

The Effect of Low-Dose Continuous Estrogen and Progesterone Therapy with Calcium and Vitamin D on Bone in Elderly Women

A Randomized, Controlled Trial

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Background: Hormone replacement therapy (HRT), the mainstay of osteoporosis prevention, is limited because of dose-related risks, side effects, and patient acceptance. The bone-sparing efficacy and tolerability of the lowest available doses of HRT have not been adequately studied in elderly women.

Objective: To determine the bone-sparing effect of continuous low-dose HRT in elderly women.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: University osteoporosis research and clinical center.

Patients: 128 healthy white women (age > 65 years) with low bone mass recruited by word of mouth and by local advertisement. The principal eligibility criterion was spinal bone mineral density of 0.90 g/cm² or less.

Intervention: Continuous therapy with conjugated equine estrogen, 0.3 mg/d, and medroxyprogesterone, 2.5 mg/d, or matching placebo. Sufficient calcium supplementation was given to bring all calcium intakes above 1000 mg/d in both groups; supplemental oral 25-hydroxyvitamin D was given to maintain serum 25-hydroxyvitamin D levels of at least 75 nmol/L in both groups.

Measurements: Bone mineral density of the spine, hip, total body, and forearm; serum total alkaline phosphatase and serum osteocalcin levels at 6-month intervals; and 24-hour urine creatinine and hydroxyproline excretion at baseline, 12 months, and 42 months.

Results: During 3.5 years of observation, spinal bone mineral density increased by 3.5% ($P < 0.001$) in an intention-to-treat analysis and by 5.2% among patients with greater than 90% adherence to therapy. Significant increases were seen in total-body and forearm bone density ($P < 0.01$). Symptoms related to HRT (breast tenderness, spotting, pelvic discomfort, and mood changes) were mild and short-lived.

Conclusions: Continuous low-dose HRT with conjugated equine estrogen and oral medroxyprogesterone combined with adequate calcium and vitamin D provides a bone-sparing effect that is similar or superior to that provided by other, higher-dose HRT regimens in elderly women. This combination is well tolerated by most patients.

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Postmenopausal hormone replacement therapy (HRT) is the cornerstone of osteoporosis prevention (1–15). However, the severity of side effects and problems associated with long-term HRT (15–20) are dose related (17, 21–25) and have limited the number of persons who experience its bone-sparing effects (15). Thus, only about 20% of women who could benefit from HRT are actually taking it, and about 30% of prescriptions for HRT are unfilled (15, 20).

The lowest available doses of HRT have not been tested for efficacy in preventing bone loss, particularly in elderly women. Several investigations into various aspects of low doses of HRT have been reported (5, 21–24, 26–33); however, results have been inconsistent, and several studies have shown no bone effects (22, 26–28, 31, 33). The lowest dosage that produces bone effects has been thought to be 0.625 mg of conjugated equine estrogens per day (34) or its equivalent. Most studies did not ensure adequate vitamin D and calcium intake, few specifically evaluated older women, and many had large numbers of dropouts.

Our primary hypothesis was that continuous administration of conjugated equine estrogen, 0.3 mg/d, combined with medroxyprogesterone, 2.5 mg/d, in elderly postmenopausal women would prevent bone loss in the spine over 3.5 years compared with placebo in the context of adequate calcium and vitamin D nutrition.

Methods

Patients

We recruited a convenience sample of 128 healthy white women older than 65 years of age by using local media advertising and word of mouth. The principal entry criterion was a spinal bone mineral density of 0.90 g/cm² or less (T score ≤ -1.336), as measured by dual-energy x-ray absorptiometry. Exclusion criteria were previous hip fracture, treatment with estrogen or calcitonin in the past 6 months, any treatment with bisphosphonates or fluoride, treatment with corticosteroids of more than 6 months' duration, any corticosteroid treatment in the past 6 months, endometrial thickness more than

Eligible patients screened (n=301)	
Excluded (n=173)	
By exclusion criteria (n=116)	
By patient choice (n=57)	
	Randomization
Received placebo (n=64)	Received HRT (n=64)
Followed at 6-month intervals	Followed at 6-month intervals
Stopped taking placebo Remained in study (n=2)	Stopped HRT Remained in study (n=7)
Withdrawn Lost to follow-up (n=10)	Withdrawn Lost to follow-up (n=11)
Completed trial (n=54)	Completed trial (n=53)

Figure 1. Results of randomization. HRT = hormone replacement therapy.

