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Effect of Estriol on Bone Loss in Postmenopausal Japanese Women: A Multicenter Prospective Open Study

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Abstract

Objectives: To assess the effects of oral estriol on the bone mineral density (BMD) and bone metabolism in postmenopausal women.

Methods: Seventy-five natural postmenopausal women with a BMD of more than 10% below the peak bone density were treated for 50 weeks with 2 mg/day estriol (E_3) cyclically and 0.8 g/day of calcium lactate continuously. BMDs at L_2–L_4 were measured by dual energy X-ray absorptiometry (DXA).

Results: The BMD increased 1.79% ($p < 0.01$ vs. pretreatment) after 50 weeks, accompanied with decrease of biochemical markers of bone turnover. With regard to climacteric symptoms, Kupperman's menopausal index improved ($p < 0.01$ vs. pretreatment) after 5 weeks of treatment. As to the incidence of adverse events genital bleeding was observed in only 8.0% of the subjects. Endometrial histology and cytology showed neither abnormalities nor hyperplasia during and after the treatment.

Conclusions: Estriol prevented postmenopausal bone loss and improved climacteric symptoms effectively with low incidence of genital bleeding.

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Key words: estriol, menopause, bone mineral density, bone metabolism, estrogen replacement therapy

Introduction

Estrogen replacement therapy after natural or artificial menopause effectively alleviates not only climacteric symptoms and senile vaginitis but also prevents osteoporosis, and is also expected to prevent arteriosclerotic diseases.[1-4] This treatment, accordingly, has been widely recognized as useful for improving and maintaining the quality of life in postmenopausal women.

However, estrogen replacement therapy for the purpose of prevention and treatment of osteoporosis and arteriosclerotic diseases has to be continued for a long period of time. Genital bleeding during treatment is one of the major causes for discontinuation of treatment. Moreover, unopposed estrogen treatment has been suspected to increase the risk for endometrial cancer, and concomitant use of progestin has been recommended. However, the occurrence of adverse events due to the addition of progestin as well as genital bleeding remain unsolved.

Estriol (E_3) is an estrogen with considerably weaker endometrial proliferating effects than estradiol.[5,6] Accordingly, E_3 therapy is associated with less frequent genital bleeding and may not require concomitant use of progestin. Although there have been a few reports on the clinical effects of E_3 on bone mineral density (BMD), including a study on osteoporosis in relatively elderly subjects in Japan,[7] there has been no report on the effects of E_3 on BMD determined by dual energy X-ray absorptiometry (DXA), a bone mineral measurement method which is considered to be the most accurate and precise method available at present.

The purpose of the present investigation was to assess the effects of E_3 in postmenopausal women on BMD measured by DXA and various bone metabolic markers.

Table 1. Characteristics of the subjects

Age (years)	53.1 ± 0.6	(n = 75)
Postmenopausal Period (years)	4.7 ± 0.6	(n = 75)
BMI (kg/m^2)	21.4 ± 0.3	(n = 75)
Spine BMD (g/cm^2)	0.831 ± 0.014	(n = 48)
K.I.	18.6 ± 1.6	(n = 47)
LH (mIU/m*l*)	30.6 ± 1.6	(n = 58)
FSH (mIU/m*l*)	100.4 ± 4.6	(n = 58)

Values are means ± SEM.
BMI: body mass index, Spine BMD: spine (L_2–L_4) bone mineral density, K.I.: Kupperman's menopausal index, LH: luteinizing hormone, FSH: follicle stimulating hormone

Subjects and Methods

The current study was conducted as a multicenter prospective open trial from 1992 to 1994. Subjects were 75 postmenopausal women (mostly within 5 years after menopause) who visited the outpatient clinic of 8 institutions and in whom BMD of the lumbar spine (L_2–L_4) in the anterior-posterior (AP) projection was more than 10% below the peak bone density of Japanese women (PBD; 1.028 ± 0.083 g/cm^2 determined by QDR-1000).[8]

Subjects were given E_3 (Estriel, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan) and calcium lactate. E_3 was administered in a cyclic manner; that is, 2 mg/day E_3 was administered orally for 4 weeks, then withdrawn for one week. Calcium lactate was administered continuously at a daily dose of 0.8 g (Ca 104 mg/day). Cyclic treatment was continued for 50 weeks.

The subjects' characteristics are given in Table 1. The pretreatment mean BMD at L_2–L_4 was 19% lower than the PBD for Japanese women.

