Bone Mass Response to Discontinuation of Long-term Hormone Replacement Therapy

Results From the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study

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Background: Accelerated bone loss after stopping hormone therapy (HRT) is postulated to explain the lack of hip-fracture protection conferred by former HRT use. The abbreviation HRT (traditionally standing for “hormone replacement therapy”) is used herein because of its wide recognition in the field. However, the pharmacological doses of estrogens and progestins used are not truly “replacement” in nature.

Objectives: To determine whether women lose bone mineral density (BMD) after stopping HRT; to assess whether their rate of loss is significantly greater than that of women not undergoing HRT, and to determine whether long-term HRT is associated with continued gains in BMD.

Methods: A total of 495 women who were adherent to assigned treatment in the 3-year Postmenopausal Estrogen/Progestin Interventions randomized controlled trial (PEPI-RCT) and who had an additional BMD measurement during the PEPI Safety Follow-up Study were observed for an average of 3 years during and 4 years after the PEPI-RCT.

Results: Women who stopped HRT after 1 year during the PEPI-RCT had annual rates of BMD change of −0.54% (hip) and −0.81% (spine) during the following 2 years. Those who underwent HRT for 3 years during the PEPI-RCT and then discontinued it had annual changes of −1.01% (hip) and −1.04% (spine). Rates of BMD loss among women who stopped HRT during or after the PEPI-RCT did not differ significantly from those of women who did not undergo HRT, who lost bone at a rate of approximately 1% yearly during the first year of the PEPI-RCT and about half that rate afterward. Women who continued HRT after the PEPI-RCT did not show additional BMD gains.

Conclusions: Our results do not support the hypothesis that bone is lost at an unusually fast rate after discontinuation of HRT, nor do they suggest that long-term HRT leads to additional BMD gain beyond that evident after 3 years.

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POSTMENOPAUSAL hormone therapy (HRT) is a complex intervention that may have substantial long-term benefits such as primary prevention of heart disease, osteoporosis, and several other chronic diseases.1 The abbreviation HRT (traditionally standing for “hormone replacement therapy”) is used herein because of its wide recognition in the field. However, the pharmacological doses of estrogens and progestins used are not truly “replacement” in nature. However, this pharmacological treatment is not risk free. One of the most feared potential complications of long-term HRT is breast cancer.2 Although studies of breast cancer risk related to postmenopausal hormone use have had mixed outcomes,3 some have shown that cancer risk increases with longer duration of estrogen use.4,5

The concern about cumulative risk as a function of long-term HRT has fueled efforts to maximize potential benefits and minimize possible risks of this therapy. One optimization strategy would be to limit the duration of HRT; but this raises the question of when during the postmenopause period HRT should be provided. If, for example, we wanted to confine HRT use to 10 years, should we recommend that women undergo it early after menopause but then stop, or would it be advisable to defer HRT until later in the postmenopause period? Evidence-based answers to these questions are limited and may be heterogeneous and organ specific. Understanding what happens to bone when women stop HRT would provide part of the answer to this complex problem.

Cohort studies6,7 report that former HRT use (for up to 10 years) confers no hip-fracture protection. Therefore, starting HRT early in the postmenopause period with subsequent discontinuation may not be the preferred strategy to prevent hip fracture. In
SUBJECTS AND METHODS

THE PEPI-RCT

The PEPI-RCT was a randomized, double-masked, placebo-controlled, clinical trial designed to compare the effects of estrogen, alone or in combination with 1 of 3 progestin regimens, on heart disease risk factors. By protocol requisites, participants were between 45 and 64 years old and were between 1 and 10 years postmenopause. The 4 active PEPI-RCT treatment regimens were as follows (each included the identical 0.625-mg daily dose of conjugated oral equine estrogen): (1) unopposed oral conjugated equine estrogen; (2) conjugated equine estrogen plus 2.5 mg daily of medroxyprogesterone acetate; (3) conjugated equine estrogen plus 10 mg of cyclical medroxyprogesterone acetate taken on days 1 through 12 each month; and (4) conjugated equine estrogen plus 200 mg of cyclical micronized progesterone taken on days 1 through 12 each month. Between December 1989 and February 1991, 7 academic medical centers enrolled 875 women from the following regions: Baltimore, Md; Iowa City, Iowa; Los Angeles, Calif; Palo Alto, Calif; San Antonio, Tex; San Diego, Calif; and Washington, DC. The PEPI-RCT was 3 years in duration; the PEPI-RCT bone measurements were taken at baseline, 12 months, and 36 months.