6 mm as measured by transvaginal ultrasonography, history of breast cancer, and smoking more than 10 cigarettes per day. Persons with hysterectomy were not excluded. Thyroid hormone replacement was accepted provided that the serum thyroid-stimulating hormone level was normal. Good health was documented by clinical examination and blood chemistry profile.

The protocol was reviewed and approved by the Creighton University institutional review board, and each patient provided written, informed consent.

Study Protocol

Patients were randomly assigned to one of two groups. One group received continuous conjugated equine estrogen, 0.3 mg/d, and medroxyprogesterone, 2.5 mg/d; the other received identical-appearing placebo pills. The patients were assigned to treatment or placebo in randomly permuted blocks of two patients each. A faculty member of the School of Pharmacy, who was outside of the Osteoporosis Research Center, performed and maintained the assignment to treatment or placebo, the randomization code, the receiving and storage of bulk medication, and the preparation of the active and placebo pills for dispensing during the trial. Patients returned unused pills, which were counted.

The scheduled duration of observation for each patient was 3.5 years. Recruitment began in September 1992, and the last patient completed 3.5 years of observation in June 1997. **Figure 1** shows the results of randomization and the final study sample. Visits 1 through 11 were scheduled at 0, 1, 2, 3, 6, 12, 18, 24, 30, 36, and 42 months. At each visit, we measured bone mineral density of the spine, the primary outcome measure, along with bone mineral density at other sites; performed a brief physical examination; and took a detailed his-

tory concentrating on symptoms (breast tenderness, spotting, pelvic discomfort, and mood changes) related to HRT. Mammography, which was funded as part of the protocol, was performed on entry, and we encouraged annual mammography as part of personally funded health maintenance programs. We followed published guidelines for performing endometrial sampling (35): whenever bleeding was heavier than a normal menstrual period, lasted longer than 10 days at a time, occurred more often than monthly, or occurred later than 10 months into therapy. Serum total alkaline phosphatase and osteocalcin levels were measured at each scheduled visit and at 8 and 34 weeks. Twenty-four-hour urine calcium, creatinine, and hydroxyproline levels were measured at baseline, 12 months, and 36 months. Lateral lumbar and thoracic spine radiographs were obtained at 0 and 42 months.

At entry, a 7-day diet diary was analyzed, and patients whose calcium intakes fell below 1.0 g/d ($n = 111$) received a calcium supplement in the form of calcium carbonate, 300 mg of calcium per tablet, sufficient to bring total calcium intake up to a minimum of 1 g/d. Median supplementation was 600 mg/d. Serum 25-hydroxyvitamin D level was measured on each patient on entry, and those with levels less than 75 nmol/L ($n = 102$) were supplemented with oral 25-hydroxyvitamin D sufficient to raise the level to at least 75 nmol/L. Serum 25-hydroxyvitamin D levels were monitored as needed to ensure that they remained at 75 nmol/L or higher throughout the study. One hundred two patients required oral 25-hydroxyvitamin D. After the first 12 months, the dose stabilized at 50 μ g once or twice weekly in every patient (equivalent to 50 to 200 μ g of conventional vitamin D daily [36]). The highest steady-state blood level of 25-hydroxyvitamin D was 182 nmol/L. We performed 433 measurements of 25-hydroxyvitamin D during the study, including 86 measurements at visit 11; in every case, blood levels were greater than 75 nmol/L.

