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Natural History of Bone Loss over 6 Years among Premenopausal and Early Postmenopausal Women

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The aims of this prospective cohort study were to determine rates of premenopausal and early postmenopausal bone loss, age at onset of bone loss, and whether rates of bone loss depend on baseline bone mineral density (BMD). The cohort of 614 women aged 24–44 years at baseline from the longitudinal Michigan Bone Health Study was followed for 6 years beginning in 1992–1993. Up to five BMD measurements of the lumbar spine (L_{2-4}) and the femoral neck were obtained through 1998–1999 by using dual x-ray absorptiometry and were standardized (as *z* scores) relative to a young adult, female BMD distribution. Regression models were used to estimate rates of BMD change and to examine BMD as a function of age. At the lumbar spine, the rate of BMD change for premenopausal women varied with time. At the femoral neck, the rate of change was –1.6% (95% confidence interval: –0.9%, –2.3%) of a *z* score annually (annual loss of 0.3% of baseline BMD (g/cm^2)). Evidence for age at onset of bone loss at the lumbar spine was inconclusive. Bone loss began by the midtwenties at the femoral neck. Additional annual change of –0.7% (95% confidence interval: –0.2%, –1.2%) of a *z* score was observed at the femoral neck for each unit increase in BMD *z* score at baseline. *Am J Epidemiol* 2002;156:410–17.

bone density; longitudinal studies; menstrual cycle; osteoporosis, postmenopausal; premenopause

Abbreviations: BMD, bone mineral density; BMI, body mass index; TCHS, Tecumseh Community Health Study.

Low bone mineral density (BMD) is a major risk factor for osteoporotic fracture. The prevalence of osteoporosis, or having a BMD that is 2.5 standard deviations below the mean of a young adult referent population, has been estimated on the basis of the Third National Health and Nutrition Examination Survey (1) to be 20 percent among United States women aged 50 years and older. As the population ages, low BMD will be a public health problem of increasing importance.

Low BMD can arise from an early onset of bone loss, a high rate of bone loss, or both. Most epidemiologic studies of bone loss have focused on postmenopausal women. Accumulating evidence suggests, however, that the onset of bone loss occurs prior to the last menstrual period (2). The natural history of bone loss and normal rates of bone loss in women approaching the menopausal transition are just beginning to be described.

Studies that have examined age-related changes in BMD among premenopausal women are conflicting. Some cross-sectional studies have reported no age differences in BMD at the lumbar spine (3, 4) or the femoral neck (3) among premenopausal women. Other studies have reported some differences in BMD by age at the lumbar spine (5) and the femoral neck (6–9). In some longitudinal studies, the rate of premenopausal bone loss has been estimated to occur at 0.7–1.3 percent per year at the lumbar spine (10, 11) and 0.3 percent per year at the femoral neck (12, 13). By contrast, the annual rate of perimenopausal bone loss has been reported to be more than 2 percent at the lumbar spine (14, 15) and 0.6 percent at the femoral neck (16). The annual rate of postmenopausal bone loss has been calculated to be 1.3–1.5 percent at the lumbar spine and 1.4 percent at the femoral neck (17).

Age at onset of bone loss is also not well described, and estimates have ranged widely. Earlier studies suggested that onset of trabecular bone loss occurred between ages 20 and 40 years (18). Recent cross-sectional data indicate that bone loss in both the femoral neck and the lumbar spine may begin

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TABLE 1. Response rates for the Michigan Bone Health Study, by year, for 660 eligible women, Tecumseh, Michigan, 1992–1998

Year	No. of age-eligible study participants	No. of ineligible participants (pregnant or deceased)	No. of nonparticipants	Response rate (%)
1992	580	19	61	88
1993	567	9	84	86
1994	540	12	108	82
1995	508	11	141	77
1998	487	9	164	74

as early as late adolescence (19) or as late as age 39 years in the femoral neck and age 49 years in the lumbar spine (20).

The importance of attaining greater peak bone mass prior to the age at onset of bone loss is receiving increasing public health attention because greater peak bone mass is considered to be a means of attenuating the effects of postmenopausal bone loss (21, 22). However, higher bone mass has been associated with greater rates of bone loss (23). Understanding the relation between peak bone mass, the rate of subsequent bone loss, and the time over which that loss is sustained will be crucial to evaluating the effect of the public health interventions aimed at increasing or sustaining peak bone mass.

We used data from a population-based, prospective cohort study to examine the 6-year natural history of bone loss in the lumbar spine and the femoral neck in women aged 30–50 years at the most recent measure. The analysis aimed to answer two questions: First, if premenopausal bone loss exists, what is the rate of loss and the age at onset? Second, are rates of bone loss greater in those who have greater BMD at baseline?

