg/d and 0.3 mg/d CEO groups, there were no significant differences in the femoral neck (P=0.46 and P=0.34, respectively) or spine BMD (P=0.54 and P=0.06, respectively) when comparing women who took oestrogen alone with those who received combined treatment.

Table 1. Baseline characteristics of participants by treatment group

	Control, n=35 Mean (SD)	CEO 0.625 mg/d, n=35 Mean (SD)	CEO 0.3 mg/d, n=35 Mean (SD)	P value
Age (years)	48.5 (3.0)	48.2 (2.9)	47.7 (2.4)	0.44
Duration of menopause (months)	6.0 (5.3)	8.2 (7.5)	6.2 (7.2)	0.34
Body weight (kg)	59.4 (10.6)	57.3 (10.1)	53.2 (11.5)	0.09
Height (cm)	150.9 (26.6)	152.8 (9.6)	151.8 (27.3)	0.94
No. of women who smoked	2	1	2	0.79
No. of women who drank alcohol	2	2	1	0.74
Daily duration of exercise (min)	6.9 (6.9)	6.4 (7.0)	6.4 (6.7)	0.95
Calcium intake (mg/d)	609 (500)	534 (223)	658 (601)	0.54
No. of women who received medroxyprogesterone acetate	0	17	13	0.41

Table 2. Mean femoral neck bone mass density

Treatment	Baseline BMD* Mean (SD)	12-month BMD Mean (SD)	Change in BMD Mean (95% CI)	P value
Control	0.871 (0.125)	0.840 (0.120)	-0.031 (-0.049 to -0.014)	0.001†
CEO 0.3 mg/d alone	0.853 (0.079)	0.828 (0.072)	-0.025 (-0.059 to 0.008)	0.12
CEO 0.3 mg/d+MPA‡	0.778 (0.138)	0.775 (0.135)	-0.002 (-0.048 to 0.044)	0.89
CEO 0.3 mg/d (total)	0.828 (0.104)	0.810 (0.096)	-0.018 (-0.042 to 0.007)	0.14
CEO 0.625 mg/d alone	0.841 (0.144)	0.834 (0.130)	-0.006 (-0.030 to 0.017)	0.54
CEO 0.625 mg/d+MPA	0.749 (0.106)	0.763 (0.113)	0.014 (-0.032 to 0.060)	0.44
CEO 0.625 mg/d (total)	0.806 (0.134)	0.807 (0.116)	0.002 (-0.018 to 0.021)	0.87

* BMD bone mass density (g/cm^2)
† Statistically significant
‡ MPA medroxyprogesterone acetate

Table 3. Mean spinal bone mass density

Treatment	Baseline BMD* Mean (SD)	12-month BMD Mean (SD)	Change in BMD Mean (95% CI)	P value
Control	1.117 (0.177)	1.071 (0.154)	-0.046 (-0.067 to -0.025)	<0.001†
CEO 0.3 mg/d alone	1.177 (0.176)	1.135 (0.146)	-0.042 (-0.079 to -0.005)	0.03†
CEO 0.3 mg/d+MPA‡	1.014 (0.254)	0.969 (0.187)	-0.045 (-0.134 to 0.044)	0.24
CEO 0.3 mg/d (total)	1.123 (0.211)	1.079 (0.174)	-0.043 (-0.074 to -0.012)	0.01†
CEO 0.625 mg/d alone	1.085 (0.162)	1.079 (0.129)	-0.006 (-0.040 to 0.027)	0.67
CEO 0.625 mg/d+MPA	1.038 (0.114)	1.030 (0.158)	-0.008 (-0.059 to 0.044)	0.71
CEO 0.625 mg/d (total)	1.065 (0.143)	1.058 (0.138)	-0.007 (-0.031 to 0.018)	0.55

* BMD bone mass density (g/cm^2)
† Statistically significant
‡ MPA medroxyprogesterone acetate

At the end of the 1-year study, the losses in femoral neck and spine BMD for the control group were 3.6% and 4.0%, respectively. In the CEO 0.3 mg/d group, losses in femoral neck and spine BMD were 2.2% and 3.9%, respectively. In contrast, women in the CEO 0.625 mg/d group showed little change in the BMD of either the femoral neck (0.2% gain) or the spine (0.7% loss).

There was a statistically significant difference in the reduction in spinal BMD (0.039 [0.016] g/cm^2; P=0.02) but not in the femoral neck BMD (0.027 [0.014] g/cm^2; P=0.06) of women belonging to the control group when compared with those from the CEO 0.625 mg/d group. The differences in the reduction of both spinal BMD (0.003 [0.017] g/cm^2; P=0.86) and femoral neck BMD (0.014 [0.014] g/cm^2; P=0.33) were not significant between the control group and the CEO 0.3 mg/d group.

There was no correlation, as shown by linear regression analysis, between the calcium intake and the baseline BMD of women in this study (P=0.87).

Serum lipid levels

There were no significant changes in concentrations of total cholesterol and triglyceride between the three groups (Tables 4 and 5). The use of a lower dosage of oestrogen (CEO 0.3 mg/d) and medroxyprogesterone acetate was associated with a non-significant reduction in the serum cholesterol concentration (P=0.30).