Bone mineral density at L_2–L_4 was determined 3 times (before and after 25 and 50 weeks of therapy) by XR-26 (Norland Corporation, Fort Atkinson, WI), DPX (Lunar Corporation, Madison, WI) or QDR-1000 (Hologic, Inc., Waltham, MA). The results were examined at each institute first, and then re-examined at the Department of Nu-

clear Medicine, Kawasaki Medical School, on a blind basis. Data were excluded from the final analysis, if severe scoliosis, deformations or fractures at L_2 to L_4, osteoarthritic changes or extraosseous calcifications were detected. Bone mineral density data obtained using various models of DXA, were converted into QDR-1000 on the basis of the report by the Silver Science Research Group sponsored by the Ministry of Health and Welfare of Japan.[9]

Serum levels of calcium (S-Ca), inorganic phosphorus (P), alkaline phosphatase (ALP) and osteocalcin (BGP), and urinary levels of calcium (U-Ca), creatinine (Cr), total hydroxyproline (OHP), deoxypyridinoline (D-Pyr) and pyridinoline (Pyr) were determined before and after 5, 15, 25 and 50 weeks of treatment. Urinary biochemical markers were expressed as a ratio of OHP/Cr, D-Pyr/Cr and Pyr/Cr.

Climacteric symptoms were evaluated using the Kupperman's menopausal index before and after 5, 15, 25 and 50 weeks of treatment.

Total cholesterol (TC), HDL cholesterol (HDL-C) and triglyceride (TG) were determined before and after 25 and 50 weeks of treatment. LDL cholesterol (LDL-C) was calculated according to Friedewald's equation: LDL-C = (TC)-(HDL-C)-(TG/5).

Endometrial smears and biopsies were performed before and after 25 and 50 weeks of treatment. Breasts were also examined by palpation, ultrasound or mammography, if needed.

All the results were expressed as the mean ± SEM. The effect of treatment on Kupperman's menopausal index in each group was assessed by the Wilcoxon's one sample test, and the paired Student's *t*-test was used for the other measurements.

Results

1. *Effects on BMD and Biochemical Parameters of Bone Metabolism*

Forty-eight subjects were adopted in determination of BMD of spine (L_2–L_4) as the result of exclusion criteria mentioned in Subjects and Methods. The mean percent change was + 1.79% after 50 weeks of treatment, indicating a significant increase from the pretreatment value ($p < 0.01$; Fig. 1).

Changes in various bone metabolic parameters are shown in Fig. 2. The ALP significantly decreased from 73.3 U/*l* before treatment to 68.9 U/*l* ($p < 0.05$) after 15 weeks of treatment. The D-Pyr/Cr ratio also significantly decreased from 6.61 pmol/μmolCr before treatment to 6.30 pmol/μmolCr ($p < 0.05$) after 15 weeks of treatment.

2. *Stratified Analysis Based on Pretreatment Values of BMD and the Number of Years after Menopause*

Subjects were stratified into 2 subgroups according to their pretreatment value of BMD: a subgroup with more than 20% below the PBD and another with less than 20% below the PBD. The bone mass at the end of treatment in the subgroup with more than 20% below the PBD increased 2.08 ± 0.90% ($p < 0.05$), while in the subgroup with less than 20% below the PBD it increased 1.52 ± 0.95%.

With regard to the number of years after menopause, subjects were stratified into 3 subgroups: those who had entered the menopause less than 2 years previously, those who had entered this phase 2 years or more but less than 5 years previously, and those who had entered menopause 5 years or more previously. With respect to increases in BMD, an increase of 2.93 ± 1.34% ($p < 0.05$) was noted in the subgroup of women who had entered the menopause 5 years or more previously. However, the percent increase in BMD was not significant in the other 2 subgroups.

3. *Effects on Climacteric Symptoms*

Kupperman's menopausal index was 18.6 ± 1.6 ($n = 47$) before treatment, but improved to 11.9 ± 1.6 ($n = 35$) after 5 weeks of treatment ($p < 0.01$), and reached 9.5 ± 1.4 ($n = 42$) after 15 weeks of treatment. Thereafter, it remained at almost the same level until the end of treatment.