MATERIALS AND METHODS

Study population

The data used in this study were collected as part of the longitudinal Michigan Bone Health Study. The sampling frame consisted of women identified by family records from the Tecumseh Community Health Study (TCHS), a population-based, prospective cohort study established in 1959 to study risk factors associated with common chronic and infectious diseases. Eligible women were daughters of the original TCHS participants who were premenopausal and between ages 20 and 40 years in 1988. Of those contacted, 539 women (greater than 80 percent participation) were successfully recruited into the Michigan Bone Health Study by using letters or telephone calls and in-person visits. In 1992, the sampling frame was expanded to include women whose parents had not participated in the TCHS. Of the 135 female residents who were contacted by using a population-based sampling frame (Kohl's Directory) that included age, name, address, and telephone number, 121 (90 percent) were enrolled. The 1992 cohort was composed of 660 women aged 24–44 years.

Data were collected in 1992–1993, 1993–1994, 1994–1995, 1995–1996, and 1998–1999. There were 614 women (93 percent of the 1992 cohort) who had at least one BMD measurement. Reasons for and magnitude of nonparticipation included refusal (7–18 percent in any given year), having moved from the area (1–5 percent in any given year), health reasons (1–2 percent in any given year), and six deaths. Deferred participation occurred when women were pregnant (1–3 percent in any given year). Ninety-five percent of the study population had at least one follow-up visit, and 64 percent had BMD measurements at all five points in time. Response rates by year based on the entire cohort of 660 women are presented in table 1. Written informed consent was obtained from all participants, and approval for the conduct of the study was obtained from the University of Michigan Institutional Review Board.

Measurements

BMD. Bone mineral content (g) and bone width (cm) were measured by one of two certified technicians at the lumbar spine (L_{2-4}) and at the femoral neck with dual-energy x-ray absorptiometry (DPX-L analysis software version 1.3y, Lunar Corporation, Madison, Wisconsin), a safe, noninvasive method for determining the mineral content per linear area of bone. Coefficients of variation for the dual-energy x-ray absorptiometry measurements of the lumbar spine and femoral neck were less than 1.0 percent. Areal BMD (g/cm^2) was calculated by dividing bone mineral content by the square of bone width for both skeletal sites and then was standardized relative to Lunar Corporation's database of a normally distributed young adult (aged 20–45 years), female population to obtain z scores. The World Health Organization has defined osteoporosis in terms of similarly standardized BMD measurements in which women with standardized BMD measurements of –2.5 or below are classified as having osteoporosis.

Demographic, reproductive, and physical measurements. At each examination, participants completed questionnaires to describe or update their demographic characteristics and their menstrual and pregnancy histories. Age determination was based on self-reported date of birth. Height (cm) and weight (kg) were measured by using a stadiometer and a calibrated balance-beam scale, respectively, with participants wearing a single layer of light clothing without shoes. Body mass index (BMI) (kg/m^2) was calculated as weight (kg)/height (m^2) and was categorized as underweight, normal, overweight, obese, and severely obese, with 20, 25, 30, and

40, respectively, as cutpoints (24). The number of pregnancies was the sum of those pregnancies of at least 6 months duration. Estrogen use during the previous year was based on self-report and was confirmed by visual inspection of preparations.

Menopausal status. Menopausal status was defined based on each woman's self-report of the frequency of menstrual bleeds per year, self-report of gynecologic surgery, and treatment with chemotherapy. Medical records were reviewed for 70 percent of the surgical cases, and of these, confirmation of self-report occurred for 73 percent of single oophorectomies, 78 percent of hysterectomies, and 88 percent of double oophorectomies. Women were classified as premenopausal if they reported either 1) at least nine menstrual bleeds annually or 2) fewer than nine annual menstrual bleeds and pregnancy, breastfeeding, single oophorectomy, use of a hormonal preparation that suppresses bleeding, or use of fertility drugs with resumption of regular menses. Women who reported breastfeeding were categorized as premenopausal because they reported regular menstrual cycles in subsequent years, and evidence indicates that bone lost during breastfeeding is regained with the return of menses (25). Otherwise, women who reported fewer than nine menstrual bleeds per year were classified as having irregular menses. Women were considered postmenopausal if they reported the absence of a menstrual bleed in the previous 12 months, if they had undergone a double oophorectomy, or if they reported having undergone chemotherapy. Menopausal status was treated as a time-varying covariate in regression analyses.