Side effects

The proportion of women with side effects was comparable between the CEO 0.3 mg/d and CEO 0.625 mg/d groups. All the reported side effects were mild; weight gain in four women, irregular vaginal bleeding in four, breast discomfort in six, headache in two, and nausea in two.

Discussion

This study demonstrated that the use of CEO 0.625 mg/d is more effective than CEO 0.3 mg/d in maintaining the BMD. The finding that BMD can be maintained is different from the results of most western studies,[15,17-19] which have shown that the BMD increases by more than 3% after 1 year of oestrogen treatment. The short duration of the menopause of the participants in this study may in part explain this finding. The longer the duration of menopause, the greater the increase in BMD if oestrogen is given.[2,17] Although we followed up the women for only 1 year, the increase in BMD was expected to be the greatest after oestrogen treatment.[17] Further studies are needed to explore whether

Table 4. Mean fasting serum cholesterol concentration

Treatment	Baseline TC* Mean (SD)	12-month TC Mean (SD)	Change in TC Mean (95% CI)	P value
Control	5.2 (0.9)	5.4 (0.9)	0.2 (-0.1 to 0.6)	0.17
CEO 0.3 mg/d alone	4.8 (0.9)	5.3 (0.7)	0.5 (0.0 to 1.1)	0.18
CEO 0.3 mg/d+MPA†	5.5 (0.7)	5.3 (0.8)	-0.2 (-0.5 to 0.2)	0.30
CEO 0.625 mg/d alone	5.5 (0.7)	5.7 (0.6)	0.2 (-0.2 to 0.6)	0.18
CEO 0.625 mg/d+MPA	5.8 (0.8)	5.4 (0.4)	-0.4 (-0.9 to 0.2)	0.16

* TC fasting serum cholesterol level (mmol/L)
† MPA medroxyprogesterone acetate

Table 5. Mean fasting serum triglyceride concentration

Treatment	Baseline TG* Mean (SD)	12-month TG Mean (SD)	Change in TG Mean (SD)	P value
Control	1.0 (0.4)	1.0 (0.6)	0.0 (-0.2 to 0.2)	0.95
CEO 0.3 mg/d alone	0.9 (0.4)	0.9 (0.4)	0.0 (-0.1 to 0.1)	0.63
CEO 0.3 mg/d+MPA†	0.9 (0.1)	0.8 (0.4)	-0.1 (-0.4 to 0.2)	0.46
CEO 0.625 mg/d alone	1.1 (0.6)	1.2 (0.7)	0.1 (-0.3 to 0.5)	0.63
CEO 0.625 mg/d+MPA	1.1 (0.6)	1.0 (0.4)	-0.1 (-0.5 to 0.2)	0.37

* TG fasting serum triglyceride level (mmol/L)
† MPA medroxyprogesterone acetate

higher doses of oestrogen or a longer duration of oestrogen use can increase the BMD.

The mean daily calcium intake of women in this study was approximately 600 mg. Although this figure is higher than that found in previous studies (<400 mg),[20,21] it is still less than half of the recommended daily intake.[22] Health education about the optimal intake of calcium needs to be promoted, especially for postmenopausal women. Oestrogen and calcium act synergistically to prevent bone loss. By giving a calcium supplement of at least 1000 mg/d, the bone mass can be maintained with CEO 0.3 mg/d.[23] Whether giving a calcium supplement as well as CEO 0.3 mg/d or CEO 0.625 mg/d can significantly maintain or increase the BMD of postmenopausal Chinese women requires further investigation.

In general, CEO 0.3 mg/d did not protect postmenopausal Chinese women against bone loss. Although this dosage may relieve vasomotor symptoms, the routine practice of prescribing long-term therapy of CEO 0.3 mg/d to prevent osteoporosis may need revision: a dosage of CEO 0.625 mg/d may be preferred to CEO 0.3 mg/d. If women have been taking CEO 0.3 mg/d for some years, the indications for oestrogen replacement therapy should be reviewed. If there is no definite indication for long-term therapy, stopping the CEO 0.3 mg/d treatment should be considered. If there is still a need to prevent osteoporosis but the equipment for measuring the BMD is not available, the dosage of CEO should be increased to at least 0.625 mg/d after the patient has received appropriate counselling. Alternatively, if the BMD can be measured and is found to be low, the dosage of CEO may also be increased to 0.625 mg/d. However, if women are reluctant to take a higher dose of CEO because of side effects or other reasons, serial measurements of their bone density can give objective evidence to guide further therapy.

The effect of progestogen on the BMD depends on the type of hormone given. While gestronol hexanoate and norethisterone have been shown to prevent loss of bone,[24,25] it appears that medroxyprogesterone acetate does not have this effect.[17,26] In our study, we did not find any added benefit of combined CEO and medroxyprogesterone acetate treatment on the BMD, compared with unopposed CEO treatment. Nevertheless, the sample size was too small for subgroup analysis.

In conclusion, it appears that the minimum effective dosage of CEO to prevent osteoporosis in postmenopausal Chinese women is 0.625 mg/d. The routine practice of prescribing long-term therapy of CEO 0.3 mg/d to prevent osteoporosis should be reconsidered.

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