THE PSFS

All PEPI-RCT participants were invited to return for the PSFS. This was an observational study that monitored potential toxicity end points related to long-term postmenopausal hormone use (ie, mammograms and endometrial histologic analyses). During the PSFS, women were no longer assigned to randomized treatments. Rather, if they were taking postmenopausal hormones, these were privately prescribed. At the termination of the PSFS, a BMD evaluation of the lumbar spine and hip was offered to all participants. The PSFS BMD was measured between 3 and 5 years after the participants had completed the PEPI-RCT.

ELIGIBILITY FOR THE PSFS BONE ANALYSIS

Participants in the present study attended the PSFS BMD visit, completed the PSFS assessment of hormone therapy use, and were adherent to their assigned (active or placebo) treatment during each of the intervals of the PEPI-RCT (baseline to 12 months and 12 months to 36 months). The latter restriction was applied because the present study is concerned with the effects of long-term HRT on BMD and with patterns of BMD loss after HRT discontinuation.

THE STUDY SAMPLE

The final PEPI-RCT visit was attended by 847 women (97% of the original 875 PEPI-RCT participants). Among these, treatment adherence to unopposed conjugated equine estrogen therapy was relatively lower (63%) in women with a uterus than in those without; this was due to protocol-mandated cessation of study drug treatment when a woman developed endometrial hyperplasia. For the other active and placebo treatments, adherence ranged from 79% to 84% and did not vary significantly by assignment. Because our group previously found no differences in spine or hip BMD outcomes among active treatments, and for power considerations, we combined all active treatments into a single analysis group for the present study. Of the 560 women who came to the PSFS BMD visit, 495 women met the criteria for this analysis, representing 57% of the original PEPI-RCT sample and 58% of those who attended the final PEPI-RCT visit. Characteristics of participants in the present analysis and those of women included in the PEPI-RCT but who did not qualify for the present study are given in Table 1.

ASSESSMENT AND CODING OF ESTROGEN AND PROGESTIN USE

The PEPI-RCT protocol defined adherence to assigned treatment as having taken at least 80% of the expected medication, assessed by pill count, during the interval since the last scheduled BMD measurement (ie, baseline to 12 months and 12 to 36 months). After the PEPI-RCT, treatment was not randomized; women were classified as postmenopausal hormone users (yes/no) according to self-report at the time of their PSFS BMD visit. If at the PSFS BMD visit a woman reported that she had discontinued taking hormones since the PEPI-RCT, we did not assess the exact time at which she had stopped taking

contrast, numerous studies show that postmenopausal hormone use prevents loss of bone mineral density (BMD) or increases it slightly. Why then do patients who discontinue HRT (especially after long-term treatment) not accrue sustained antifracture benefit as a result of former hormone use prevents loss of bone mineral density (BMD) or increases it slightly. Why then do patients who discontinue HRT (especially after long-term treatment) not accrue sustained antifracture benefit as a result of former hormone use? An accelerated rate of bone loss after stopping HRT is a postulated explanation for the lack of hip-fracture risk reduction in former hormone users. However, few studies directly assess the pattern of BMD loss after stopping HRT.

Much remains to be learned about the skeletal effects of long-term HRT. Estrogen’s antiresorptive action on bone is well established, but unresolved is whether estrogen causes additional gain in bone mass after the bone remodeling transient has been closed (transient is the time during which bone changes from a higher to a lower turnover state causing gain in bone mass). Because the length of the bone remodeling transient is dependent on the bone turnover state, it is difficult to know how long BMD must be observed to infer that such additional gains have occurred. However, follow-up beyond 3 years is likely to be beyond the range of the remodeling transient.