Statistical analysis

Line graphs of BMD versus time were produced by using Splus (Mathsoft, version 3.4 release 1 Sun OS 5.3, Cambridge, Massachusetts) to examine patterns of bone loss for individual women and to establish whether the variance of BMD was changing over time. Excluding baseline BMD, the repeated BMD measurements among the individual women were modeled as a function of time by fitting linear mixed models using PROC MIXED (SAS Proprietary Software, Release 6.12, SAS Institute, Inc., Cary, North Carolina). These models incorporated a random intercept term to account for the correlation among repeated measures from individual women (26). Curvilinear relations of BMD with time were examined by including quadratic terms for time, and rates of BMD change for women with irregular menses and for postmenopausal women were estimated by incorporating irregular menses by time and postmenopausal by time interaction terms into the main effects models. For the lumbar spine, rates of BMD change were calculated by evaluating the first derivative of the model function by year. At the femoral neck, BMD was linear with respect to time, and the rate of BMD change for premenopausal women was estimated from the beta coefficient for time. The rates of BMD change for women with irregular menses and for postmenopausal women were given by the sum of the beta coefficient for time and the beta coefficient for the appropriate interaction term. Similarly, the effect of baseline BMD on the rate of BMD change was examined by incorporating into the models baseline BMD as a covariate as well as a baseline BMD by time interaction term. Results were adjusted for BMI.

The age at onset of bone loss at the lumbar spine was taken to be the mean age at the inflection point of the quadratic lumbar spine BMD function. For assessment of the age at onset of bone loss at the femoral neck, another mixed model was fit to describe the dependence of BMD as a linear function of age. For this model, age was centered at 24 years, the lowest age of any observation, allowing the intercept to be interpreted as the population average BMD at age 24. The beta coefficient for age was interpreted as the annual rate of BMD change beginning at age 24 years.

The impact of missing data in this longitudinal study was assessed by calculating the number of missing visits for each woman and using the chi-square test to determine whether being missing at any time was associated with age category, menopausal status at first observation, or baseline quartile of BMD. A greater proportion of those aged 24–29 years at baseline than of any other age group were missing at every data collection. This pattern probably reflects the number of pregnant women among this relatively small age subset. No differences in the proportion of missing data by menstrual cycling status or baseline BMD were detected. In addition, logistic regression was used to determine that the odds of being missing at any visit did not depend on either BMD or BMI measured at the previous visit. In addition, no appreciable differences in the regression coefficients were observed when the analysis was limited to the women with no missing data on BMD ($n = 395$).

RESULTS

A description of baseline characteristics of the study population is presented in table 2. The age range at baseline was 24–44 years, with more than two thirds of the women being at least 35 years of age. The majority of this population met current definitions of overweight or obese. Estrogen use was not prevalent at baseline.

A description of how the menopausal status of the cohort changed over the 6-year period of the study is presented in table 3. Three quarters of the study population remained premenopausal throughout the study. Among those women for whom menstrual cycles were changing or had changed, the menopausal transition was experienced with a variety of menstrual patterns. Irregular menses is experienced by some, but not all, women prior to natural or surgical menopause. Irregular menses can also be a transient event, after which regular menses resumes.

The estimates for the rates of bone change at the lumbar spine and femoral neck for women of different menopausal statuses were evaluated with the linear, mixed-model regressions shown in table 4. Figures 1 and 2 show fitted curves and lines with 95 percent confidence levels for the BMD z score of the lumbar spine and femoral neck, respectively, for pre- and postmenopausal women. Rate of BMD change at the lumbar spine varied over the study period as shown in table 5, while the rate of BMD change at the femoral neck was constant. When the upper confidence limit for this rate of change has a negative value or when the graphic represen-

TABLE 2. Baseline demographic and reproductive characteristics of the study population, Tecumseh, Michigan, 1992 (*n* = 614)

	No.	%
Baseline age (years)*		
24–29	57	9.3
30–34	138	22.5
35–39	212	34.5
40–44	207	33.7
Sum of pregnancies ≥6 months†		
0	103	18.0
1	73	12.7
2	216	37.7
3	132	23.0
≥4	49	8.6
Baseline BMI†,‡		
<20 (underweight)	36	6.2
20–24.9 (normal weight)	230	39.9
25–29.9 (overweight)	172	29.8
30–39.9 (obese)	117	20.3
>40 (severely obese)	22	3.8
Use of estrogens in previous year†		
Yes	38	6.6
No	539	93.4

* Baseline age calculated from date of birth data available on all 614 study participants.
† $n < 614$ due to incomplete participation in 1992.
‡ BMI, body mass index.

