

Timing of Postmenopausal Estrogen for Optimal Bone Mineral Density

The Rancho Bernardo Study

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Objective.—To determine the effect of the timing of initiation and the duration of postmenopausal estrogen therapy on bone mineral density (BMD).

Design.—Cross-sectional study.

Setting.—White, middle-class to upper middle-class community-dwelling women.

Participants.—A total of 740 women aged 60 to 98 years who participated in a study of osteoporosis.

Measurements.—Questionnaire, validated medication use, and height and weight. Bone mineral density at the ultradistal radius and midshaft radius using single-photon absorptiometry (SPA) and at the hip and lumbar spine using dual-energy x-ray absorptiometry (DEXA).

Results.—Of the 740 women, 69% had used oral estrogen after menopause and 30% were current users. Five groups of estrogen use were identified: never users, past users who started at menopause, past users who started after age 60 years, current users who started after age 60 years, and current users who started at menopause. At all 4 bone sites, current users who started at menopause had the highest BMD levels, which were significantly higher than never users or past users who started at menopause (with 10 years' duration of use). These differences persisted after controlling for all major risk factors for osteoporosis. Among current users, there was no significant difference in BMD levels at any site between those who started estrogen at menopause (with 20 years of use) and those who started after age 60 years (with 9 years of use).

Conclusions.—Estrogen initiated in the menopausal period and continued into late life is associated with the highest bone density. Nevertheless, estrogen begun after age 60 years and continued appears to offer nearly equal bone-conserving benefit.

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IN THE 1970s, exogenous estrogen was observed to reduce postmenopausal bone loss^{1,2} and lower the risk of spinal and

extremity fractures.³⁻⁶ Subsequently, estrogen therapy was prescribed for postmenopausal women with the usual recommendation to begin at the time of menopause and continue for 10 years. This recommendation was based on the rapid bone loss observed at menopause,⁷ and the expectation that even if bone loss resumed after discontinuing estrogen, the delay in bone loss would reduce fracture risk.^{8,9} Today, estrogen is generally believed to be the most effective

prevention and treatment for osteoporosis in postmenopausal women.

There is, however, little agreement on the optimal time to start or stop estrogen. Recently, after examining the duration of use necessary to obtain a prolonged effect on bone density in elderly women, Felson and colleagues¹⁰ concluded that women should take estrogen for at least 7 years after menopause, but also noted this length of treatment did not preserve bone density for those older than 75 years. This suggested that lifetime estrogen replacement would be necessary to prevent osteoporosis.

However, concern about breast cancer and other possible risks associated with extended estrogen use and the awareness that bone loss continues or even accelerates in old age¹¹ have raised questions about when to initiate therapy and whether therapy should be discontinued. To address these questions, we examined the past and current use of estrogen replacement therapy in a population-based sample of older, white postmenopausal women who had a high proportion of past and current estrogen use. We hypothesized that current estrogen use was better than past use for the maintenance of bone density and that current therapy begun years after menopause might be as beneficial as continuous treatment begun at the time of menopause.

METHODS

A study of osteoporosis was conducted from February 1988 to November 1991. During this period, 909 ambulatory white women aged 60 to 98 years from a middle-class community (Rancho Ber-

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Table 1.—Age-Adjusted Sample Characteristics by Estrogen Replacement Onset Status and Current or No Current Use in Women Aged 60 Years and Older, Rancho Bernardo, Calif, 1988-1991*

Variable	Never Users (n=229)	Past Early Users (n=229)	Past Late Users (n=56)	Current Late Users (n=29)	Current Continuous Users (n=197)
Age, y	75.8 (74.8-76.8)	74.0 (73.0-75.0)	79.1 (77.2-81.0)	77.6 (74.9-80.3)	70.8 (69.8-71.8)
Body mass index, kg/m ²	25.0 (24.5-25.5)	24.6 (24.1-25.1)	25.4 (24.4-26.4)	23.8 (22.4-25.2)	24.2 (23.6-24.8)
Age at menopause, y	48.6 (47.8-49.2)	45.9 (45.1-46.7)	48.5 (46.8-50.2)	48.9 (46.6-51.2)	45.4 (44.5-46.3)
Total daily calcium, mg	856.2 (783.4-929.0)	956.2 (882.9-1029.5)	1014.4 (865.1-1163.4)	1073.7 (873.0-1274.4)	1095.0 (1014.4-1175.6)
Duration of estrogen use, y	...	9.7 (8.4-11.0)	1.6 (0.0-4.8)	8.9 (5.5-12.3)	20.4 (19.1-21.7)
Mean difference between age started estrogen and age at menopause, y	...	1.2 (0.3-2.1)	19.8 (17.9-21.7)	18.3 (15.8-20.8)	2.0 (1.04-3.0)
Current thiazide hormone use	23.0	23.5	24.7	34.6†	21.5
Current thyroid hormone use	16.2	20.4	13.2‡	18.5	26.9§
Bilateral oophorectomy	7.4	23.2	7.9	12.4	34.1¶
Current smokers	11.0	8.8	2.2	2.1	9.8
Exercise ≥3 times/wk	66.0	71.1	44.3#	87.8**	70.1
Alcohol use	72.7	70.9	80.5††	73.6	81.0‡‡

