Effects of Ultralow-Dose Transdermal Estradiol on Bone Mineral Density: A Randomized Clinical Trial

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OBJECTIVE: Because small increments in levels of endogenous plasma estradiol are associated with higher postmenopausal bone mineral density, we investigated the safety and effectiveness in preventing bone loss of unopposed, very-low-dose transdermal estradiol for postmenopausal women.

METHODS: This was a randomized, placebo-controlled, double-blind trial with 2-year follow-up at 9 United States clinical centers. The study population comprised 417 postmenopausal women, aged 60–80 years, with intact uterus and bone mineral density z scores of –2.0 or higher, who were randomly assigned to receive either unopposed transdermal estradiol at 0.014 mg/d (n = 208) or placebo (n = 209). All participants received calcium and vitamin D supplementation. Lumbar spine and total hip bone mineral density change was measured by dual-energy X-ray absorptiometry; endometrial hyperplasia incidence was assessed by endometrial biopsy.

RESULTS: Median plasma estradiol level in the estradiol group increased from 4.8 pg/mL at baseline to 8.5 pg/mL at 1 year ($P < .001$ versus baseline) and to 8.6 pg/mL at 2 years ($P < .001$ versus baseline) and was unchanged in the placebo group. Lumbar spine bone mineral density increased 2.6% in the estradiol group and 0.6% in the placebo group (between-group difference 2.0%, $P < .001$). Mean total hip bone mineral density increased 0.4% in the estradiol group and decreased 0.8% in the placebo group (between-group difference 1.2%, $P < .001$). Osteocalcin levels and bone-specific alkaline phosphatase were lower in the estradiol group than the placebo group ($P < .001$ each). Endometrial hyperplasia developed in 1 woman in the estradiol group but in none of the placebo group (difference in 2-year rates 0.5%, 95% confidence interval 0–7.3%).

CONCLUSION: Postmenopausal treatment with low-dose, unopposed estradiol increased bone mineral density and decreased markers of bone turnover without causing endometrial hyperplasia. (Obstet Gynecol 2004;104:443–51. © 2004 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: I

For more than 20 years, standard postmenopausal hormone therapy (HT) has included 0.625 mg of conjugated equine estrogen or its equivalent. Because recent randomized trials showed adverse effects of standard-dose estrogen-progestin combination therapy,[1,2] physicians are being encouraged to prescribe the lowest effective dose of HT for the shortest time necessary.[3,4]

Evidence accumulated during the past decade indicates that lower-than-standard doses of estrogen relieve menopausal symptoms[5–8] and preserve bone density.[9–15] Several half-strength estrogen formulations have been approved by the U.S. Food and Drug Administration (FDA) for use in these 2 indications. However, even unopposed half-strength preparations are associated

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with increased endometrial cancer risk[16,17]; therefore, for endometrial protection in women with a uterus, progestin must be added to the HT regimen.

Doses of estrogen lower than half strength have been assumed ineffective for preserving bone mass. This belief originates in part from evidence that lower doses of estrogen do not prevent bone loss in oophorectomized young women.[18,19] However, in older postmenopausal women, levels of endogenous plasma estradiol that would be considered very low in premenopausal women (< 20 pg/mL) are associated with higher bone density and lower risk of hip and vertebral fractures compared with undetectable levels.[20,21] Therefore, we designed a study using an ultralow dose (0.014 mg/d) of transdermal estradiol–about a quarter of the usual 0.05 mg/d dose–to raise serum estradiol levels in postmenopausal women to a mean of about 10–15 pg/mL. We hypothesized that the resultant small increase in serum estradiol level would increase bone density without causing endometrial hyperplasia and thus would not require concurrent administration of progestin.