The Postmenopausal Estrogen/Progestin Interventions randomized controlled trial (PEPI-RCT) was a 3-year randomized, placebo-controlled, clinical trial of 4 active HRT regimens; one of its major outcome measures was BMD. The PEPI Safety Follow-up Study (PSFS) monitored safety end points after the completion of the trial. As part of the PSFS, participants had BMD testing an average of 4 years after the PEPI-RCT was completed. We used data from the PEPI-RCT and the PSFS
them. These women were coded as having stopped HRT at the end of the PEPI-RCT. The PEPI-RCT debriefing interviews indicated that most women who stopped taking hormones did so very soon after the trial ended.

We grouped participants into 5 categories of hormone use over the course of the PEPI-RCT and the PSFS: (1) continuous hormone users; (2) those who stopped taking hormones after 1 year; (3) those who stopped taking hormones after 3 years; (4) those who started taking hormones after the PEPI-RCT; and (5) those who had not used hormones. The numbers of women with each hormone use pattern are depicted in Figure 1.

BONE DENSITY MEASUREMENTS

The PEPI-RCT BMD protocol has been described in detail. Briefly, dual-energy x-ray absorptiometry scans of the lumbar spine (L2-L4), total hip, and hip subregions were done at baseline, 12 months, and 36 months using Hologic 1000 QDR instruments (Hologic Inc, Waltham, Mass). Under the BMD quality control program, a daily Hologic spine phantom scan was taken. To identify morphologic abnormalities and ensure that all BMD values were within 1% of the standard, the quality control center reviewed all participant BMD scans. Daily phantom scans were also reviewed. All unacceptable scans were reanalyzed. Replicate measures, with repositioning, were performed on each participant at each visit. At the PSFS BMD visit, the same BMD instruments and quality control methods were used as in the RCT, but the quality control center had moved from the Mayo Clinic, Rochester, Minn (Heinz W. Wahner, MD) to Stanford University, Stanford, Calif (R.M.), for the PSFS. For the present analyses, only spine and total hip BMDs were considered.

ASSESSMENT AND CODING OF COVARIATES

Age (years), current smoking status (yes/no), self-reported alcohol intake ($\geq$1 drink per day, yes/no), and intensity-based physical activity level were based on self-report. The composite index of physical activity was constructed by averaging the ordered responses to activity across 3 domains of home, work, and leisure activity, where 1 indicated light activity; 2, moderate; and 3, heavy. Participants were classified as relatively slightly active (average response $<2$), moderately active (average response 2-0.29), and highly active (average response $\geq$3). These covariates were analyzed in a time-varying manner; ie, the values of age, smoking, and physical activity at each of the BMD measures were used in the analysis.

The following variables were assessed only during the PEPI-RCT, so their value at the 36-month PEPI-RCT visit was used: body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters); education (no college, at least some college, and postcollege); employment (employed outside the home, homemaker, or other [retired, unemployed, student, or disabled]); and ethnicity (black, Hispanic, and other [almost exclusively white]). Total daily calcium intake was based on a modified version of the food frequency questionnaire developed by Block et al from which total calcium from diet and supplements was calculated.

STATISTICAL ANALYSES

The outcome measure for this study was BMD at the lumbar spine and total hip, and the major exposure variable was postmenopausal hormone use. Separate hierarchical linear models were fitted to the longitudinal spine and hip BMD measures using maximum likelihood methods in which current HRT status was included as a time-varying covariate. Post–PEPI-RCT hormone use was more common in younger women, whites, those with higher educational backgrounds, and those who adhered to active treatment during the RCT. Therefore, multivariable models included age, ethnicity, and education as covariates. Because the PEPI-RCT restricted chronological age and number of years since menopause, collinearity was created between these 2 variables. Therefore, controlling for age also adjusted for time from menopause. As BMI, physical activity level, smoking, alcohol use, and calcium intake might be related to HRT use and to BMD, multivariable models also included these covariates. Profiles of mean BMD values over time were computed from these models, and estimates were obtained for levels of BMD and changes in levels of BMD for women maintaining, initiating, and ceasing hormone use according to different accumulated exposures to hormones.