tation of the upper confidence limit for the BMD z score has a negative slope, there is good evidence for bone loss. The annual rate of bone change among premenopausal women ranged from –9.1 to 6.5 percent of a z score at the lumbar spine and was –1.6 percent of a z score at the femoral neck. Women with irregular menses experienced annual rates of BMD change ranging from –6.1 to 9.5 percent of a z score at the lumbar spine and an annual rate of change of –1.5 percent of a z score at the femoral neck. Postmenopausal women had annual rates of BMD change ranging from –13 to 2.6 percent of a z score at the lumbar spine and an annual rate of change of –4.2 percent of a z score at the femoral neck. No independent effect of baseline age was observed after the addition of menopausal status, indicating that there is no cross-sectional age-cohort effect, whereby women of a given age in 1992 had different BMD than did women who were that age in 1998. Plotting BMD versus time for individual women revealed only a few women who exhibited a high degree of bone loss over the 6-year follow-up. The interaction observed at the femoral neck between baseline BMD and time suggested that an additional annual BMD change of –0.7 percent of a z score occurred for each unit increase in BMD at baseline.

The mean age at baseline among premenopausal women in this cohort was 36 years, and the mean age of the population at onset of bone loss at the lumbar spine is estimated to be 38–39 years, based on the inflection point of the curvilinear function. Restriction of analysis to specific age groups, however, suggests that bone loss also exists among younger age groups. For estimation of the age at onset of bone loss at the femoral neck, another linear mixed model was fit with BMD regressed on age (centered at age 24 years). This analysis was limited to the premenopausal women who remained premenopausal throughout the observation period, and there was no evidence of nonlinearity at the femoral neck over the 26-year age range. A negative beta coefficient for the age term indicated statistically significant ($p = 0.002$) bone loss beginning as early as age 24 years (data not shown).

DISCUSSION

To our knowledge, this is the first report to estimate rates of premenopausal bone loss over a 6-year time period among women in a population-based setting by using repeated BMD measures and linear, mixed-model regressions. The women were between ages 24 and 44 years at baseline. This study found strong evidence of premenopausal bone loss. At the lumbar spine, the annual rate of premenopausal bone change varied between a maximum rate of bone accrual of 6.5 percent of a z score in 1992 and a maximum rate of bone loss of 9.1 percent of a z score in 1998. The annual rate of postmenopausal bone loss at the femoral neck was 1.6 percent of a z score. No additional effect of baseline age was observed. These rates of loss correspond to a maximum annual loss of 0.5 percent of baseline BMD at the lumbar spine and 0.3 percent of baseline BMD at the femoral neck. Our results are consistent with the longitudinal study by Prior et al. (27) that documented premenopausal bone loss at the lumbar spine over 5 years. Previously, Sowers et al. (12) observed premenopausal bone loss in the same population that was limited to the femoral neck. With the added power provided by an additional 3 years of follow-up and a larger analysis set, we were able to detect accelerating premenopausal bone loss at the lumbar spine consistent with previously reported results of Riggs et al. (11). In addition, Shaw et al. (28) calculated annual rates of change at the lumbar spine to be 0.2 percent among Taiwanese women aged 30–33 years and 0.6 percent among women aged 40–49 years after 5–6 years of follow-up. Baran et al. (29) calculated 1 percent per year vertebral bone loss over 3 years of follow-up among women who comprised the control arm of a dairy intervention trial. Melton et al. (30) found an annual rate of bone loss of 1.0 percent at the femoral neck over 16 years of follow-up and across a 64-year age range, with no variation in the rate of loss with age.

At least two studies have reported greater bone loss at the total femur after 1 year of follow-up in women with irregular menstrual cycles than in women with regular cycles (31, 32). In our study, however, women with irregular menses did not demonstrate increased rates of loss. The relatively small number of women with irregular menstrual cycles in our

TABLE 3. Menstrual cycle experience, by menopausal status at first observation, Tecumseh, Michigan, 1992–1998 (*n* = 614)

	No.	%
Premenopausal at first observation	556	90.6
Premenopausal at all times measured	459	74.8
Developed irregular cycles and then resumed regular cycles	13	2.1
Developed irregular cycles and remained	43	7.0
Developed irregular cycles and then became postmenopausal	12	2.0
Became postmenopausal directly	28	4.6
Irregular menses at first observation	20	3.3
Became regular	4	0.7
Remained irregular	11	1.8
Became postmenopausal	5	0.8
Postmenopausal at first observation	38	6.2

sample may have precluded our ability to identify small differences in rates. Our designation of irregular menses did not distinguish women with changing menses prior to menopause from those experiencing a transient oligomenorrhea. Moreover, this classification could have included women whose infrequent cycles occurred in spite of sufficient or even high estrogen levels, such as those with polycystic ovarian syndrome. The heterogeneity of any group of women with irregular menstrual bleeding may obscure relations between rate of bone loss and fluctuating estradiol levels experienced by women who were truly perimenopausal.