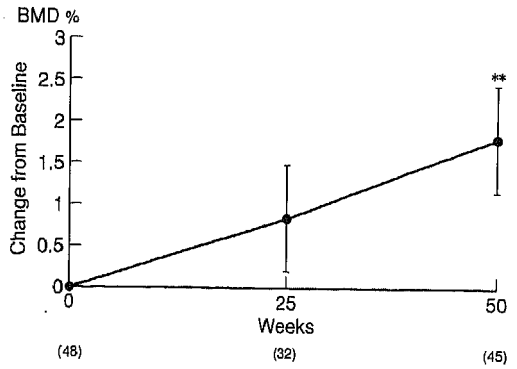

Fig. 1. Change of bone mineral density during 50 weeks of treatment with estriol 2 mg/day and calcium lactate 0.8 g/day.
Figures in parenthesis are the number of patients evaluated at each determination point.
Mean ± SEM ** $p < 0.01$ vs. pretreatment

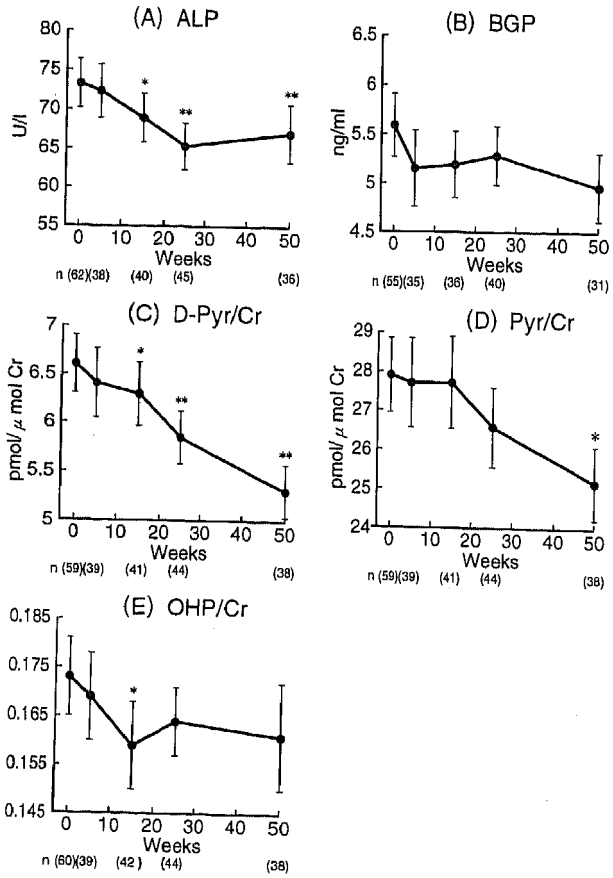

Fig. 2. (A) serum total alkaline phosphatase activity, (B) serum total osteocalcin, and the ratio of (C) deoxypyridinoline, (D) pyridinoline and (E) hydroxyproline to creatinine in urine during 50 weeks of treatment with estriol 2 mg/day and calcium lactate 0.8 g/day.
Figures in parenthesis are the number of patients evaluated at each determination point.
Mean ± SEM * $p < 0.05$ vs. pretreatment ** $p < 0.01$ vs. pretreatment

Table 2. Incidence of adverse events

	n (%)
Genital bleeding	6 (8.0)
Mastalgia	1 (1.3)
Vaginal discharge	1 (1.3)
Edema of external genitalia	1 (1.3)
Low abdominal pain lower	1 (1.3)
Urticaria	1 (1.3)
Skin eruption	1 (1.3)
Headache	1 (1.3)

Thirteen episodes were noted in 10 out of 75 subjects (13.3%).

4. Effects on Clinical Laboratory Values

The mean pretreatment values of lipid metabolic parameters (TC, TG, HDL-C, LDL-C) were within the normal range, and remained within the normal range during the 50 weeks of treatment. The subgroup of subjects ($n = 22$) with a mean pretreatment TC value of 220 mg/d*l* or more showed a significant decrease of approximately 6% from 250.9 ± 3.9 mg/d*l* before treatment to 232.9 ± 5.7 mg/d*l* after 50 weeks of treatment ($p < 0.05$). No significant changes were noted in the subgroup of subjects ($n = 27$) with a mean pretreatment TC value of less than 220 mg/d*l*.

No abnormalities were observed in parameters of hepatic function such as GOT, GPT, γ-GTP or in blood biochemistry, general hematology and urinalysis during therapy.

5. Safety of Treatment

Neither abnormalities nor hyperplasia were observed in the subjects examined with regard to endometrial cytology and histology during and after the treatment. No abnormalities were observed in breast examined for all cases. Adverse events occurred in 13.3% of the subjects. Adverse events are shown in Table 2. One of the major adverse events was mild genital bleeding which was noted in 8.0% of the subjects.