Laboratory Methods

The clinical laboratory tests were performed by the university reference laboratory. We measured serum total alkaline phosphatase and urine creatinine levels by an automated method (Gilford Systems, Oberlin, Ohio), serum osteocalcin levels by a commercial kit (INCSTAR Corp., Stillwater, Minnesota), and serum 25-hydroxyvitamin D levels by a competitive binding assay (Nichols Institute Diagnostics, San Juan Capistrano, California). Urine calcium, creatinine, and hydroxyproline levels were measured on an aliquot of each 24-hour collection, calcium level was measured by atomic absorption spectrophotometry, and hydroxyproline level was measured by our routine method (37). Urine cal-

Table 1. Baseline Data*

Characteristic	HRT Group (n = 53)	Placebo Group (n = 54)	HRT Group Dropouts (n = 11)	Placebo Group Dropouts (n = 10)
Age, y	73.15 ± 5.00	73.96 ± 5.30	72.39 ± 5.70	70.93 ± 3.49
Height, m	1.551 ± 0.163	1.576 ± 0.066	1.604 ± 0.083	1.475 ± 0.243
Weight, kg	63.0 ± 13.6	62.7 ± 10.5	66.8 ± 12.6	60.5 ± 14.7
Calcium intake, mg/d	685 ± 250	761 ± 288	599 ± 154	674 ± 214
Spine bone mineral density, g/cm ²	0.791 ± 0.101	0.765 ± 0.094	0.782 ± 0.107	0.695 ± 0.138
Spine bone mineral density T-score	-2.648 ± 0.915	-2.884 ± 0.857	-2.730 ± 0.971	-3.523 ± 1.252
Femoral neck bone mineral density, g/cm ²	0.652 ± 0.083	0.628 ± 0.096	0.652 ± 0.109	0.601 ± 0.081
Femoral neck bone mineral density T score	-3.275 ± 0.833	-3.520 ± 0.962	-3.280 ± 1.095	-3.786 ± 0.814
Total-body bone mineral content, g	2162 ± 252	2090 ± 261	2214 ± 162	1942 ± 283
Forearm bone mineral density, g/cm ²	0.466 ± 0.076	0.440 ± 0.084	0.473 ± 0.063	0.424 ± 0.079
Alkaline phosphatase level, IU/L	71.0 ± 21.3	77.9 ± 21.9	69.9 ± 14.6	89.6 ± 30.6
Osteocalcin level, µg/L	5.3 ± 2.0	5.1 ± 1.7	4.3 ± 1.6	5.3 ± 2.3
Calcium:creatinine ratio	0.1481 ± 0.0756	0.1402 ± 0.0911	0.1850 ± 0.1113	0.1497 ± 0.0739
Hydroxyproline:creatinine ratio	18.6 ± 5.4	19.4 ± 6.1	18.2 ± 3.9	19.7 ± 8.3

* All values are given as the mean ± SD. To convert alkaline phosphatase values to µkat/L, multiply by 0.01667. To convert osteocalcin values to nmo/L, multiply by 0.0171. HRT = hormone replacement therapy.

cium and hydroxyproline were expressed as the ratios of calcium to creatinine and hydroxyproline to creatinine. Radiographic morphometry was performed on standard lateral spine radiographs by using methods described elsewhere (38, 39).

Bone Densitometry

All bone mineral measurements were made by using dual-energy x-ray absorptiometry with a Norland XR-26 machine (Norland, Fort Atkinson, Wisconsin) for the first 44 calendar months of the study and a Hologic QDR 2000⁺ (Hologic, Waltham, Massachusetts) for the last 12 calendar months. Software and hardware changes were accompanied by dual, same-day measurements with each software or hardware to create algorithms that would allow us to convert to a common software–hardware combination. Our long-term precision, as assessed by using the method of Gluer and colleagues (40), is 1.17% for spine bone mineral density, 1.57% for femoral neck bone mineral density, 1.10% for total-body bone mineral content, and 1.13% for forearm bone mineral density.

Statistical Analysis

The minimum important difference in spinal and femoral bone mineral density between placebo and HRT was projected to be 4.5% at the end of 3.5 years, and the projected power was 0.88 to 0.93 for an α value of 0.05 with 52 patients completing the study in each of two groups. We performed intention-to-treat analysis of the change from baseline on both the primary spine bone mineral density measurements and on total-body bone mineral content, femoral neck bone mineral density, and forearm bone mineral density by using SAS PROCEDURE MIXED (41), a repeated-measures analysis of variance. The 21 patients who dropped out in the first year of the study were not included in the intention-to-treat analysis because few data were available

from them. Data from the 9 patients who stopped therapy but remained under observation were included in the entire PROCEDURE MIXED analysis as if they had continued therapy.