METHODS

Ultra-Low-dose Transdermal estRogen Assessment (ULTRA) was a randomized, double-blind, placebo-controlled, 2-year trial conducted at 9 clinical centers in the United States. The trial was coordinated at the University of California San Francisco and was funded by Berlex Laboratories (Montville, NJ), the manufacturer of Menostar, the transdermal estradiol patch used in this trial. Participants were women, aged 60–80 years, who had a uterus and were at least 5 years beyond menopause. Participants could have osteoporosis (t score < –2.5), but all were required to have bone mineral density normal for age (z score ≥–2.0 at the lumbar spine). Women were excluded from participating in the study if they had unexplained uterine bleeding; endometrial hyperplasia or endometrium of 5 mm or more in double thickness; abnormal mammogram suggestive of breast cancer; a history of metabolic bone disease; cancer (except nonmelanoma skin cancer); coronary disease, stroke, or transient ischemic attack; venous thromboembolism; uncontrolled hypertension; uncontrolled thyroid disease; liver disease; fasting triglyceride level more than 300 mg/dL or fasting glucose level more than 180 mg/dL; had ever taken fluoride, calcitonin, or bisphosphonates; or had taken estrogen or progestin within 3 months before randomization. The institutional review board of each clinical center and the coordinating center approved the study protocol, and informed consent was obtained from all participants.

Study coordinators assigned treatment numbers to participants sequentially by order of arrival at clinical centers; numbers were printed on labels adhered to the study medication and were randomly allocated in blocks of 4 and in a 1:1 ratio to treatment or placebo according to a computer-generated randomization scheme. Participants, investigators, and outcome assessors were blinded to treatment assignment, and no unblinding occurred during the trial.

Treatment consisted of a 3.25-cm^2 area estradiol patch or an identical placebo patch. The patch, releasing approximately 0.014 mg estradiol transdermally per day, was applied to a clean dry area of the abdomen once weekly. Patches that became detached could be replaced once during the 1-week period. All study participants received oral supplements of 400 mg calcium twice daily and 400 IU vitamin D once daily.

At baseline, we obtained information on demographics, health habits, health history, and medication use. Participants underwent a standardized physical examination, including breast and pelvic evaluation and Papanicolaou testing. All participants had baseline endometrial aspiration biopsy. If the uterine cavity could not be entered by the biopsy instrument, the woman was excluded from participating in the study. If the biopsy sample was insufficient for pathological evaluation, transvaginal ultrasonography was performed to measure double endometrial thickness.

All participants had baseline mammograms within 6 months before randomization. Fasting blood tests included measurements of routine hematology and chemistries: serum osteocalcin (enzyme-linked immunosorbent assay [ELISA], CIS Biointernational, Gifsur Yvetter, France); bone-specific alkaline phosphatase (immunoradiometric assay, Tandem-R Ostase, Hybritech, Inc, San Diego, CA); estradiol (double-antibody sequential radioimmunoassay [lower limit of detection 1.4 pg/mL], Diagnostics Products Corporation, Los Angeles, CA); estrone (competitive radioimmunoassay, Diagnostic Systems Laboratories, Inc, Webster, TX); and sex-hormone–binding globulin (per immunoradiometric assay, Orion Diagnostica, Geneva, Switzerland). Blood testing was not timed to coincide with the day the patch was changed.

Bone mineral density of the L2–L4 lumbar spine and total hip was measured by dual X-ray absorptiometry with Hologic model 2000 and 4500 densitometers (Hologic, Inc, Waltham, MA). The same phantom was used to cross-calibrate machines at different study sites. Bone density was analyzed by a central reading facility at the University of California San Francisco, which provided correction factors to adjust for differences between sites

and for changes in performance of each densitometer over time.

At follow-up visits that occurred every 4 months during the trial, adherence was measured by patch counts, and adverse events were ascertained. Annually or at the end of follow-up, all baseline measures except demographics and health history were repeated. At annual followup visits, endometrial biopsy was attempted for all participants. If the biopsy could not be performed or if endometrial tissue was insufficient for pathologic diagnosis, transvaginal ultrasonography was performed; if the double endometrial stripe was 5 mm or greater, we attempted to obtain endometrial tissue either by repeat aspiration biopsy or by dilation and curettage. At the discretion of the site principal investigator, uterine evaluation also was done for women who reported clinically significant uterine bleeding. All endometrial biopsy specimens were evaluated independently by 2 pathologists blinded to treatment assignment (Global Medical Services Group, Thousand Oaks, CA). If the 2 pathologists disagreed on the diagnosis, a third blinded pathologist adjudicated the case; adjudication was required in 23 of 1,107 cases (2.1%).

