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Original Article

The Contribution of Bone Loss to Postmenopausal Osteoporosis

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Abstract. We have addressed the relative importance of peak bone mass and subsequent rate of loss in determining postmenopausal women's bone mass in old age, by examining longitudinal measurements of radial mid-shaft bone mass on various samples of healthy white postmenopausal women. Using both the variance estimate of age-specific rates of bone loss and the population variance in bone mass, we determined that rates of loss could contribute importantly to future bone mass. However, since we found a small negative correlation between initial bone mass and rate of loss, it was necessary to estimate the effect of bone loss as the complement of the contribution of initial bone mass. We found that the influence of bone loss (relative to initial bone mass) increases as the women age, such that by about age 70, the contribution of initial bone mass and rate of loss approached equality. However, estimated rates of bone loss were not very stable over time, so it was difficult to identify long-term 'fast-losers'. We conclude that the rate of postmenopausal bone loss is an important contributor to osteoporosis at old age, but it is difficult to identify long-term fast-losers, thereby reducing the clinical value of assessments of rates of change in bone mass early in the postmenopause.

Keywords: Bone loss; Bone mass measurements; Osteoporosis; Peak bone mass; Postmenopause; Rate of bone loss

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Introduction

The early identification of those women at the highest risk of osteoporotic fractures would be of great clinical importance in the ultimate prevention of these fractures. Because of this, it is important to determine whether peak bone mass or subsequent rate of bone loss is more important in determining a woman's ultimate risk of osteoporosis so that interventions, such as estrogen replacement therapy, may be most effectively applied. Some believe that peak bone mass is relatively more important, so that women who start out with high bone mass will have little risk of osteoporosis even if they lose bone at a higher rate than most of their peers [1]. However, others have concentrated on identifying those 'fast losers' who, they believe, have the greatest probability of developing osteoporosis and its attendant fractures [2].

To directly address this question requires data that relate women's peak bone mass and rate of bone loss to their subsequent fractures. However, since no one has followed large numbers of menopausal women for a long enough period to observe enough fractures to address this question directly, we have focused on contributions to bone mass in old age, since bone mass has been shown to serve as an index of risk of subsequent fractures [3,4]. We have used longitudinal measurements of bone mass in several populations of varying ages to assess the relative importance of peak bone mass and rate of loss on bone mass at old age. This was achieved by answering the following three questions analytically. What is the variability of rates of loss compared to the variability of peak bone mass? Is a woman's rate of bone loss positively or negatively correlated with her peak bone mass? Is the observed rate of bone loss persistent through the postmenopausal years, e.g., do 'fast losers' remain 'fast losers'? The answers were then integrated to give an overall assessment of the role of bone loss in postmenopausal osteoporosis, and the clinical importance of measuring rates of bone loss.

Methods

Study Subjects and Statistical Methods

Different but overlapping samples of subjects were used to address the three questions. All of the analyses were based on bone mass measured at the midshaft radius using single-photon absorptiometry [5]. The study subjects were drawn from our existing studies on the natural course of bone loss through menopause. All were postmenopausal white women without any metabolic bone disease, and none was taking any medication known to affect bone metabolism.

For comparing the variability of rates of bone loss with that of initial mass, we used the results from our published study [6] on 268 healthy postmenopausal women who had longitudinal measurements of bone mass. These subjects had 3 to 45 (mean=20) repeated measurements of bone mass over periods of 6 weeks to 7 years (mean=4 years). The age at entry ranged from 50 to 95 years (mean=67). From this study, we obtained separate estimates of the variance due to measurement error and the variance of the true rates of bone loss. In the current study, we evaluated the impact of this variance of rates of bone loss against the variance of peak bone mass to answer the first question regarding the relative magnitude of the variability of bone loss compared to the variability of bone mass.

To answer the second question concerning the correlation between initial bone mass and rate of loss, we used the bone measurements on 86 subjects who had at least two measurements within 3 years of their last menstrual period (LMP), followed by at least three measurements made over a period of no less than a year. For those subjects who had their LMP while they were in the study, we used only post-LMP data. All subjects had bone mass measurements made every 4 months; the total number of measurements per subject ranged from 5 to 22 (mean=12). The first two measurements of each subject were averaged to give the subject's initial bone mass. Subsequent data excluding these first two points were used to obtain a least-squares slope as an estimate of an individual's rate of bone loss. Pearson's correlation was calculated between the subject's initial bone mass and rate of bone loss, with and without weighing the observation by the inverse of the variance of the rate of loss.

In addition, we selected data from 34 of these postmenopausal women with bone mass measurements within 2 years of age 50 and repeated within 2 years of age 60, with an interval of 8–12 years, to estimate the correlation of bone mass 10 years apart.