To obtain the best precision for the baseline bone mineral density value for each patient, we performed a regression of bone mineral density measurements from the first year as a function of time of observation for each patient. The baseline bone mineral density value was taken as the intercept of bone mineral density at zero time and was used as the denominator in determining the percent change in bone mineral density from baseline at each time point in the study. A comparison of the baseline bone mineral density for each site calculated as the zero-time intercept with the measured bone mineral density at baseline revealed no significant difference. The value for change at each visit for each patient was calculated as follows: change = $[(\text{bone mineral density}_i - \text{bone mineral density}_b) - 1] \times 100$, where bone mineral density_{*i*} is the bone mineral density at time *i* and bone mineral density_{*b*} is the bone mineral density at baseline. In addition, for the femoral neck, we normalized the values in both groups to the placebo means by dividing by the placebo means at each measurement point.

Role of Funding Sources

Our funding sources had no role in the collection, analysis, or interpretation of the data in this project and did not participate in the decision to submit the study for publication.

Results

Baseline Data

The baseline data characterizing the study sample are presented in **Table 1**. None of the differ-

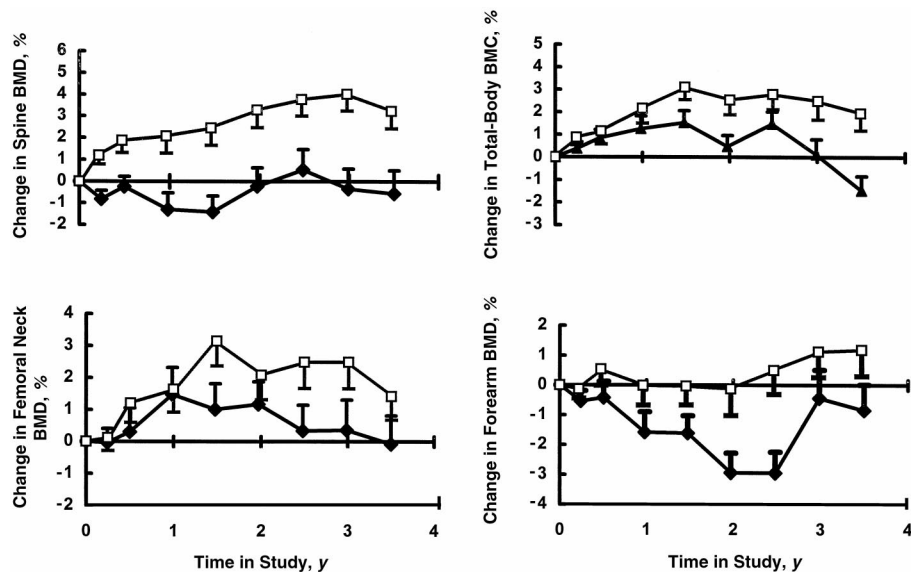


Figure 2. Percentage change in spine bone mineral density (BMD) (top left), femoral neck bone mineral density (bottom left), total-body bone mineral content (BMC) (top right), and forearm bone mineral density (bottom right) in the hormone replacement therapy group (diamonds) and placebo group (squares). The effect of hormone replacement therapy was significant at all sites ($P < 0.01$) except the femoral neck ($P = 0.19$). Bone mass remained the same or increased in the placebo group at the spine, total body, and femoral neck and decreased at the forearm. Error bars represent SEs.

ences in means between groups was significant except for the difference between the ages of patients who remained in the placebo group (73.9 ± 5.3 years) and placebo group dropouts (70.9 ± 3.5 years; $P = 0.05$). This difference is considered a chance occurrence given the number of comparisons. Estrogen use during the 6 months before the start of the study was an exclusion criterion. Before 6 months, in the placebo group, 33 patients were never users of HRT, 28 were ever users, and 2 were indeterminate; in the HRT group, 30 patients were never users, 34 were ever users, and 0 were indeterminate. Of patients who continued to receive study medication during the entire 3.5 years, pill counts revealed return of 4.0% to 9.3% of unused pills, for an adherence estimate of 90.3% to 96.0%. Thus, in no case did a patient who continued to receive study medication the entire 3.5 years return more than 9.3% of the prescribed pills over the entire study and, in the best case, returned 4.0% of the prescribed pills.