Primary outcomes of the study were percentage change from baseline in lumbar spine bone mineral density and incidence of endometrial hyperplasia at 2-year follow-up. Secondary skeletal outcomes included change in total hip bone mineral density; change in markers of bone turnover, including serum osteocalcin and bone-specific alkaline phosphatase levels; and incidence of clinical fracture.

Baseline differences between treatment groups were assessed by analysis of variance and Cochran-Mantel-Haenszel tests, as appropriate, with adjustment for site. Percentage change in bone mineral density was compared by using linear regression models with adjustment for baseline value and site. The primary analysis was by intention to treat, without regard to adherence. Outcomes for women without 1-year and 2-year measurements were computed by carrying forward the most recent postrandomization measurements, including those obtained at study-discontinuation visits. Finally, modified intention-to-treat analyses were performed that omitted bone mineral density measurements obtained after study medication was discontinued.

A projected sample size of 406 women was specified to provide 95% power in 2-sided tests with a 5% type I error rate to detect a between-group difference of 2 percentage points in the change in lumbar spine bone mineral density from baseline to 2-year follow-up. This estimate was based on the assumption that the standard deviation of the primary outcome would be 3 percentage points and that the outcome would be unavailable for 15% of women in each group. Change in bone turnover markers was calculated by subtracting the baseline value from the mean of the values at 1 and 2 years for each participant. For each group, all adverse events with incidence rates of 2% or more and that differed between groups ($P < .05$) are reported, as are all serious adverse events (ie, death, hospitalization, cancer, or permanent disability).

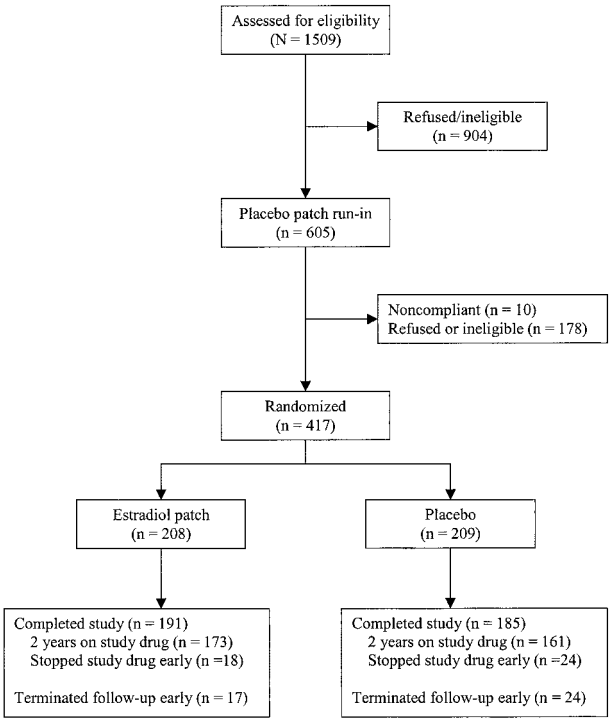

Fig. 1. Process flow chart illustrates recruitment, enrollment, and follow-up of study participants.
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RESULTS

Between November 1999 and November 2000, 1,509 women were screened for eligibility; 605 enrolled in a 1-week run-in phase, during which they received a placebo patch to assess compliance with and tolerance to the transdermal system. During the run-in period, no women showed clinically significant skin sensitivity to the patch, but 10 women were excluded from the study because of noncompliance, and 178 were either found ineligible or refused to continue screening (Fig. 1). Thus, between February and November 2000, a total of 417 women eligible for participation in the study were randomly assigned to treatment with transdermal estradiol (n = 208) or placebo (n = 209).