RESULTS

Most relevant demographic, anthropometric, and behavioral characteristics were similar in PEPI-RCT participants who were included in and excluded from the PSFS bone analysis (Table 1). Average BMI was 1 kg/m$^2$ lower in PSFS bone study subjects than in those not included in the present analysis. Table 1 also illustrates that the distributions of PEPI-RCT treatment assignments differed between those included and those not included in the PSFS bone analysis. Mean baseline values of lumbar spine and total hip BMD in present study participants were similar to those in the women who were excluded (Table 1). The BMD values measured at 36 months were also similar in these groups (data not shown).

Figure 1 illustrates participants’ hormone use during the PEPI-RCT and the PSFS. Continuous users of postmenopausal hormones for the duration of the PEPI-RCT and the PSFS follow-up period numbered 247; 35 women stopped active treatment after 12 months in the PEPI-RCT and persisted in nonuse of hormones during the PSFS. A group of 87 women ceased HRT when the PEPI-RCT ended, while 68 women only started using hormones at the end of the PEPI-RCT. Finally, 38 women who were adherent to placebo during the PEPI-
On average, during the first year of the PEPI-RCT, women adherent to HRT had statistically significant annual BMD gains (95% confidence intervals) of 1.41% (1.23%-1.59%) and 3.48% (3.28%-3.68%) at the hip and spine, respectively (Table 2). Between 12 and 36 months, continued adherence to active therapy led to further statistically significant mean increases in BMD: 0.41% (0.21%-0.61%) per year (hip) and 0.82% (0.62%-1.02%) per year (spine). Persistent HRT use between the PEPI-RCT and the PSFS did not produce additional BMD increment at the hip. By contrast, in continuous hormone users, a small but statistically significant increase in spinal BMD was evident between the end of the PEPI-RCT and the PSFS BMD measurement (0.32% per year). Rates of bone loss after HRT discontinuation can be approximated by examining the annual percentage of BMD lost among women who stopped HRT after 1 or 3 years of use (Table 2). Women who stopped HRT after the first 12 months of the PEPI-RCT experienced statistically significant changes of −0.54% (−1.03% to −0.05%) per year at the hip and −0.81% (−1.32% to −0.30%) per year at the spine between the 12- and 36-month BMD tests. The 35 women who remained nonusers of hormones after the PEPI-RCT ended did not manifest further bone loss, with statistically nonsignificant average annual changes of −0.49% (−1.10% to 0.12%) (hip) and −0.47% (−1.14% to 0.20%) (spine) per year. Women who stopped HRT after the PEPI-RCT had significant BMD loss; average rates were −1.01% (−1.40% to −0.62%) (hip) and −1.04% (−1.45% to −0.63%) (spine) per year.

During the first 12 months of the PEPI-RCT, women who did not undergo HRT had statistically significant declines in BMD: −1.02% (−1.35% to −0.69%) at the hip and −1.04% (−1.39 to −0.69%) at the spine. In these women, bone loss continued at roughly half this rate during the second 2 years of the RCT (Table 2). After the trial ended, we did not detect statistically significant bone loss in those who did not undergo HRT.

Figure 2 illustrates the BMD effects of initiating, continuing, or stopping HRT during the 7 years of RCT and PSFS observation. Continuous hormone users gained a small amount of spinal BMD but did not experience further hip BMD increases after the PEPI-RCT. Rates of decline in spine and hip BMD were similar in those who stopped HRT after 12 months (stopping during the PEPI-RCT) or 36 months (stopping after the PEPI-RCT). Finally, rates of BMD loss at the spine and hip in women not undergoing HRT during the first 3 years of the PEPI-RCT were of similar magnitude to rates of loss evident in women who stopped HRT during or after the PEPI-RCT.

Models of BMD change over time as a function of HRT patterns were adjusted for age, education, employment, ethnicity, BMI, calcium intake, current smoking, alcohol intake, and physical activity (Table 3). Only 1
difference was apparent compared with unadjusted results; continued hormone use after the PEPI-RCT did not produce further increases in spine BMD measured between PEPI-RCT year 3 and PSFS BMD visits.

Self-reported fractures were ascertained at the PSFS bone visit, but the small number of fractures (n=69) was too low to provide adequate statistical power to assess differences among categories of women undergoing HRT during and after the PEPI-RCT (data not shown).