Comparison of our findings on perimenopausal bone loss with those found in other studies is difficult because of the lack of consistency in the definition of perimenopausal status. Studies of BMD among perimenopausal women define perimenopausal status based on experience of menopausal symptoms (33), a particular age range (34), measures of follicle-stimulating hormone (12, 35), or a specific time

TABLE 4. Multiple linear mixed model regressions* of bone mineral density at the lumbar spine and femoral neck, Tecumseh, Michigan, 1992–1998 (*n* = 614)

	Lumbar spine			Femoral neck		
	Beta	(SE)†	*p* value	Beta	(SE)	*p* value
Intercept	–0.054	(0.025)	0.03	–0.036	(0.015)	0.021
Time (years)	0.065	(0.015)	0.0001	–0.016	(0.004)	0.0001
Time^2 (years^2)	–0.013	(0.002)	0.0001			
Menopausal status						
Premenopausal	Referent			Referent		
Irregular menses	–0.086	(0.050)	0.09	–0.077	(0.053)	0.15
Postmenopausal	–0.097	(0.049)	0.05	–0.076	(0.050)	0.13
Time (years) × irregular menses	0.030	(0.012)	0.01	0.001	(0.012)	0.93
Time (years) × postmenopausal	–0.039	(0.009)	0.0001	–0.026	(0.010)	0.010
Baseline BMD† (*z* score)	0.975	(0.009)	0.0001	0.940	(0.013)	0.0001
Time (years) × baseline BMD (*z* score)				–0.007	(0.003)	0.01

* Adjusted for body mass index.
† SE, standard error; BMD, bone mineral density.

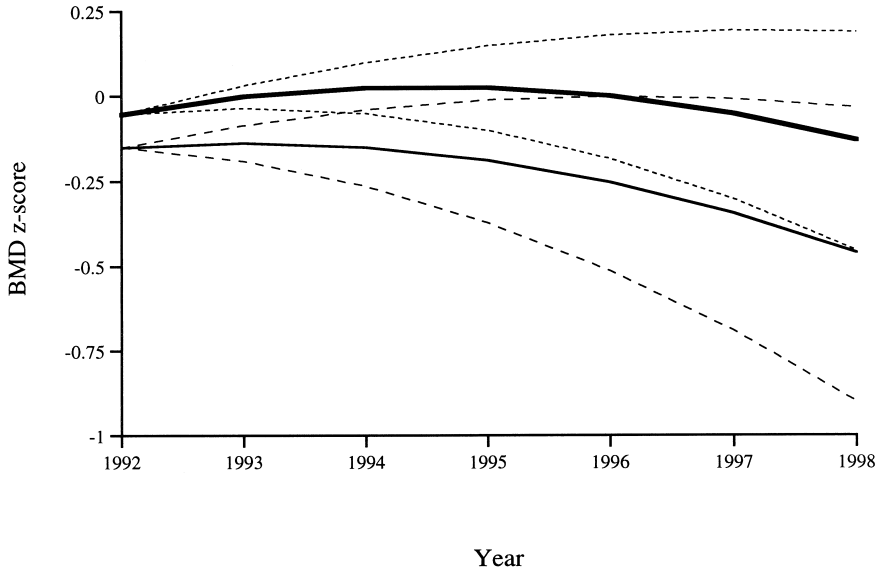

FIGURE 1. Bone mineral density of the lumbar spine versus year of study for 614 women from Tecumseh, Michigan, from 1992 to 1998 for premenopausal (thick, solid line) and postmenopausal (thin, solid line) women. Ninety-five percent confidence intervals are represented for premenopausal (small-dashed line) and postmenopausal (large-dashed line) women about the estimates.

period prior to menopause (36). We operationalized changing ovarian function based on frequency of menstrual cycles and allowed a woman's status to vary with time. This approach may more correctly capture how the duration of particular menstrual characteristics affects bone loss.

Postmenopausal women experienced a period of stable BMD at the lumbar spine followed by a maximum rate of loss of 13.0 percent of a z score (or 1 percent of baseline BMD). At the femoral neck, the 4.2 percent of a z score loss corresponded to 0.6 percent of baseline BMD. Although the study population included a small proportion of women taking hormone replacement therapy, our estimates of postmenopausal rate of bone loss are slightly greater than the 0.7–0.8 percent annual rate of vertebral bone loss estimated among women given a placebo in ipriflavone trials (37, 38). On the other hand, our estimate is less than the 1.6 percent rate of loss at the femoral neck among postmenopausal women taking placebo in an alendronate trial, although the latter group was 6 years beyond their last menstrual period, on average, at baseline (39).