The mean (± SD) baseline age of participants was 67 (± 5) years, and 92% were white. Mean bone mineral

Table 1. Baseline Characteristics of 417 Women Enrolled in the ULTRA Transdermal Estradiol Study

	Treatment (n = 208)	Placebo (n = 209)	P*
Age (y)	66.8 ± 5.1	66.7 ± 4.8	1.0
White (%)	92.8	91.9	.7
Some college (%)	63.5	63.6	1.0
Current smoker (%)	7.7	6.2	.6
Dietary calcium (mg/d)	746 ± 447	691 ± 425	.2
Body mass index (kg/m^2)	28.3 ± 5.3	28.0 ± 5.3	.6
Age at menopause (y)	49.9 ± 4.7	50.5 ± 4.6	.2
Estradiol (pg/mL)	4.8 (2.7, 8.0)	4.7 (2.7, 8.3)	.6
Estrone (pg/mL)	29.6 (23.5, 37.7)	29.9 (22.6, 37.1)	.8
Sex hormone binding globulin (mmol/L)	45.1 ± 20.1	44.5 ± 20.8	.8
Lumbar spine BMD (g/cm^2)	0.94 ± 0.15	0.96 ± 0.14	.05
Total hip BMD (g/cm^2)	0.84 ± 0.12	0.84 ± 0.12	.5
Lumbar spine BMD *t* score	−1.33 ± 1.31	−1.13 ± 1.26	.05
Total hip BMD *t* score	−0.89 ± 0.95	−0.84 ± 0.99	.5
Osteocalcin (ng/mL)	21.3 ± 7.8	20.7 ± 6.9	.6
Bone-specific alkaline phosphatase (ng/mL)	11.6 ± 5.4	11.0 ± 5.1	.3

ULTRA, Ultra-Low-dose Transdermal estRogen Assessment; BMD, bone mineral density.

Data are presented as mean ± standard deviation, percentage, or median (interquartile range).

* *P* values for categorical data are obtained from the generalized Cochran-Mantel-Haenszel test, stratified by clinic site. *P* values for continuous variables are from analysis of variance (ANOVA) or rank ANOVA, adjusted for site.

density *t* score at the lumbar spine was –1.2, and 17% of participants had lumbar spine or total hip *t* score of –2.5 or less. Randomization produced comparable groups: At baseline, no statistically significant differences were seen between groups except for about 2% lower lumbar spine bone mineral density in the treatment group compared with the placebo group (Table 1).

Among women assigned to treatment with estradiol, 191 of 208 (92%) completed the trial, compared with 185 of 209 (89%) in the placebo group (Fig. 1). Reasons for withdrawing from the study were similar in the 2 treatment groups. Among women who completed the trial, 18 in the treatment group (9%) and 24 in the placebo group (13%) stopped taking the study medication before the end of the trial ($P = .3$). Among women who continued to use the study drug through 2 years, patch counts showed that 84% used at least 75% of the expected number of patches. About 95% of participants in both groups used calcium and vitamin D during the trial.

At baseline, median plasma estradiol level was 4.8 pg/mL (interquartile range 2.7, 8.0) and did not differ between treatment groups (Table 1). Median plasma estradiol level (obtained a mean of 3 days after patch change) in the estradiol group increased from 4.8 pg/mL to 8.5 pg/mL (interquartile range 5.2, 13.5) at 1 year ($P <$ .001 versus baseline) and to 8.6 pg/mL (interquartile range 4.4, 13.9) at 2 years ($P <$ .001 versus baseline). Median plasma estradiol in the placebo group decreased from 4.7 pg/mL (interquartile range 2.7, 8.3) to 3.8 pg/mL (interquartile range 1.5, 7.9) at 1 year ($P <$ .001 versus baseline) and to 4.3 pg/mL (interquartile range 1.7, 8.0) at 2 years ($P = .02$ versus baseline). Levels of sex-hormone–binding globulin did not show a statistically significant change during the trial in either treatment group.

Compared with baseline values, lumbar spine bone mineral density increased 0.5% at 1 year and 0.6% at 2 years in the placebo group and increased 2.1% at 1 year and 2.6% at 2 years in the estradiol group (Fig. 2). The between-group difference was 1.6% at 1 year (95% confidence interval [CI] 0.9–2.2, $P <$ .001) and 2.1% at 2 years (95% CI 1.3–2.8, $P = .001$). The 2-year, between-group differences were similar in women with bone mineral density of –2.5 or less and those above this level, 2.3% (95% CI 0.4–4.1) and 2.0% (95% CI 1.2–2.8), respectively. A test of interaction showed no statistically significant difference in the effect of treatment ($P = .82$) related to bone mineral density category.