**COMMENT**

This study addresses 2 long-standing, unresolved questions: (1) What are the BMD effects of stopping HRT? and (2) Do long-term users of estrogen continue to gain bone? Our results indicate that women who stopped HRT lost bone, but that their rate of loss was not appreciably different from those women who did not undergo HRT. Our data do not support the existence of further BMD gains (beyond those seen at 3 years) among women who continued HRT for approximately 4 additional years after the PEPI-RCT, for a cumulative average exposure of slightly longer than 7 years.

In a large, comprehensive, cohort study, Cauley and colleagues found that former users of postmenopausal hormones were not protected from hip fracture—even if they had previously used hormones for 10 years or more. Values of BMD in current vs former users of HRT are concordant with these observed hip fracture results. Despite past long-term HRT, average axial and appendicular BMDs in women who quit HRT are similar to those of untreated women.

Why is there no apparent fracture reduction or BMD benefit related to long-term prior HRT? One possibility is that the reason for hormone discontinuation is associated with greater hip fracture risk or with a higher rate of bone loss. For example, if HRT were stopped after a stroke, it would be difficult to disentangle the negative skeletal consequences of hemiparesis and deconditioning from the effects of stopping HRT (an illustration of confounding). Although not formally controlling for comorbidity, studies that have examined the relation between estrogen cessation, fracture, and BMD were adjusted for physical activity, which is an imperfect but reasonable proxy for the presence of significantly limiting illness.

Accelerated (fast) bone loss after discontinuation of HRT is a second potential reason why former estrogen use does not prevent hip fracture or substantially preserve BMD. However, the accelerated loss would need

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**Table 2. Mean Unadjusted Annualized Percentage Changes in Bone Mineral Density (BMD) of the Hip and Spine by Time of BMD Measurement and Postmenopausal Hormone Replacement Therapy in Women Enrolled in PEPI-RCT and PSFS**

<table>
<thead>
<tr>
<th>HRT Status and BMD Measurement Site</th>
<th>Baseline to Year 1</th>
<th>Year 1 to Year 3</th>
<th>Year 3 to PSFS-BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Started to use HRT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>1.41 ± 0.09 (1.23 to 1.59)</td>
<td>...</td>
<td>0.10 ± 0.23 (−0.35 to 0.55)</td>
</tr>
<tr>
<td>Spine</td>
<td>3.48 ± 0.10 (3.28 to 3.68)</td>
<td>...</td>
<td>0.96 ± 0.24 (0.49 to 1.43)</td>
</tr>
<tr>
<td><strong>Continued to use HRT</strong></td>
<td>...</td>
<td>0.41 ± 0.10 (0.21 to 0.61)</td>
<td>...</td>
</tr>
<tr>
<td>Hip</td>
<td>...</td>
<td>0.82 ± 0.10 (0.62 to 1.02)</td>
<td>...</td>
</tr>
<tr>
<td>Spine</td>
<td>...</td>
<td>−0.54 ± 0.25 (−1.03 to −0.05)</td>
<td>...</td>
</tr>
<tr>
<td><strong>Terminated HRT</strong></td>
<td>...</td>
<td>−0.81 ± 0.26 (−1.32 to −0.30)</td>
<td>...</td>
</tr>
<tr>
<td>Hip</td>
<td>...</td>
<td>−0.49 ± 0.31 (−1.10 to 0.12)</td>
<td>...</td>
</tr>
<tr>
<td>Spine</td>
<td>...</td>
<td>−0.47 ± 0.34 (−1.14 to 0.20)</td>
<td>...</td>
</tr>
<tr>
<td><strong>Sustained HRT termination</strong></td>
<td>...</td>
<td>−1.02 ± 0.17 (−1.35 to −0.69)</td>
<td>...</td>
</tr>
<tr>
<td>Hip</td>
<td>−1.04 ± 0.18 (−1.39 to −0.69)</td>
<td>−0.44 ± 0.17 (−0.77 to −0.11)</td>
<td>−0.33 ± 0.25 (−0.82 to 0.16)</td>
</tr>
<tr>
<td>Spine</td>
<td>−1.04 ± 0.18 (−1.39 to −0.69)</td>
<td>−0.62 ± 0.18 (−0.99 to −0.27)</td>
<td>0.12 ± 0.26 (−0.39 to 0.63)</td>
</tr>
</tbody>
</table>