Bone Density

Bone density measurements are illustrated in **Figure 2** as the percentage change from baseline (\pm SE). All patients—54 in the placebo group and 53 in the HRT group—who remained under observation are included in the analysis, regardless of whether they continued to receive the test medication (**Figure 1**).

Bone mineral density of the spine increased significantly in the HRT group from baseline and compared with the placebo group ($P < 0.001$ for HRT compared with placebo). It increased most rapidly

in the first 6 months and peaked at 3 years, when there was a gain of 4.0% (95% CI, 2.49% to 5.51%) over baseline values. The value at 3.5 years was 3.23% (CI, 1.64% to 4.82%), which does not differ significantly from the value at 3 years. The value in the placebo group was -0.35% (CI, -2.16% to 1.46%) at 3 years and -0.57% (CI, -2.67% to 1.53%) at 3.5 years.

Total-body bone mineral content changed significantly in the HRT group from baseline and compared with the placebo group ($P < 0.015$ for HRT compared with placebo) and increased steadily for 1.5 years to a gain of 3.10% (CI, 1.92% to 4.28%). The value for the placebo group at 1.5 years was 1.52% (CI, 0.47% to 2.57%). After 1.5 years, the fluctuations in mean total-body bone mineral content in the HRT group were not significant.

Femoral neck bone mineral density in the HRT group increased steadily for 1.5 years, then decreased somewhat by 3.5 years. The overall treatment effect for bone mineral density data did not reach statistical significance ($P = 0.19$), even though values were higher in the HRT group than in the placebo group at every time point. However, when we adjusted for the change due to the remodeling transient (by normalizing the values in both groups to the placebo means at each measurement point), the slopes of the resulting data over time were 0% per year for the placebo group and 0.51% per year (CI, 0.16% to 0.85%) for the HRT group ($P = 0.068$ for comparison with placebo). When the same analysis was carried out including only the patients who adhered to therapy, the slope for the HRT

group increased to 0.62% per year (CI, 0.27% to 0.97%).

The overall treatment effect for radius bone mineral density was significant ($P < 0.01$) in favor of HRT. The placebo group showed a decrease from baseline; this effect was blocked by HRT in the treatment group. Moreover, the HRT group showed a 1.18% (CI, -0.59% to 2.95%) increase over baseline values at 3.5 years ($P < 0.001$ compared with placebo), when the placebo group showed a loss of -0.84% (CI, -2.53% to 0.84%).

The intention-to-treat analysis supports the bone-sparing efficacy of low-dose HRT, but because the analysis included persons in the treatment group who did not receive HRT for the entire observation period, the magnitude of the potential treatment effect is underestimated. Thus, we reanalyzed the data on bone mineral density of the spine excluding patients who remained under observation but did not take the test medication (**Table 2**). The change among patients who adhered to therapy was close to 5% at all time points beyond 1.5 years. The other bone sites also showed a greater effect with adherence, although the difference was not as large (data not shown).

Biochemical Markers and Radiographs

Changes in biochemical markers are shown in **Figure 3**. Both alkaline phosphatase and osteocalcin levels began to decrease by 8 weeks. The pretreatment alkaline phosphatase level in the HRT group was $1.19 \mu\text{kat/L}$ (CI, 1.10 to $1.29 \mu\text{kat/L}$). The nadir

Table 2. Change in Spine Bone Mineral Density in the Hormone Replacement Therapy Group*

Study Year	Mean Change (\pm SE) in Spine Bone Mineral Density	
	All Patients Who Received HRT	Patients Who Adhered to HRT
	%	
2.0	3.29 ± 0.83	4.78 ± 0.77
2.5	3.77 ± 0.77	5.24 ± 0.67
3.0	4.01 ± 0.77	5.11 ± 0.78
3.5	3.23 ± 0.80	4.60 ± 0.77