Total hip bone mineral density decreased in the placebo group and increased in the treatment group. At 1 year, the percentage difference between groups was 0.8% (95% CI 0.3–1.4, $P <$ .001); at 2 years, the difference was 1.2% (95% CI 0.6–1.8, $P <$ .001). The on-treatment osteocalcin level (mean of 1 and 2 years) decreased by a median of 9.2% (interquartile range –24.3, 10.1, $P <$ .001) from baseline in the placebo group and decreased by a median of 22.3% (interquartile range –35.1, 8.1, $P <$ .001) in the treatment group ($P <$ .001 for the between-group difference). The on-treatment, bone-specific alkaline phosphatase level decreased by a median of 3.1% (interquartile range –26.4, 24.8, $P > .8$) in the placebo group and decreased by a median of 22.4% (interquartile

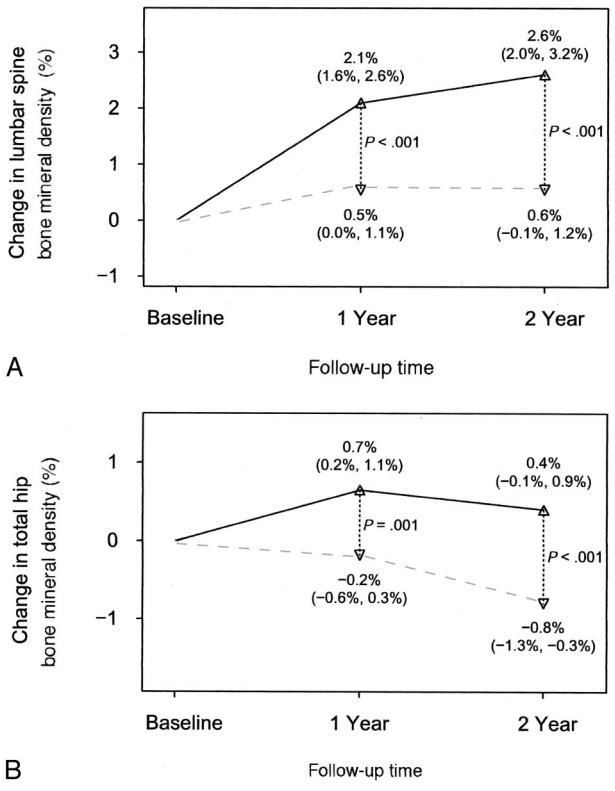

Fig. 2. A. Graph of mean lumbar spine bone mineral density shows mean percentage change from baseline with 95% confidence interval and significance level. **B.** Graph of mean total hip bone mineral density in study participants shows mean percentage change from baseline. *Unbroken line*, estradiol; *dashed line*, placebo.

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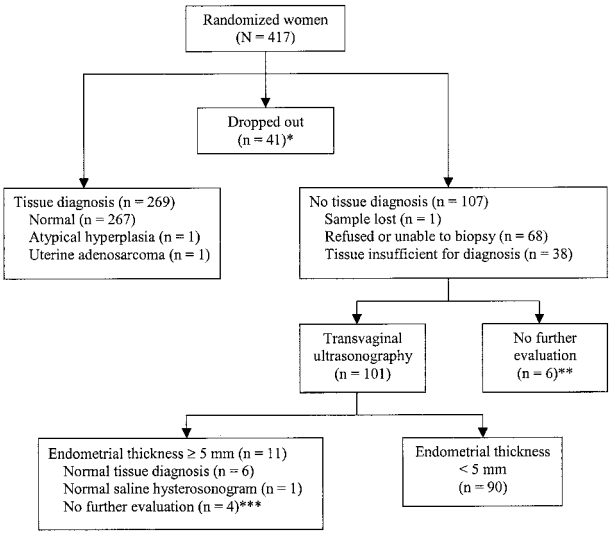

Fig. 3. Flow chart shows endometrial evaluations in study participants after 2 years of follow-up. * Twenty-four women were assigned to placebo and 17 to estradiol; median treatment duration was 7.7 months. ** All women had normal results at 12-month evaluation (5 by biopsy, 1 by transvaginal ultrasonography); 2 had hysterectomy for descensus at 13 months. *** One woman had been taking standard-dose continuous combined hormone therapy for 1 year (endometrial thickness 7.5 mm); 2 had been off study drug for 10–12 months (endometrial thickness 5.0 mm and 5.4 mm); 1 opted to have follow-up by local physician (endometrial thickness 6.2 mm).