*PEPI-RCT indicates Postmenopausal Estrogen/Progestin Interventions randomized controlled trial; PSFS, PEPI Safety Follow-up Study; HRT, hormone therapy; and CI, confidence interval. HRT use includes equine estrogen use alone or in combination with one of 3 progestins during the RCT. In the PSFS, HRT could be any estrogen alone or combined with any progestin.
to be great enough (ie, faster than the rate of loss observed in a similar, nontreated, group of postmenopausal women) and/or persist long enough to bring the BMDs of those women formerly undergoing HRT down to the level of those who were untreated over similar periods of observation.

Our data and those of previously published reports do not support the hypothesis that cessation of HRT leads to a faster rate of bone loss than that observed in the appropriate reference group of untreated women. In the PEPI-RCT and the PSFS, the rates of spine and hip bone loss in women during the first 3 years of HRT discontinuation are statistically indistinguishable from the bone loss rates in untreated women. Similarly, after completion of a 2-year randomized study of HRT vs placebo, Christiansen and colleagues rerandomized participants to either continue or stop active treatment for another 12 months. Using forearm bone mineral content as the outcome, these investigators found that women who stopped HRT lost bone at a rate of roughly 2% per year, the same as that of the placebo group. These results were corroborated by a 6-year, open-label extension phase of a 2-year clinical trial performed with women who had experienced their final menses within the last 2 years (early menopause). The authors reported that the rate of forearm BMD loss among 28 women who had stopped HRT was similar to that of untreated women, about 2% yearly. In contrast, the work of Lindsay and colleagues is widely cited to support the concept of accelerated bone loss after HRT discontinuation. However, careful scrutiny of these results casts doubt on that interpretation; the conclusion rests on selecting the appropriate referent. Lindsay et al performed an observational study in 14 surgically menopausal women who elected to stop using HRT after 4 years and 14 women who had never used HRT after surgery. Follow-up was done 4 years after HRT cessation; the annualized rate of decline in metacarpal bone mineral content was 2.5% per year in those who stopped HRT. This rate was virtually identical to the 2.6% per year decline observed during the first 4 years of observation in the untreated group of surgically menopausal women. Of note, in the surgically menopausal women who did not take HRT, the rate of bone loss slowed substantially after the first 4 years—to about 0.5% per year.

To date, the PEPI-RCT remains the longest duration placebo-controlled clinical trial that measured BMD as a function of randomization to postmenopausal HRT. By intention-to-treat analysis, those assigned to active treatment experienced an approximate gain of 3% in spine BMD and 1.5% in total hip BMD at 1 year. During the next 24 months, compared with the 1-year values, small but statistically significant increases in spine BMD (1%) and hip BMD (0.6%) were detected. We repeated these analyses in the present study (the participants in our long-term follow-up were a subset of the entire trial sample). The additional statistically significant gains in spine and hip BMD between the 12- and 36-month measurements were replicated. If we assume that the bone remodeling transient is 1 year, then both the trial results and the findings of our present subset analysis argue for a small but measurable increase in BMD after the completion of the transient phase.

Do those who continue to take hormones for longer than 3 years gain more bone than is present at 3 years of treatment? In the PSFS observational study, no statistically significant bone gain (or loss) was observed at the spine or hip between the 3-year PEPI-RCT BMD and the 7-year PSFS BMD among women undergoing continuous HRT. This suggests that the BMD stabilized by 3 years. While cross-sectional analyses have reported higher BMD values among women undergoing long-term HRT, these studies cannot describe the trajectory of BMD change related to HRT. In one small study, serial measures of fore-

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### Table 3. Mean Adjusted Annualized Percentage Changes in Bone Mineral Density (BMD) of the Hip and Spine by Time of BMD Measurement and Postmenopausal Hormone Replacement Therapy in Women Enrolled in PEPI-RCT and PSFS*