*Data are presented as means (95% confidence intervals) for the first 6 variables and percentages for the second 6 variables. Past early users are women who began taking estrogen before age 60 years, but no longer use estrogen; past late users are women who began taking estrogen at or after age 60 years, but no longer use estrogen; current late users are current estrogen users who began taking it at or after age 60 years; current continuous users are current estrogen users who began taking estrogen before age 60 years.

†Compared with never users, $P=.04$.

‡Compared with current continuous users, $P=.02$.

§Compared with never users, $P=.001$.

||Compared with never users, $P<.001$; compared with past late users, $P=.02$.

¶Compared with all 4 other groups, $P=.001$.

#Compared with all 4 other groups, $P=.002$.

**Compared with never users, $P=.03$.

††Compared with past early users, $P=.05$.

‡‡Compared with past early users, $P=.04$.

nardo) in Southern California participated in the study. They completed a standardized questionnaire that included health habits and medical history, dietary supplements, and medications. The names of medications, doses, and routes of administration were obtained by a nurse and validated by an examination of pills and prescriptions that were brought to the clinic. Information on age at initiation of medications and on total years of use was also collected. Alcohol use was categorized as drinking 3 or more days per week; those who reported engaging in exercise 3 or more times per week were considered regular exercisers. Height and weight were measured with women in light clothing without shoes; body mass index (BMI), a measure of obesity, was calculated as weight in kilograms divided by the square of height in meters. Calcium intake was estimated from a semiquantitative diet assessment questionnaire.¹² Total calcium intake was calculated as dietary calcium plus calcium from nutritional supplements.

Bone mineral density (BMD) (grams per square centimeter) was measured at the ultradistal radius and at the mid-shaft radius by single-photon absorptiometry (SPA) (Lunar model SP2B, Madison, Wis) and at the hip and spine using dual-energy x-ray absorptiometry (DEXA) (Hologic QDR-1000, Waltham, Mass). Axial scans were standardized daily against a phantom. The manufacturers' precision errors were 3% for SPA and 1% to 1.5% for DEXA.

Age adjustment was calculated by the direct method using the total female age distribution of the Rancho Bernardo cohort. Differences in proportions were calculated using the Mantel-Haenszel statistic with a 2-tailed test of significance. P values were used to determine significant differences in proportion due to small sample size within the groups. Analysis of covariance was performed using a multiple linear regression model that included all the covariates. The multivariate model included continuous variables of age, BMI, total calcium intake, and categorical variables of bilateral oophorectomy, current smoking, alcohol use, exercise, and current use of thiazide diuretics, thyroid hormone, and oral corticosteroids. The estrogen use groups were determined a priori with estrogen use classified as never, past, or current and stratified by initiation before and after age 60 years. Because multiple comparisons were planned, orthogonal contrasts were used in the SAS General Linearized Model (GLM) procedure, which yields exact comparisons, reducing the possibility of a type I error.¹³ Statistical significance of differences in BMD levels was determined using 95% confidence intervals (CIs). All analyses were performed using SAS software (SAS Institute, Inc, Cary, NC).

A total of 740 women were available for analyses after excluding women for the following reasons: nonoral estrogen use ($n=21$); oral estrogen use on an as-needed basis ($n=2$), or to treat osteoporosis ($n=105$); use of other sex hor-

mones (diethylstilbesterol, progesterone alone, testosterone, or tamoxifen) ($n=25$); or missing data for estrogen use ($n=16$). Because equivalent bone responses are obtained from daily administration of 0.625 mg of conjugated estrogens, 1.25 mg of estropipate, 1.0 mg of estradiol, or 0.02 mg of estinyl estradiol,¹⁴ estrogen preparations were converted to equivalent conjugated estrogen dosages for analysis.