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range −41.1, 1.4, $P < .001$) in the treatment group ($P < .001$ for the difference between groups). During the trial, a clinical fracture was diagnosed in 10 women in the placebo group and in 4 women in the treatment group ($P = .17$).

After 2 years of follow-up, 376 of the 417 women had an endometrial biopsy; 41 women discontinued follow-up early and did not have endometrial evaluation after 2 years (Fig. 3). Of these 41 women, 24 had been assigned to receive placebo and 17 to receive estradiol; among the 17 women assigned to receive estradiol, median duration of treatment was 7.7 months. Of the 376 women who had biopsy, 269 specimens were adequate for diagnosis; all showed no serious abnormality except for 2 women in the treatment group: One woman had focal atypical hyperplasia, and one woman had uterine adenosarcoma. Of the 107 women who had no endometrial tissue diagnosis, 6 refused further follow-up, 101 underwent transvaginal ultrasonography, and 11 had endometrial thickness of 5 mm or greater. Of these 11 women, 6 had endometrial biopsy or dilation and curettage that showed normal tissue, 1 had a normal saline hysterosonogram, and 4 had no further endometrial evaluation. Simple (nonhyperplastic) endometrial polyps were found at biopsy or by hysteroscopy in 3 (1.4%) women assigned to estradiol compared with 2 (0.9%) women assigned to placebo. The woman in the estradiol group who had atypical endometrial hyperplasia after 2 years of treatment reported no uterine bleeding and had a biopsy that showed normal endometrial tissue after 1 year. After discontinuing the study drug and receiving 10 mg medroxyprogesterone acetate twice daily for 3 months, subsequent biopsy showed atrophic endometrium.

Of the 191 women in the estradiol group and the 185 in the placebo group who completed the trial, all but 10 (3 assigned to estradiol and 7 assigned to placebo) had mammography at the end of the trial. Three women in the treatment group and 5 in the placebo group had abnormal mammograms, and breast cancer developed in 3 women (1 in the treatment group and 2 in the placebo group). Moderate-to-severe skin reactions to the

Table 2. Adverse Events Reported During the ULTRA Transdermal Estradiol Study

	Treatment (n = 208)	Placebo (n = 209)	P*
Serious adverse events	24 (11.5)	24 (11.5)	1.0
Cancer	3 (1.4)	5 (2.4)	.5
Hospitalization	22 (10.6)	20 (9.6)	.7
Death	0	0	NA
Other adverse events†			
Cervical polyp	12 (5.8)	4 (1.9)	<.04
Vaginal discharge	22 (10.6)	3 (1.4)	<.001
Hernia	1 (0.5)	7 (3.3)	.03
Herpes zoster	1 (0.5)	9 (4.3)	.01
Rash‡	6 (2.9)	21 (10.0)	.003

ULTRA, Ultra-Low-dose Transdermal estRogen Assessment.
Data are presented as n (%).
* *P* value from χ^2 test.
† Includes adverse events that were reported by more than 2% of participants in either group and that were statistically different between treatment groups at $P < .05$.
‡ At anatomic site other than site of patch application.

patch system were reported by 6 women in the placebo group and by 1 woman in the treatment group ($P = .12$).

Overall incidence of serious adverse events was similar in the 2 groups: 24 women in the treatment group reported 36 events, and 24 women in the placebo group reported 34 events ($P = 1.0$; Table 2). Cancer was diagnosed in 3 women in the treatment group (1 breast, 1 lung, and 1 uterine adenosarcoma) and in 5 women in the placebo group (2 breast, 1 colon, 1 cervix, and 1 liposarcoma). No adverse treatment effects were observed from hematology or chemistry test results obtained at 1-year and 2-year follow-up. Adverse events that differed between treatment groups are summarized in Table 2; prevalence of vaginal discharge and of cervical polyps was more common in the treatment group than in the placebo group.

As expected, per-protocol or modified intention-to-treat analyses resulted in greater treatment differences for lumbar spine and total hip bone mineral density. For example, bone mineral density differences observed at 24 months were about 20–25% greater than with the strict intention-to-treat criterion (2.5% versus 2.1% for spine; 1.5% verus 1.2% for total hip).