* HRT = hormone replacement therapy.

occurred at 6 months and stabilized thereafter at about $1.06 \mu\text{kat/L}$, a value about 11% below baseline values. The osteocalcin level in the HRT group was 0.09 nmol/L (CI, 0.08 to 0.10 nmol/L) before treatment and 0.06 nmol/L (CI, 0.05 to 0.07 nmol/L) at 3.5 years. Neither the alkaline phosphatase level nor the osteocalcin level changed significantly in the placebo group; mean respective values were $1.34 \mu\text{kat/L}$ (CI, 1.24 to $1.45 \mu\text{kat/L}$) and 0.07 nmol/L (CI, 0.06 to 0.08 nmol/L), respectively, at 3.5 years.

The ratio of hydroxyproline to creatinine in the HRT group was $20.2 \mu\text{mol/mmol}$ (CI, 18.3 to $22.0 \mu\text{mol/mmol}$) before treatment, $14.1 \mu\text{mol/mmol}$ (CI, 12.3 to $15.9 \mu\text{mol/mmol}$) at 12 months, and $15.4 \mu\text{mol/mmol}$ (CI, 13.8 to $17.0 \mu\text{mol/mmol}$) at 3.5 years. The ratio did not change significantly in the placebo group; values were $19.5 \mu\text{mol/mmol}$ (CI, 17.7 to $21.2 \mu\text{mol/mmol}$) at baseline and $18.3 \mu\text{mol/mmol}$ (CI, 16.4 to $20.2 \mu\text{mol/mmol}$) at 3.5 years.

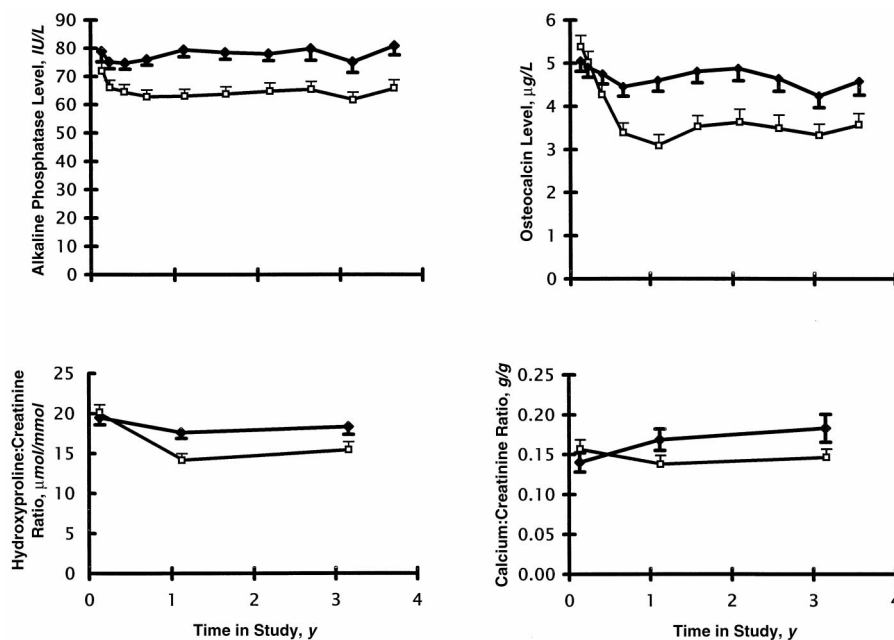


Figure 3. Total alkaline phosphatase level (top left), 24-hour urinary calcium:creatinine ratio (bottom right) in the hormone replacement therapy group (diamonds) and placebo group (squares). Values shown are the mean \pm SE. The treatment effect of hormone replacement therapy was significant for all four bone markers. To convert alkaline phosphatase values to $\mu\text{kat/L}$, multiply by 0.01667. To convert osteocalcin values to nmol/L , multiply by 0.0171.

Table 3. Patients Who Discontinued Therapy*

Reason for Withdrawal	Dropouts	
	Placebo Group	HRT Group
	<i>n</i>	
HRT side effects†	1	2
Death	1	2
Prescribed HRT by physician	1	1
Hip fracture	1	0
Stroke	1	1
Miscellaneous	5	5

* HRT = hormone replacement therapy.