RESULTS

Of the 740 women who met the inclusion criteria, 69% had used postmenopausal oral estrogen, including 30% who were current users and 39% who were past users. Estrogen use was classified as never, past, or current and stratified by initiation before or after age 60 years. Age 60 years was chosen a priori to reflect the once common recommendation to take estrogen at or soon after menopause for about 10 years. Five patterns of estrogen use were identified: (1) never users, (2) past early users (started before age 60 years with no current use), (3) past late users (started at age 60 years or older with no current use), (4) current late users (started at age 60 years or older with current use), and (5) current continuous users (started before age 60 years with current use).

As shown in Table 1, current continuous users were younger at the time of the clinic visit and at menopause, had the highest mean total daily calcium intake, and were more likely to have had bilateral oophorectomy than women in

Table 2.—Age-Adjusted Mean Bone Mineral Density by Estrogen Use Status in Women, Rancho Bernardo, Calif, 1988-1991*

Measurement Site	Never Users (n=229)	Past Early Users (n=229)	Past Late Users (n=56)	Current Late Users (n=29)	Current Continuous Users (n=197)
Ultradistal radius	0.215 (0.207-0.223)	0.226 (0.218-0.234)	0.239 (0.219-0.259)	0.243 (0.213-0.273)	0.257 (0.247-0.267)
Midshaft radius	0.564 (0.554-0.574)	0.575 (0.565-0.585)	0.599 (0.576-0.622)	0.615 (0.585-0.645)	0.633 (0.623-0.643)
Total hip	0.754 (0.734-0.774)	0.766 (0.746-0.786)	0.795 (0.765-0.825)	0.802 (0.762-0.842)	0.815 (0.795-0.835)
Lumbar spine	0.852 (0.832-0.872)	0.875 (0.855-0.895)	0.897 (0.857-0.937)	0.926 (0.866-0.986)	0.969 (0.949-0.989)

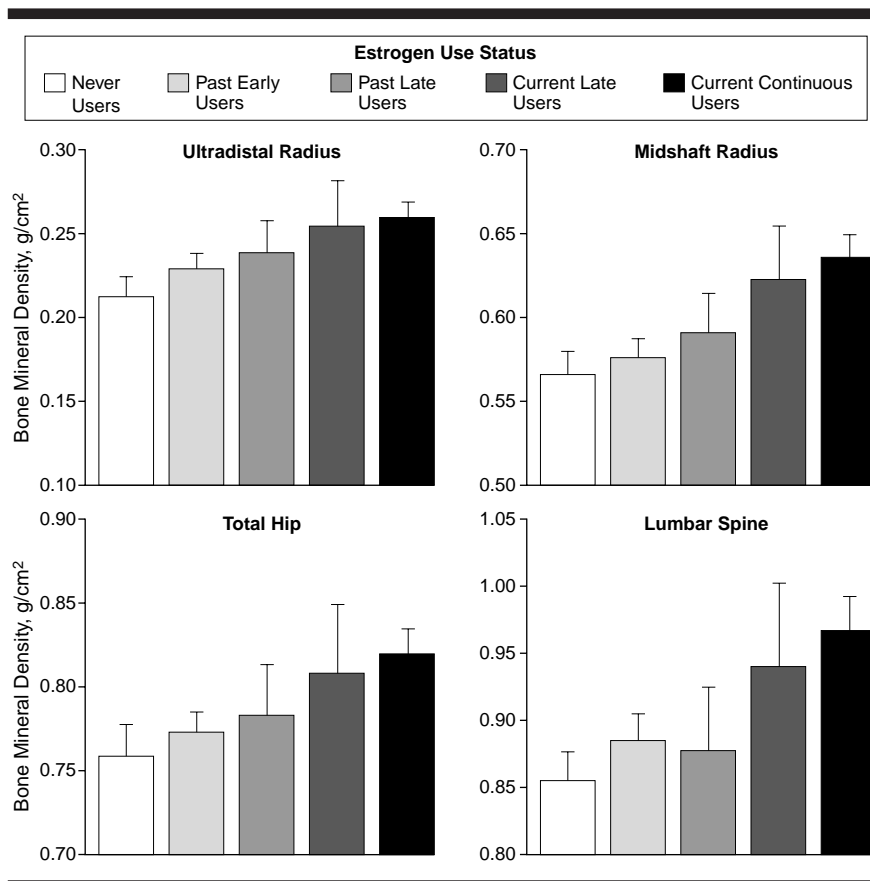
*Mean bone mineral density is presented in g/cm² (95% confidence interval). For an explanation of estrogen user groups, see the first footnote to Table 1.

the other 4 groups ($P < .01$). Current late users were more frequent users of thiazide diuretics, and current continuous users were more likely to use thyroid hormone.