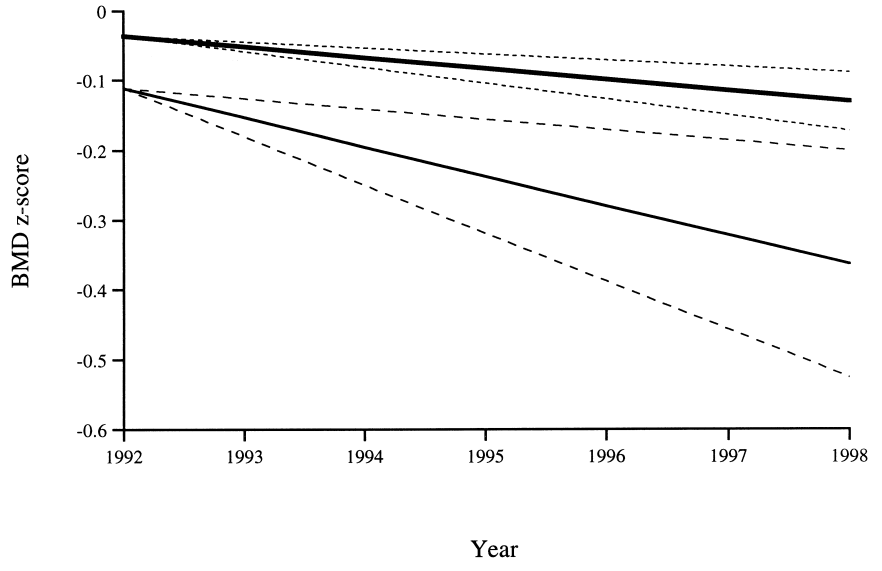

FIGURE 2. Bone mineral density of the femoral neck versus year of study for 614 women from Tecumseh, Michigan, from 1992 to 1998 for premenopausal (thick, solid line) and postmenopausal (thin, solid line) women. Ninety-five percent confidence intervals are represented for premenopausal (small-dashed line) and postmenopausal (large-dashed line) women about the estimates.

TABLE 5. Rate of change in bone mineral density (*z* score/year) at the lumbar spine, by menopausal status and by year, Tecumseh, Michigan, 1992–1998

Year	Premenopausal		Irregular menses		Postmenopausal	
	Rate of change	95% CI*	Rate of change	95% CI	Rate of change	95% CI
1992	0.065	0.035, 0.094	0.095	0.042, 0.147	0.026	–0.023, 0.073
1993	0.039	0.003, 0.076	0.069	0.008, 0.129	0.00	–0.057, 0.055
1994	0.013	–0.029, 0.058	0.043	–0.026, 0.111	–0.026	–0.091, 0.037
1995	–0.013	–0.061, 0.040	0.017	–0.060, 0.093	–0.052	–0.125, 0.019
1998	–0.091	–0.157, –0.014	–0.061	–0.162, 0.039	–0.130	–0.227, –0.035

* CI, confidence interval.

Women who began the study with higher BMD at the femoral neck had slightly greater rates of loss than did those who began the study with lower BMD. Although no such effect was observed at the lumbar spine, this finding might be an indication of a slight "floor" effect, in which there is a limit to the amount of bone mineral the body can lose while still maintaining adequate physiologic functioning. Although some may argue that this finding represents a statistical regression to the mean, the repeated-measures methodology suggests that there is a low probability of attributing this observation solely to greater random error for the highest BMD measurements. Rather, a low baseline BMD might be the result of a prior loss of bone that has stabilized or might indicate a genetic predisposition conducive to lower BMD but not necessarily a higher rate of bone loss.

Age at onset of bone loss was determined from the functional form of BMD loss at each skeletal site. At the femoral neck, our evidence suggests that onset of bone loss occurred before age 24 years. This finding is consistent with that of Haapasalo et al. (40), who demonstrated bone loss as early as the third decade at the femoral neck. However, we were unable to define the age at onset of bone loss at the lumbar spine with the same degree of consistent evidence. When bone loss was examined over the 6-year time frame of the study, the BMD of the lumbar spine appeared to accrue until the mid- to late thirties, followed by almost immediate decline. This finding is consistent with results of smaller, cross-sectional studies by Szejnfeld et al. (41) and Soda et al. (42). When bone loss at the lumbar spine was examined as a function of age, which spanned more than 25 years, the evidence suggested that onset is much earlier. In either case, these results challenge the perception that bone loss is solely a function of changes in the reproductive endocrine environment around the time of menopause.