DISCUSSION

In older postmenopausal women, one quarter of the usual dose of transdermal estradiol improved bone mineral density at both spine and hip, decreased bone turnover, and did not increase the rate of endometrial hyperplasia during 2 years of follow-up.

During the past 20 years, studies of estrogen for preventing postmenopausal bone loss have led to progressive reduction in what is considered the minimum effective dose. Early studies examined younger women after oophorectomy and concluded that doses less than 0.625 mg of conjugated equine estrogen or equivalent were ineffective.[18,19] Later, researchers using more precise measurement techniques showed bone mineral density preservation with 0.3 mg of conjugated estrogen (or its equivalent) in early postmenopausal women[9–15] and in older postmenopausal women.[22] A recent report[23] showed a statistically significant increase for hip, wrist, spine, and total body bone mineral density among women aged 65 years and older who were taking 0.25 mg of oral micronized estradiol daily for 3 years.

In older postmenopausal women, levels of plasma estradiol that would be considered very low in premenopausal women may be adequate to prevent bone loss and fractures. Older women (mean age 72 years) who had plasma estradiol levels in the range of 5–20 pg/mL had about 7% higher bone mineral density and half the risk of hip and spine fractures, compared with women who had undetectable levels of estradiol (< 5 pg/mL).[20,21] Similar results were seen in younger women (mean age 64 years) who participated in a 5-year observational study[24]: Women whose baseline serum estradiol levels were less than 11 pg/mL later had twice the risk of fracture than did women with levels of serum estradiol (> 15 pg/mL). In a 6-month clinical trial,[25] women treated with placebo lost bone mass, and women receiving 7.5 μg/d estradiol by a transvaginal ring system had reduced bone turnover markers and increased radial bone mass; this treatment did not increase endogenous estradiol more than a few picograms per milliliter. Among women who received ultralow-dose oral estradiol (0.25 mg/d) for 3 years or more, mean spine and hip bone mineral density increased.[23] In that trial, treatment resulted in estradiol levels that were reported to be approximately 3 times higher than levels achieved in our trial; this difference may have resulted from differences in estradiol assays or from differences in effective doses.

When given in combination with calcium and vitamin D, standard-dose estrogen reduces osteocalcin levels about 35% from baseline levels.[14] Low-dose oral estrogen (0.3 mg conjugated estrogens)[14,26] or low-dose transdermal estradiol (0.025 mg/d)[27] reduces osteocalcin levels by about 25–30%, and ultralow-dose oral micronized estradiol (0.25 mg) reduces osteocalcin levels 8–27% from baseline values.[26] Calcium with vitamin D typically reduces osteocalcin levels 5–10%.[14] In our trial, levels of alkaline phosphatase and osteocalcin decreased 22% from baseline in women treated with ultralow-dose transdermal estradiol, suggesting that ultralow-dose estradiol effectively reduces bone turnover.

Increased risk of endometrial hyperplasia and cancer among women exposed to unopposed estrogen appears to be dose-related. Standard doses of estrogen produce a 15–20% annual rate of endometrial hyperplasia.[28,29] Studies of endometrial effects of half-strength unopposed estrogen therapy show variable results: In a 2-year trial[11] that included 100 postmenopausal women treated with 0.3 mg of esterified estrogen, no increase in hyperplasia rate was observed compared with rates in women receiving placebo; in contrast, a case-control study[17] showed that use of 0.3 mg unopposed estrogen or equivalent was associated with substantially increased risk of endometrial cancer. In a small randomized trial[30] studying endometrial effects of a vaginal ring (which delivered 7.5 μg of estradiol per day and increased serum estradiol levels as much as did the transdermal system used in our trial), no increase was observed in sonographically determined endometrial thickness among the 30 treated women monitored for 12 months. We found no increased risk of endometrial hyperplasia among women treated with ultralow-dose estrogen. The low rate of hyperplasia we observed in the study group in our trial is consistent with hyperplasia rates seen in other studies of elderly women receiving placebo.[29,31]

Women in the treatment group had a higher incidence of cervical polyps observed at pelvic examination and a higher risk of vaginal discharge than did women in the placebo group. Because we examined such a large number of potentially adverse outcomes, these differences between groups might have occurred by chance. Cervical polyps are of minimal clinical significance. The clinical significance of vaginal discharge is not known but could be an indication of improved vaginal lubrication or an unwelcome side effect of treatment.