† Two patients in the placebo group and seven patients in the HRT group discontinued therapy but stayed in the study.

The ratio of calcium to creatinine in the HRT group was 0.157 g/g (CI, 0.133 to 0.181 g/g) before treatment, 0.138 g/g (CI, 0.116 to 0.160 g/g) at 12 months, and 0.146 g/g (CI, 0.126 to 0.166 g/g) at 3.5 years. In the placebo group, the ratio of calcium to creatinine was 0.140 g/g (CI, 0.116 to 0.164 g/g) at 12 months and 0.183 g/g (CI, 0.148 to 0.218 g/g) at 3.5 years; this 32% increase was attributable to calcium and vitamin D supplementation.

The lateral spine films available for morphometric analysis revealed three incident vertebral deformities among 50 patients in the HRT group and four among 51 patients in the placebo group ($P > 0.2$).

Adverse Events and Dropouts

Ten patients dropped out of the placebo group and 11 dropped out of the HRT group. All dropouts occurred during the first year, and most occurred in the first few months. Reasons for dropping out are listed in **Table 3**. Nine additional patients (7 in the HRT group and 2 in the placebo group) stopped taking the medication but remained under observation for the full 3.5 years. All 9 patients stopped therapy because of symptoms thought to be related to HRT (breast tenderness, spotting, pelvic discomfort, and mood changes), and all were included in the analysis. The proportion of patients receiving HRT who stopped therapy (18 of 64 patients) compared with those receiving placebo who stopped therapy (12 of 64 patients) was not significant.

Side effects thought to be related to HRT were mild, short lived, and easily tolerated by most patients. Forty-nine patients receiving HRT and 27 patients receiving placebo described breast changes (tenderness and sensitivity), none of which were severe. Twenty-nine patients receiving HRT experienced vaginal spotting or change in the nature of vaginal discharge; 3 of 64 patients (2 receiving HRT and 1 receiving placebo) met at least one of the criteria for endometrial biopsy during the study. One patient receiving HRT who underwent endometrial biopsy had atrophic endometrium; the other

underwent elective hysterectomy for pelvic floor abnormalities and also had atrophic endometrium. Endometrial biopsy in the patient in the placebo group revealed endometrial carcinoma.

Most side effects associated with HRT disappeared within 6 months. Only 6% of patients in the placebo group and 11% of patients in the HRT group had symptoms lasting more than 12 months. No patient had vaginal spotting or bleeding beyond 12 months, and no thromboembolic episodes occurred.

Discussion

Our results show that over a 3-year period, continuous oral administration of conjugated equine estrogen, 0.3 mg/d, and medroxyprogesterone, 2.5 mg/d, combined with adequate intake of calcium and vitamin D produced a significant bone-sparing effect in elderly women. Furthermore, when there is at least 90% adherence to the regimen, the gain is almost 5% for the spine, about 2.6% for total-body bone mineral content, and about 1.6% for the hip and loss at the forearm is prevented. No significant losses occurred at the spine or total body in patients who received placebo plus calcium and vitamin D; this result is consistent with those of other studies of calcium supplementation in this age group (42, 43). Moreover, as **Figure 2** shows, an early increase in bone mineral density was seen at both the hip and the total body in the placebo group, which is consistent with a small remodeling transient. Nevertheless, the data clearly show that HRT plus calcium and vitamin D was substantially more beneficial than calcium and vitamin D alone.

The bone remodeling marker changes in this study are in general agreement with those reported by Raisz and colleagues (44). Both formation and resorption markers decreased over the first year of treatment and remained stable thereafter. Estrogen is known to suppress activation of remodeling, an effect that produces a remodeling transient because of reduction in the remodeling space (45). Although the marker changes were complete at about 1 year, the bone mineral density changes suggest that the skeletal transient lasted about 2 years. Because mineralization at remodeling sites continues for some time after matrix deposition is complete (46, 47), this could account, at least in part, for this disparity.