Our study findings are consistent with the two-phase theory of bone loss (18) whereby a higher rate of bone loss associated with menopause is superimposed on an underlying lower rate of bone loss beginning earlier. This two-phase theory could be explained by two concurrent biologic mechanisms. First, there may be a natural, age-related perturbation in the balance of calcium homeostasis related to decreasing intestinal calcium absorption and increasing levels of parathyroid hormone beginning in young adulthood (43). These metabolic alterations have been associated with bone loss in the elderly (44) but have not been investigated in younger populations. Around the time of the menopause, declining estradiol may influence the degree of bone matrix degradation via a reduction of osteoclast activity inhibition (45).

Our population-based study was not subject to selection bias to the same degree as earlier studies with volunteer or clinic-based samples in which a participant's entry into the study depended on access to health care. Our study was limited by the homogenous ethnic background of the study population. Known differences in BMD by ethnicity (1) suggest the need for care in generalizing these results to populations of African, Asian, or Hispanic ethnicities or to populations living in other geographic regions. Caution should also be used when generalizing these results to populations with a lower average BMD at baseline or those with a lower prevalence of overweight and obese women. It is unknown whether rates of bone loss differ among populations of normal and underweight women.

In conclusion, this study demonstrated bone loss in young adult women at both the lumbar spine and femoral neck. We found no evidence that a large segment of the premenopausal population experiences a rapid rate of loss. Thus, the population attributable risk of rapid bone loss on low BMD or "early" osteoporosis is probably insufficient to warrant screening of the general population of young adults. Yet, variability in rates of loss and the duration over which these rates are sustained will determine BMD at any point in time. Continued studies of the natural history of bone loss among young women may allow us to identify groups of women potentially at risk for osteoporosis.

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REFERENCES

1. Looker AC, Johnston CC Jr, Wahner HW, et al. Prevalence of low femoral density in older U.S. women from NHANES III. J Bone Miner Res 1995;10:796–802.
2. Sowers MFR, Galuska DA. Epidemiology of bone mass in pre-