Our study had several strengths, including adequate numbers of women who took supplemental calcium and vitamin D; sufficient length of follow-up; and objectively measured outcomes, side effects, and adverse events. For study participants continuing estradiol, adherence was excellent; for participants stopping the estradiol regimen, the 2-year follow-up was nearly complete. Our study design provided adequate power to determine that the rate of endometrial hyperplasia in the estrogen-treated women was, at worst, no more than 7.3% higher than in the control placebo-treated women.

None of the women in our study were in the early postmenopausal phase, when endogenous estradiol levels remain somewhat higher and bone loss tends to be more rapid than we observed. In that circumstance, higher doses of hormone therapy might be required to prevent bone loss. We observed fewer fractures in women randomized to estradiol than in those randomized to placebo, but our study had inadequate power to determine if ultralow-dose estradiol therapy reduces fracture risk. Data from an observational study[32] showed a lower incidence of fracture in women using standard doses of estrogen but did not show similar protection among women using lower doses. In our trial, however, the magnitude of reduction in bone turnover markers and difference in bone mineral density between women treated with ultralow estradiol and those receiving placebo were similar to values observed in women who received raloxifene, a drug that reduces risk of vertebral fracture about 68% within 1 year of treatment[33] and 36% after 3 years of treatment.[31] The ratio of fractures in control subjects versus estradiol-treated women observed in the 3-year clinical trial of ultralow-dose oral estradiol (3:1) closely mirrors our results.[23]

Our findings further support evidence that lower-than-standard doses of estrogen may have beneficial effects. In response to reported adverse effects of standard-dose hormone therapy,[1,2] about 40% of women have discontinued hormone therapy.[34] Instead of stopping hormone therapy entirely, some women might seek lower-dose, progestin-free hormone therapy to preserve bone mineral density. However, neither long-term fracture protection nor long-term safety has been shown for lower-than-standard estrogen doses. Compared with oral estrogen intake, transdermal delivery of estradiol is less likely to cause adverse changes in hepatic coagulation factors,[35] which may result in lower risk of venous thromboembolism.[36] However, the cardiovascular safety of this dose and route of estrogen cannot be assumed.

Our results suggest that estrogen deficiency among elderly women should be redefined–not in comparison with premenopausal levels but in consideration of the physiologic effects of estradiol in this age group. In premenopausal women, serum estradiol ranges from about 50 to 200 pg/mL, depending on the phase of the menstrual cycle. In contrast, most older postmenopausal women have levels below 10 pg/mL.[20,21] At baseline, about 13% of the women enrolled in our trial had undetectable estradiol levels ($<$ 1.4 pg/mL), and median estradiol level was 5 pg/mL. By increasing serum estradiol a small amount to a level well below the premenopausal range, we were able to prevent bone loss. Ideally, serum estradiol measurement could be used to guide management of women receiving ultralow-dose estrogen therapy, but only a few laboratories use the sensitive radioimmunoassay capable of accurately measuring such low levels of estradiol. Most clinical laboratories use the automated ELISA, for which the FDA-approved lower limit of sensitivity is 15 pg/mL (Diagnostic Products Corporation. Immulite Estradiol: technical bulletin

PILKE2-5, 2003-08-12. Los Angeles: Diagnostic Products Corporation; 2003).

Postmenopausal women with low or undetectable levels of estradiol have lower risk for breast cancer than do women with slightly higher levels.[37] We do not know if the small increases in circulating estradiol that result from ultralow-dose estradiol therapy will result in increased risk of breast cancer. A large observational study[38] recently reported that the increased risk of breast cancer associated with estrogen therapy use was not dose- or route-related but was statistically significantly higher with added progestins.

In conclusion, treating older postmenopausal women with ultralow doses of transdermal estrogen improves bone mineral density and reduces bone turnover without increasing the rate of endometrial hyperplasia. Larger, long-term trials are needed to determine other potential benefits and harms of ultralow-dose estradiol therapy.

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