The longest duration of estrogen use was in current continuous users who had used estrogen for an average of 20 years. On average, they began estrogen 2 years after menopause. Among women who started estrogen after age 60 years, current users started an average of 18 years after menopause for an average of 9 years of use, while those with no current use averaged 2 years of use and started 20 years after menopause. The mean time since discontinuing estrogen was 17.2 years for past early users and 8.2 years for past late users.

The estrogen dose and frequency for current continuous users was 0.63 mg (95% CI, 0.59-0.67 mg) for 24.7 days per month (95% CI, 23.9-25.5 days). For current late users, it was 0.48 mg (95% CI, 0.40-0.56 mg) for 23.6 days per month (95% CI, 21.5-25.7 days). Of the current estrogen users, 87% were taking conjugated equine estrogen (Premarin, Wyeth-Ayerst Laboratories, Philadelphia, Pa). In addition, 7.5% used estropipate (Ogen, Abbott Laboratories, North Chicago, Ill); 3.5%, estradiol (Estrace, Mead Johnson Laboratories, Evansville, Ind); and 1.4%, ethinyl estradiol (Estinyl, Schering, Kenilworth, NJ). Only one third of the current users were taking estrogen with progesterone.

Age-adjusted BMD levels by use group are shown in Table 2. Differences in mean BMD by user groups were similar after controlling for age, BMI, total calcium intake, bilateral oophorectomy, current smoking, alcohol use, exercise, current use of thiazide diuretics, thyroid hormone, and oral corticosteroids. The multiply adjusted data are shown in the Figure. Current users of estrogen had the highest BMD levels at all 4 sites, independent of the duration of use. Among current users, there was no statistically significant difference in BMD between those who started estrogen at menopause and those who started after age 60 years. The average current age of those who started estrogen after age 60 years was 78.6 years



Mean bone mineral density (gm/cm²) (95% confidence interval) by estrogen use groups adjusted for age, body mass index, total calcium intake, bilateral oophorectomy, current smoking, alcohol use, exercise, and current use of thiazide diuretics, thyroid hormone, and oral corticosteroids.

and their average age at initiation was 68.8 years. Only 45 women started estrogen after age 65 years, of whom 18 were current users. Their mean BMD levels were similar to those starting after age 60 years and were significantly higher than never users (ultradistal radius, $P = .01$; midshaft radius, $P = .02$; hip, $P = .003$; and lumbar spine, $P = .04$). Only 35 women started estrogen after age 70 years, too few for meaningful analysis.

Among past estrogen users, women who started estrogen after age 60 years had higher mean BMD levels than those who started earlier, although the years of use were fewer (2 vs 10 years). Of the 56 women who began estrogen after age 60 years, but were not current users, 21 started in their seventh decade, 28 in their eighth decade, and 9 in their ninth

decade. Past early users and current late users had a similar duration of use (10 vs 9 years); however, current late users had higher mean BMD levels at all sites.

Compared with never users, current continuous users had 20% higher mean BMD at the ultradistal radius, 12% higher mean BMD at the midshaft radius, 8% higher mean BMD at the hip, and 13% higher mean BMD at the lumbar spine. Current late users had similar higher percentages of BMD compared with never users: 19% at the ultradistal radius, 10% at the midshaft radius, 7% at the hip, and 10% at the lumbar spine. In contrast, past users had 8% to 11% higher mean BMD at the ultradistal radius and 2% to 4% higher mean BMD at the other sites compared with never users.

COMMENT

In the Rancho Bernardo study, after the exclusion of women treated for osteoporosis, more than two thirds of the older women had used oral estrogen, and nearly one third were current users. Women who started estrogen during the menopause transition and continued to the present—an average of 20 years—had the best BMD levels at all 4 sites examined. Current users who had started after age 60 years, for an average of only 9 years' use, had surprisingly similar BMD levels. Women in their 70s who had started estrogen within 2 years of menopause but stopped it after an average of 10 years had only slightly better bone density than never users. Differences by user category were not explained by age, BMI, total calcium intake, bilateral oophorectomy, current smoking, alcohol use, exercise, or current use of thiazide diuretics, thyroid hormone, or oral corticosteroids.

As expected, current continuous estrogen users had the highest BMD levels. This has been observed in other studies^{15,16} and forms the rationale for current clinical recommendations to begin estrogen at menopause and continue into late life. The nearly equivalent results in current late users are concordant with short-term studies¹⁷⁻²⁵ of estrogen therapy in women aged 60 years and older. To our knowledge, this is the first study to show similar BMD levels at 4 skeletal sites in current early onset vs current late onset of estrogen use. Maximum increases in BMD are thought to occur during the first few years of estrogen treatment, then show a trend toward stabilization or slow decline.²⁶⁻²⁸ The bone mass benefit in older women is probably due to the same mechanism observed in younger women with reduction of bone resorption proportional to the available estrogen-dependent bone fraction.