The increase in bone mineral density reported here was equal to that reported in the Postmenopausal Estrogen/Progestin Interventions trial (48), which combined conjugated equine estrogen, 0.625 mg/d, with medroxyprogesterone, 2.5 mg/d, over 3 years (48). Ours are the most positive results for low-dose HRT reported to date. At least six other studies have shown a smaller bone-sparing effect of

low-dose estrogen. Genant and associates (29) recently reported that spine bone mineral density increased by 1.76% in response to continuous therapy with esterified estrogen (0.3 mg/d), compared with a 4.6% increase in our study. Some reasons for their smaller effect might be that estrogen was unopposed by a progestin, that their study sample was much younger than ours (51.5 ± 0.4 years), that vitamin D was not given, and that the length of observation was only 2 years. In addition, there was almost 50% loss of sampling units by the end of their study compared with only 16% in our study.

Ettinger and colleagues (5) found that 0.3 mg of conjugated estrogens per day given with a calcium supplement of 1000 mg/d prevented spinal bone loss in the immediate postmenopausal period. Conjugated equine estrogen, 0.3 mg/d, combined with medroxyprogesterone, 2.5 mg/d, has been reported to maintain forearm bone mineral density for 1 year (30) and spine bone mineral density for 2 years (32) in postmenopausal women. Speroff and coworkers (33) demonstrated a synergistic bone-sparing effect when norethindrone acetate was added to continuous treatment regimens with ethinyl estradiol. Gallagher and associates (31) found that cyclical administration of conjugated estrogens, 0.3 mg/d, coupled with medroxyprogesterone, 10 mg/d, and calcium was as effective as conjugated estrogens, 0.625 mg/d, given without a progestin in preventing bone loss in women in their early 50s. We suggest that the difference in bone mineral density response to low-dose HRT in our study compared with the others is due principally to the fact that we ensured adequate calcium and vitamin D nutrition.

Our reasons for using 25-hydroxyvitamin D as the vitamin D preparation were twofold: 1) no conventional vitamin D preparation containing only vitamin D is available for use in these circumstances, and 2) 25-hydroxyvitamin D is convenient for study purposes because it can quickly achieve and maintain adequate vitamin D status. We used the level of 75 nmol/L because data suggest that this level is required to prevent seasonal fluctuations in serum parathyroid hormone (49–51) and that this is the level below which parathyroid hormone begins to increase (52, 53). It is also the range found in young persons (54).

Unwanted symptoms (breast tenderness, spotting, pelvic discomfort, and mood changes) related to HRT were generally short lived and were not particularly severe. It is noteworthy that these symptoms occurred with considerable frequency in the placebo group, even to the extent that one patient withdrew from the study (in this patient, endometrial carcinoma was diagnosed because of persistent bleeding), and two stopped taking test medications but continued observation.

Our study had several limitations. First, we used a convenience sample, not a population-based sample, as is the case in almost all clinical trials; thus, it may not be representative of the population that receives HRT. Furthermore, the end point for efficacy was bone mineral density, a laboratory measurement and surrogate for fracture, not clinical fracture itself. In addition, the comparison of our results with the results of higher doses of HRT is a historical comparison, not a direct comparison. Finally, bone biomarkers are indices of the change in bone remodeling evoked by HRT, and their significance as markers of bone-sparing or antifracture efficacy is uncertain.

Our findings suggest that continuous low-dose HRT combined with calcium and vitamin D supplementation is a good, low-cost therapeutic option for prevention of osteoporosis in elderly postmenopausal women. Its bone-sparing effect is strong, and the side effects are tolerable and acceptable for most patients if they are suitably monitored. The risk for endometrial carcinoma resulting from this HRT regimen remains uncertain. Continuous unopposed conjugated equine estrogen, 0.3 mg/d, increases the risk for endometrial cancer (55), and endometrial cancer occurring with continuous combined HRT has been reported, mostly with dosages of conjugated equine estrogen of 0.625 mg/d (56–58). Although the risk for endometrial cancer is likely to be less with 0.3 mg of conjugated equine estrogen per day than with 0.625 mg/d, more studies are needed to accurately assess the risk of continuous low-dose HRT as we used it in this study.

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