To answer the third question about the persistence of rates of bone loss, we selected 47 subjects who had a minimum of 6 years of follow-up with at least three bone mass measurements within the first 5 years post-LMP and at least three measurements after that time. There were, on average, 11 measurements per subject in the first 5 years, and eight measurements per subject in the next 5 years. The rate of bone loss was estimated separately for these two periods using least-squares, and Pearson's correlation was estimated between the individuals' pairs of rates.

Results

Variability of Rates of Bone Loss Compared to the Variability of Peak Bone Mass

To address the first question concerning the variability of rates of bone loss, we first had to establish that individuals lose bone mass fast enough to make an impact on their subsequent bone mass relative to other women of the same age. As shown in Fig. 1, which depicts the data from two selected long-term participants in a study, it is biologically possible for one woman who started out with much higher bone mass to lose bone much faster than another woman who started out much lower, such that the substantial initial difference disappeared in about 10 years. However, on a population basis, the question is how frequently are such large differences in rates of loss observed and, thus, how important is the impact of the rates on bone mass at, say, age 70.

From our previous study [6], the bone mass at the midshaft radius of women at around age 50 is distributed with a standard deviation (SD) of about 0.07 g/cm after the measurement error was estimated statistically and then removed. The standard deviation of their 'true' rates of bone loss at any time throughout menopause is about 0.009 g/cm per year. This means that a woman who starts out with bone mass 1 SD above the mean and *consistently* loses bone at a rate 1 SD faster than the

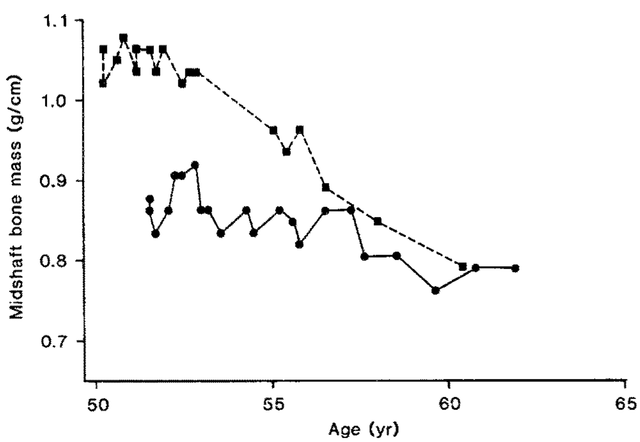

Fig. 1. Bone mass at the midshaft radius of two white postmenopausal women.

mean rate can completely lose her initial advantage in less than 10 years (0.07/0.009=7.8 years).

However, there are reasons to believe that the influence of rates is more complicated and perhaps weaker than depicted above. From the cross-sectional data of the same subjects, it was estimated that the population standard deviation of bone mass increases only by 0.00255 g/cm per year. If the long-term rates of bone loss were uncorrelated with the initial bone mass, then the standard deviation of the cross-sectional bone mass would increase at a rate equal to the standard deviation of the long-term rates of bone loss. Under these assumptions, it follows that one standard deviation of the long-term rates of bone loss would be equal to 0.00255 g/cm per year and it would take 28 years for a woman losing at a rate 1 SD faster than the mean rate to completely lose an initial advantage of having bone mass 1 SD above the mean.

These estimates showed that the variability of rates of bone loss in postmenopausal women is not negligible relative to the variability of initial mass. However, the two rather discrepant estimates of the potential effect of rates of loss were based on different assumptions. In both cases, the rates of bone loss were assumed to be independent of the initial bone mass. In the first case, an additional assumption was that short-term rates of bone loss persisted throughout the postmenopausal years, making the variance of long-term rates equal to that of short-term rates. The discrepancy between these two results led us to examine the assumptions in the model.

Correlation Between Initial Bone Mass and Rate of Loss

A positive correlation between the rate of change in bone mass and its initial value would enhance the predictive value of the latter, whereas a negative correlation would diminish the predictive value of initial bone mass. To address this question, we used the longitudinal data on 89 women to estimate the correlation between initial bone mass and its subsequent rate of change. The individual rates of bone loss were plotted against the initial mass in Fig. 2, which shows that initial values have a weak negative correlation with the rate of change ($r=-0.16$). Although the initial mass may not have a strong effect on the immediate rate of loss, this slightly negative correlation may persist throughout the postmenopausal years. Furthermore, the variance of age-specific rates of bone loss over relatively short intervals are much higher than expected from the age-related increase in the population variance in bone mass (as discussed above), suggesting that 'fast losers' may tend to slow down and vice versa. These effects constitute a mild self-correcting mechanism, whereby those subjects who have higher bone mass and have been losing slowly at any time are slightly more likely to lose faster than others with lower bone mass. This continual self-correction further complicates the prediction of future bone mass using observations made over relatively short periods of time, and slightly reduces the value of assessing rates of loss.