The Rancho Bernardo results are concordant with those predicted by Ettinger and Grady.²⁹ They assumed that women starting estrogen at age 65 years with 10 years of use gained 5% to 10% of bone mass, and they predicted the difference in BMD at age 85 years between those who used estrogen continuously since menopause and those who started at age 65 years was only 2% to 6% with similar reduction in fracture risk. Our results are discordant with a report by Cauley and colleagues,¹⁶ who found a greater reduction in fracture risk in women who started estrogen within 2 years of menopause compared with women who started estrogen more than 5 years after menopause. These differences could be due to other nonbone

benefits of estrogen or characteristics of women who are prescribed and continue estrogen.

In the Rancho Bernardo cohort, past users had low BMD levels similar to never users even when estrogen was taken for the same duration as current users. In past users, the more recent the estrogen use, the higher the BMD, independent of age. This was an unexpected finding because many of the past late users took estrogen for less than 2 years. Although we adjusted for multiple covariates, differences in lifestyle cannot be entirely excluded, although there was only a small number of women in this group.

The results of past early users are compatible with other studies suggesting that estrogen therapy taken only at the time of menopause preserves bone during use, but it may not preserve bone density late in life^{10,30,31} or protect against osteoporotic fractures.^{15-16,30,32,33} For example, Erdtsieck and associates³⁴ reported rapid loss of BMD 1 year following cessation of estrogen treatment. Felson and colleagues¹⁰ found preservation of bone density in women younger than 75 years who had taken estrogen for 7 years or more, but little residual effect on bone density in 24 elderly women aged 75 years and older, 3 of whom were current users. In another population-based study, Nguyen and colleagues³⁰ found total duration of exposure to estrogen (years of menstruation plus postmenopausal estrogen use) was associated with higher BMD and a reduced incidence of atraumatic fractures. Cauley and associates¹⁶ reported the risk for wrist fractures was reduced by 61% among current users compared with 19% among previous users of estrogen. These observations all suggest that estrogen therapy should be continued indefinitely.

In the present study, the average daily dose of estrogen among current users was significantly lower in women starting after age 60 years (0.48 mg of conjugated equine estrogen) than in continuous users (0.63 mg). A dose of 0.625 mg of conjugated equine estrogen is the dose usually recommended to prevent bone loss, based on studies by Lindsay and associates³⁵ in early postmenopausal women. However, the average dose was close to the 0.45 mg of conjugated equine estrogen that they estimated would significantly retard bone loss. Ettinger and associates³⁶ also reported low-dose conjugated estrogen (0.3 mg) combined with 1500 mg of total daily calcium provided the same level of bone protection as 0.625 mg of conjugated estrogen. In this cohort, 36% of the women had daily calcium intakes of 1000 mg or greater, and

the mean daily intake was high in both current user groups.

Because this is a cross-sectional study, causality cannot be assumed. We excluded women taking estrogen therapy for osteoporosis, which could have excluded women with very low BMD levels. Women indicated a variety of other reasons for late initiation of estrogen therapy including physician advice for prevention of heart disease or well-being. The duration of use was not validated, but responses were consistent with current use as reported and validated at 2 earlier clinic visits (1973-1975 and 1984-1987). The bioequivalence of the estrogen preparations used has not been tested in concurrent clinical trials, but meets the standard for osteoporosis therapy as outlined by Ettinger.¹⁴ Differences in hormone regimens do not explain these observations; 87% of current early-onset or late-onset users were taking conjugated equine estrogens, and progesterone use was similar in both groups. Bone density was not measured at the onset of estrogen therapy, so we cannot exclude the possibility that late-onset current users had better BMD levels before estrogen therapy. Residual confounding effects could be present in the multivariate model.

Despite these limitations, these data provide some of the strongest evidence to date that estrogen therapy should be continued into late life for the maintenance of high bone density. Past estrogen use provides little or no long-term benefit for the preservation of bone density because accelerated bone loss occurs after discontinuation of estrogen,^{9,27,28,31} rather like the accelerated bone loss at menopause. In addition, estrogen begun after age 60 years appears to offer remarkably similar bone density benefit to estrogen begun in early menopause or after oophorectomy, reflecting the skeletal impact of late estrogen use, with increases over 2 or more years followed by reduced rates of loss in the subsequent years. If late continuous use is equivalent to early-onset continuous use, estrogen therapy could be initiated at older ages when most osteoporotic fractures occur, reducing the cost and possible risks of long-term estrogen therapy. Further studies of late-onset hormone therapy are indicated.

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