menopausal women. Epidemiol Rev 1993;15:374–98.
3. Mazess RB, Barden HS. Bone density in premenopausal women: effects of age, dietary intake, physical activity, smoking, and birth control pills. Am J Clin Nutr 1991;53:132–42.
4. Hansen MA. Assessment of age and risk factors on bone density and bone turnover in healthy premenopausal women. Osteoporos Int 1994;4:123–8.
5. Arlot ME, Sornay-Rendu E, Garnero P, et al. Apparent pre- and postmenopausal bone loss evaluated by DXA at different skeletal sites in women: the OFELY cohort. J Bone Miner Res 1997;12:683–90.
6. Lindsay R, Cosman F, Herrington BS, et al. Bone mass and body composition in normal women. J Bone Miner Res 1992;7:55–63.
7. Sowers MF, Kshirsagar A, Crutchfield M, et al. Body composition, age and femoral bone mass of young adult women. Ann Epidemiol 1991;1:245–54.
8. Ravn P, Hetland ML, Overgaard K, et al. Premenopausal and postmenopausal changes in bone mineral density of the proximal femur measured by dual-energy x-ray absorptiometry. J Bone Miner Res 1994;9:1975–80.
9. Lofman O, Larsson L, Ross I, et al. Bone mineral density in normal Swedish women. Bone 1997;20:167–74.
10. Recker RR, Lappe JM, Davies M, et al. Change in bone mass immediately before menopause. J Bone Miner Res 1992;7:857–62.
11. Riggs BL, Wahner HW, Melton L, et al. Rates of bone loss in the appendicular and axial skeletons of women: evidence of substantial vertebral bone loss before menopause. J Clin Invest 1986;77:1487–91.
12. Sowers MF, Crutchfield M, Bandekar R, et al. Bone mineral density and its change in pre- and perimenopausal white women: the Michigan Bone Health Study. J Bone Miner Res 1998;13:1134–40.
13. Slemenda C, Longcope C, Peacock M, et al. Sex steroids, bone mass, and bone loss: a prospective study of pre-, peri-, and postmenopausal women. J Clin Invest 1996;97:14–21.
14. Fujiwara S, Fukunaga M, Nakamaura T, et al. Rates of change in spinal bone density among Japanese women. Calcif Tissue Int 1998;63:202–7.
15. Pouilles JM, Tremollieres F, Ribot C. The effects of menopause on longitudinal bone loss from the spine. Calcif Tissue Int 1993;52:340–3.
16. Chapurlat RD, Garnero P, Sornay-Rendu E, et al. Longitudinal study of bone loss in pre- and perimenopausal women: evidence for bone loss in perimenopausal women. Osteoporos Int 2000;11:493–8.
17. Pouilles JM, Tremollieres F, Ribot C. Variability of vertebral and femoral postmenopausal bone loss: a longitudinal study. Osteoporos Int 1996;6:320–4.
18. Mazess RB. On aging bone loss. Clin Orthop 1982;165:239–52.
19. Matkovic V, Jelic T, Wardlaw GM, et al. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis: inference from a cross-sectional model. J Clin Invest 1994;93:799–808.
20. Mazess RB, Barden H. Bone density of the spine and femur in adult white females. Calcif Tissue Int 1999;65:91–9.
21. Kulak CAM, Bilezikian JP. Osteoporosis: preventive strategies. Int J Fertil 1998;43:56–64.
22. O'Neill T, Papapoulos S. Can we prevent fractures? Baillieres Clin Rheumatol 1997;11:565–82.
23. Davis JW, Grove JS, Ross PD, et al. Relationship between bone mass and rates of bone change at appendicular measurement sites. J Bone Miner Res 1992;7:719–25.
24. Bray GA. Overweight is risking fate: definition, classification, prevalence and risks. Ann N Y Acad Sci 1987;499:14–28.
25. Sowers MF, Corton G, Shapiro B, et al. Changes in bone density with lactation. JAMA 1993;269:3130–5.
26. Verbeke G. Linear mixed models for longitudinal data. In: Verbeke G, Molenberghs G, eds. Linear mixed models in practice: a SAS oriented approach. New York, NY: Springer Verlag, 1997:63–153.
27. Prior JC, Vigna YM, Barr SI, et al. Ovulatory premenopausal women lose cancellous spinal bone: a five year prospective study. Bone 1996;18:261–7.
28. Shaw CK, Tzen KY, Chang TK. A prospective study of bone mineral density change in Taiwan. Calcif Tissue Int 1998;62:109–13.
29. Baran D, Sorenson A, Grimes J, et al. Dietary modification with dairy products for preventing vertebral bone loss in premenopausal women: a three-year prospective study. J Clin Endocrinol Metab 1989;70:264–70.
30. Melton LJ, Atkinson EJ, O'Connor MK, et al. Determinants of bone loss from the femoral neck in women of different ages. J Bone Miner Res 2000;15:24–31.
31. Perrone G, Galoppi P, Capri O, et al. Lumbar and femoral bone density in perimenopausal women with irregular cycles. Int J Fertil 1995;40:120–5.
32. Salamone LM, Gregg E, Wolf RL, et al. Are menopausal symptoms associated with bone mineral density and changes in bone mineral density in premenopausal women? Maturitas 1998;29:179–87.
33. Clements D, Compston JE, Evans C, et al. Bone loss in normal British women: a 5 year follow-up. Br J Radiol 1993;66:1134–7.
34. Pouilles JM, Tremollieres F, Ribot C. Effect of menopause on vertebral bone mass: a longitudinal study. Presse Med 1994;23:1069–73.
35. Garton M, Martin J, New S, et al. Bone mass and metabolism in women aged 45–55. Clin Endocrinol 1996;44:563–70.
36. Recker R, Lappe J, Davies K, et al. Characterization of perimenopausal bone loss: a prospective study. J Bone Miner Res 2000;15:1965–73.
37. Agnusdei D, Crepaldi G, Isaia G, et al. A double blind, placebo-controlled trial of ipriflavone for prevention of postmenopausal spinal bone loss. Calcif Tissue Int 1997;61:142–7.
38. Alexandersen P, Toussaint A, Christiansen C, et al. Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. JAMA 2001;285:1482–8.
39. Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. N Engl J Med 1998;338:485–92.
40. Haapasalo H, Kannus P, Sievanen H, et al. Development of mass, density, and estimated mechanical characteristics of bones in Caucasian females. J Bone Miner Res 1996;11:1751–60.
41. Szejnfeld VL, Atra E, Baracat EC, et al. Bone density in white Brazilian women: rapid loss at the time of menopause. Calcif Tissue Int 1995;56:186–91.
42. Soda M-Y, Mizunuma H, Honjon S-I, et al. Pre- and postmenopausal bone mineral density of the spine and proximal femur in Japanese women assessed by dual-x-ray absorptiometry: a cross-sectional study. J Bone Miner Res 1993;8:183–9.
43. Prince RL, Dick I, Devine A, et al. The effects of menopause and age on calcitropic hormones: a cross-sectional study of 655 healthy women aged 35 to 90. J Bone Miner Res 1995;10:835–42.
44. Bouillon R, Carmeliet G, Boonen S. Ageing and calcium metabolism. Baillieres Clin Endocrinol Metab 1997;11:341–65.
45. Kassem M. Cellular and molecular effects of growth hormone and estrogen on human bone cells. APMIS 1997;105(suppl 71):7–30.