Discussion

We examined estriol (E_3) for its effects on the bone loss in postmenopausal women, since there have been no reports on the clinical effects of E_3 treatment on spinal BMD evaluated by DXA. In our current study we treated postmenopausal women (4.7 years after menopause) with 2 mg/day of E_3 and 0.8 g/day of calcium lactate for one year, and determined BMD at the lumbar spine (L_2–L_4) by DXA. We observed a significant increase in BMD (1.79%, $p < 0.01$) in subjects treated with E_3.

It has been known that estrogen deficiency due to declined ovary function accelerates bone resorption. Although it also accelerates bone formation, it results in decreases in bone mass, because the extent of bone resorption is greater than that of bone formation.[10,11] In our study, ALP, a bone formation parameter, and OHP, D-Pyr and Pyr, which are parameters of bone resorption, decreased significantly during E_3 treatment. Therefore, we considered that the increases in bone mass obtained after E_3 treatment were the result of the suppression of bone turnover.

As a reference we also conducted a limited scale of clinical trial by administration of calcium lactate alone 0.8 g/day continuously in postmenopausal women ($n = 19$; age 55.1 ± 1.1; years after menopause 3.9 ± 0.9) for 25 weeks. As the result, the mean percent change of BMD (L_2–L_4) determined by DXA was decreased 1.31% compared to that of pretreatment. Additionally, none of bone metabolic parameters showed significant changes from the pretreatment value (data not shown). These data suggest that the acceleration of bone turnover usually observed after menopause was not prevented by the dose of calcium administered.

In order to identify factors involved in E_3-induced increases in bone mass, we conducted a stratified analysis based on pretreatment values of bone mass and years after menopause. The results revealed that subjects with lower pretreatment bone mass or longer postmenopausal period showed significantly higher rates of increase in bone mass after E_3 administration as compared with the pretreatment value of BMD. Lindsay *et al.*,[12] who administered conjugated

equine estrogen (0.625 mg/day) to patients with established postmenopausal osteoporosis, also reported a positive correlation between the years after menopause and annual increases in bone mass of the lumbar spine.

In this study, E_3 was found to improve Kupperman's menopausal index as early as 5 weeks after the initiation of treatment which was similar to the report by Tzingounis *et al.*,[5] indicating Kupperman's menopausal index was improved after one month of treatment with E_3.

One of the objectives of long-term ERT/HRT (hormone replacement therapy) is the prevention of arteriosclerosis, including ischemic heart disease. There have been only a few reports regarding the effects of E_3 on arteriosclerosis and lipid metabolism. In our study, the parameters of lipid metabolism showed no significant changes after 50 weeks of treatment. The mean pretreatment values of these parameters were within the normal range, which seemed to have masked the effects of E_3 on lipid metabolism. The subjects with pretreatment TC values of higher than 220 mg/d*l* showed significant decreases after E_3 treatment, but no changes were noted in subjects with TC levels of less than 220 mg/d*l*.

Estriol is known to exert a weak proliferating action on the endometrium.[5,6] According to the results of a prospective cohort follow-up study by Persson *et al.*, the relative risk for endometrial cancer was 0.5 (9.5% confidence interval 0.1 to 1.5) after exposure to mainly E_3 compounds alone for more than 3 years, whereas it was 2.7 (1.4 to 5.1) or 2.2 (1.2 to 4.4) after exposure to estradiol compounds alone or conjugated equine estrogens alone for the same period, respectively, and the cyclical addition of progestogens reduced this risk or delayed its onset.[13] In this study, we did not use concomitant progestin, but administered E_3 in a cyclic manner, that is, 4 weeks of treatment, followed by one week of rest. Genital bleeding was noted in 8% of the subjects, but the degree was mild in all cases. Subjects who were examined for endometrial cytology and histology showed neither abnormalities nor hyperplasia.

Estrogen therapy for prevention and treatment of osteoporosis has to be continued for a long time. However, compliance is low, mainly due to genital bleeding.[14] In this study, the frequency of genital bleeding was only 8% during the one-year of treatment, and compliance was good with only 8% of discontinuation, including one who dropped out because of bleeding.

Estriol alleviated climacteric symptoms, and increased bone mass, while, the incidence of genital bleeding and other adverse events were low, and compliance was good. In light of these findings, we conclude that estrogen replacement therapy using estriol has a great potential with the aim of preventing osteoporosis in postmenopausal women.

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