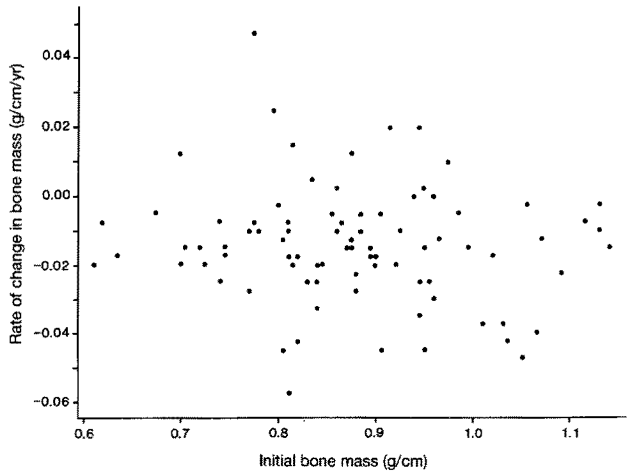

Fig. 2. Plot of rate of change in bone mass at the midshaft radius versus the initial bone mass of 89 white women immediately after menopause.

Given the problems of working with the individual estimated rates of bone loss, the contribution of rates can be estimated from how much future bone mass *cannot* be predicted by initial bone mass. The unexplained variability of bone mass at old age can only be due to measurement error and the loss of bone in the intervening years. In Fig. 3, we show how the correlation and the squared correlation decrease with increasing time span. For the interval equal to zero, the unexplained variation is due purely to mesurement error. The correlation between bone mass measurements in a 10-year interval was estimated from 34 subjects who have had bone measurements at around age 50 and 60 as described in the Methods section. The correlation for 20 years was estimated from the cross-sectional variance and the negative correlation between

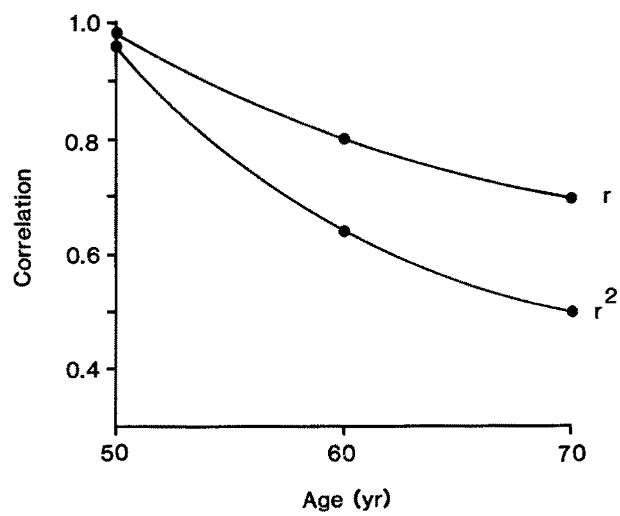

Fig. 3. Estimated correlation, r and r^2, between bone mass at age 50 and that at subsequent ages. See text for estimation procedures.

initial bone mass and rate of loss (assumed to be somewhere between −0.1 and −0.2). Fig. 3 suggests that by age 70, about half of the variance cannot be explained by the initial bone mass. A few percent of the unexplained variance is due to measurement error, but most of it is due to the bone loss in 20 years. The question remains whether or not the 'fast losers' over 20 years can be identified early on.

Persistence of the Observed Rate of Bone Loss

To examine the persistence of rates of bone loss, we calculated the rates of change in bone mass of 48 women in the first and second 5-year period after cessation of menses. The two rates were plotted against each other in Fig. 4. The correlation between these pairs of rates was 0.22, which is not very strong. If we were to classify the subjects into three groups according to their rates of loss in the first 5 years, the cross-classification with the second 5 years shows that only half of them retained their original classification (see Fig. 5). Although part of the misclassification is due to estimation error of the individual rates, their precision is about what one can expect in clinical situations. (Importantly, although the mean rate of bone loss in the second 5-year period was slower, there remained a large variance in the rate of loss.)

The finding that the increase in population variance in bone mass is smaller than expected from the variance of the instantaneous rates suggests that the non-persistence of rates is real and not simply due to measurement error. It is also consistent with the possibility that there may be a small degree of self-correction of bone mass throughout the postmenopausal years.