<table>
<thead>
<tr>
<th>HRT Status and BMD Measurement Site</th>
<th>Mean ± SE % Change in BMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline to Year 1</td>
</tr>
<tr>
<td>Started to use HRT</td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>1.53 ± 0.10 (1.33 to 1.73)</td>
</tr>
<tr>
<td>Spine</td>
<td>3.66 ± 0.10 (3.46 to 3.86)</td>
</tr>
<tr>
<td>Continued to use HRT</td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>...</td>
</tr>
<tr>
<td>Spine</td>
<td>...</td>
</tr>
<tr>
<td>Terminated HRT</td>
<td></td>
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<tr>
<td>Hip</td>
<td>...</td>
</tr>
<tr>
<td>Spine</td>
<td>...</td>
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<tr>
<td>Sustained HRT termination</td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>...</td>
</tr>
<tr>
<td>Spine</td>
<td>...</td>
</tr>
<tr>
<td>Never used HRT</td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>-0.86 ± 0.18 (-1.21 to -0.51)</td>
</tr>
<tr>
<td>Spine</td>
<td>-0.81 ± 0.19 (-1.18 to -0.44)</td>
</tr>
</tbody>
</table>

*PEPI-RCT indicates Postmenopausal Estrogen/Progestin Interventions randomized controlled trial; PSFS, PEPI Safety Follow-up Study; HRT, hormone therapy; and CI, confidence interval. Models were adjusted for age, education, employment, ethnicity, body mass index, calcium intake, current smoking, alcohol intake, and physical activity. HRT use includes conjugated equine estrogen use alone or in combination with 1 of 3 progestins during the RCT. In the PSFS, HRT could be any estrogen alone or combined with any progestin.
arm BMD taken over 4 years remained unchanged compared with baseline in 18 naturally menopausal women treated with daily 17β estradiol and norethisterone acetate.28

Our study must be interpreted in the context of its limitations. Importantly, after the trial was over, hormone treatment choices were not random: younger age, more education, and white race were positively associated with posttrial HRT continuation.29 Our models were therefore controlled for these factors, as well as others (BMI, physical activity, smoking, alcohol use, and calcium intake) that might be associated with both HRT use and BMD. During the PEPI-RCT, most women who stopped unopposed estrogen treatment did so because of the development of cystic or adenomatous endometrial hyperplasia; stopping was required by protocol.17,18 If there were a biological linkage between developing endometrial hyperplasia and the response of bone to estrogen, then results in this endometrial hyperplasia subgroup would be biased. However, no difference was evident in the pattern of BMD decline among women who stopped HRT during the PEPI-RCT (principally due to hyperplasia) and those who stopped it after the trial. Our ascertainment of HRT use after the PEPI-RCT was by self-report rather than pill count (the method used during the trial). We did not ask the exact date of HRT cessation in women who underwent HRT during the PEPI-RCT but stopped treatment after the trial. Our models assumed that those participants stopped HRT immediately after the PEPI-RCT. If this assumption was not correct, then unmeasured HRT use in the “stopped after PEPI group” might be expected to yield a falsely low estimate of the rate of BMD loss. Of the original randomized sample, 57% were included in the PSFS bone study, raising the issue of comparability of this subgroup with the original study sample. The mean BMI of the present study sample was lower than that of the women who were not in the PSFS bone study. We adjusted for BMI; further, thinner women would be more likely to demonstrate higher rates of bone loss. Finally, the PSFS was not randomized. The ideal study design for evaluating long-term effects of continuous HRT and of discontinuation of HRT would be a protracted clinical trial with randomization to stopping or continuing HRT after a lengthy initial randomization period. This 2-phase RCT design is unlikely to be implemented because of ethical concerns and poor participant acceptance. Thus, despite its limitations, the PSFS affords reasonable data to approach these important research questions.

In summary, HRT for approximately 7 years did not provide further BMD benefit beyond that accrued at 3 years. Stopping HRT did not lead to an accelerated rate of BMD decline. The latter findings argue against accelerated bone loss as an explanation for the lack of hip fracture protection afforded by former HRT use. From a clinical perspective, our results suggest that women who stop HRT may resume bone loss, but that it will not be at a very rapid rate.

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