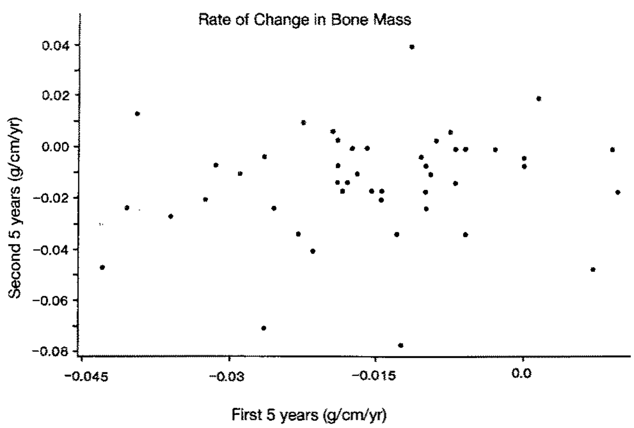

Fig. 4. Plot of rate of change in midshaft radius bone mass during 5–10 years versus 0–5 years after menopause in 47 white women.

Rate of loss in bone mass in first 5 years	Rate of loss in bone mass in next 5 years: Fast	Medium	Slow	Total
Fast	4	6	2	12
Medium	4	12	6	22
Slow	2	4	7	13
Total	10	22	15	47

r = 0.22

Fig. 5. Cross-classification of 47 white women by their rate of bone loss at the midshaft radius during 0–5 years by 5–10 years postmenopause.

Discussion

It is now generally recognized that a single measurement of bone mass is predictive of fracture incidence [3,4]. It is also clear that bone mass measurements provide the primary rational basis for the use of estrogen replacement therapy in the prevention of osteoporosis [7]. However, it has remained controversial whether clinical assessments of rates of bone loss should also be considered when considering therapies to reduce the risk of osteoporotic fractures.

In the early postmenopausal years, initial bone mass (at the time of menopause), rather than bone loss, is clearly the primary factor of importance. Evidence for this comes from the very high correlations between measurements taken several years apart, suggesting that rates of bone loss could theoretically explain only 10%–20% of the variance in bone mass at any point in these relatively early years. But, as we have shown, the biological variability in rates of loss is large enough such that, by the time women reach their early seventies, the contributions of initial bone mass and subsequent loss contribute approximately equally to the determination of bone mass. This alone, however, is not an adequate basis for recommending assessments of rates of loss for the reasons detailed below.

Although long-term bone loss becomes increasingly important in the determination of bone mass in women over age 70, it is difficult to identify those women who will lose the most bone between menopause and these later years. The difficulty is twofold. First, with the instruments currently available, the precision of single measurements is 1% or more, while rates of loss over the first postmenopausal decade average about 1% per year; these elements together make it difficult to precisely estimate an individual's rate of loss with only two or three measurements several years apart. This problem, however, will almost surely be overcome with technical advances, and recently available densitometers appear to have the necessary improvements in precision. The second aspect to this problem is the true biological variability in a woman's rate of bone loss. From the variances of cross-sectional bone mass and rates of bone loss, we concluded that bone loss is regulated by a mild self-correction mechanism, which implies adjustments of an individual's rate over time. Furthermore, correlations between rates of loss in sequential 5-year periods were weak, despite an average of 19 measurements per subject. This demonstrates that only a small proportion of 'fast losers' remain 'fast losers' over a long period of time. Because this is a biological phenomenon, it cannot be diminished by technological advances.

It should also be noted that in any calculation of rates of loss, the last bone mass measurement taken is closest to the future and, thus, may be the best predictor of future bone mass, thereby further reducing the value of estimating rates of loss. Therefore, even if calculations of rates of bone loss do not seem valuable, repeated measurements of bone mass may be valuable in certain circumstances, such as monitoring therapy. For example, although women with very low bone mass are unlikely to change their risk status, women with bone mass close to the mean may well progress to very low bone mass. Subsequent measurements of this group would not be done, however, to calculate rates of loss, but rather to reascertain bone mass as an indication of fracture risk. Finally, there is the possibility that rapid bone loss may contribute to the risk of fracture through architectural changes that are not reflected in bone mass. This may be especially true in trabecular bone, which was not measured in this study. If this were true, then rates of loss might independently predict osteoporotic fractures, particularly crush fractures. This study could not address this theoretical possibility.

In summary, the true biological variability in long-term rates of bone loss makes it difficult or perhaps impossible to identify long-term 'fast losers'. As long as we cannot, with confidence, extrapolate the rate of bone loss beyond the period of observation, the last bone measurement in this period will supply the most critical piece of information for predicting a woman's subsequent bone mass. Unless scientific advances occur which permit the accurate prediction of long-term rates of loss, it will be difficult to make clinical use of bone loss data for the classification of risk for osteoporosis.

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