Age and Activity Effects on Rate of Bone Mineral Loss

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ABSTRACT It has been postulated that the rate of mineral loss in postmenopausal women remains constant with aging and that the decreased activities of daily living associated with aging contribute to mineral loss. These hypotheses were examined by measuring the bone mineral content at the midshaft of the radius with the photon absorption technique. The estimated rate of loss was calculated in a cross-sectional study as the regression coefficient of bone mineral content vs. age and in a longitudinal study as the regression coefficient of bone mineral content vs. time.

In the cross-sectional study, Group A, which consisted of 264 women aged 50–72 yr, had an estimated rate of loss of -0.0114 ± 0.0014 (SE) g/cm per yr. Group B, which consisted of 266 women aged 73–96 yr, had an estimated rate of loss of -0.0055 ± 0.0017 g/cm per yr.

In the longitudinal study, Group C consisted of 33 women aged 51–65 yr who were followed for an average of 4.5 yr with a mean number of 16 visits per subject; they were found to have a mean rate of loss of -0.00990 ± 0.00107 g/cm per yr. Group D consisted of 38 women aged 70–91 yr who were followed for an average of 3.8 yr with a mean number of 31 visits per subjects; they were found to have a mean rate of loss of -0.00020 ± 0.00236 g/cm per yr.

The estimated and directly measured rates of loss were more rapid in the younger groups than in the older groups (A vs. B, $P<0.001$; C vs. D, $P<0.001$). These data demonstrate that the mean rate of mineral loss is not constant with aging and that in elderly subjects it is significantly slower than that of the earlier postmenopausal years. Since the elderly women were the less active, these findings suggest that factors other than decreased physical activity are more important in determining the rates of mineral loss.

INTRODUCTION

The study of the pathogenesis of postmenopausal osteoporosis has been hampered until recently by the lack of a sufficiently precise method of bone mineral measurement to detect the low rate of mineral loss which ultimately leads to the disease state. Consequently, clinical investigations have been approached primarily by means of cross-sectional (population survey) studies of subjects over a wide age range. These studies have suggested that mineral loss from the skeleton is widespread within the population, if not a universal phenomenon (1–5). Furthermore, they have demonstrated that a primary consequence of the reduction of bone mineral is an increase in the incidence of fractures (1, 3–5).

The inability to directly measure rates of mineral loss has largely prevented further studies such as the relationship of rates of loss to the development of osteoporosis, i.e., to determine if osteoporotics are rapid or slow losers of mineral, and the variables which affect rates of mineral loss. Recently, the value of the photon absorption technique to measure rates of loss of mineral has been demonstrated (6). The precision of the photon absorption method and ability to make multiple measurements on the same individual has made the direct measurement of rates feasible in longitudinal studies (6). Although this measurement is made at the radius, there is evidence from population surveys that the changes of bone mineral with age measured in the radius are as great or greater than the changes of bone mineral measured in other bones, including vertebra (7, 8). Changes in radial mass

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may also occur at a faster rate than changes in total body calcium measured by neutron activation (9). Thus, measurement of rate of mineral loss in the radius should adequately reflect changes that occur in the skeleton as a whole.

The present study examines the relationship of two variables, age and activity, to the rate of mineral loss. From previous cross-sectional and longitudinal studies, models have been developed to explain the relationship of bone loss to age. These models have generally assumed that the loss of bone after menopause is a linear function (1, 4, 10). In this paper, the relationship of age and bone loss is examined by direct measurement of rate, and evidence is presented that the function is nonlinear with a slowing of loss in older subjects. The inactivity status of older subjects has been postulated to contribute to mineral loss. From direct measurement of rates of loss in this study, no evidence was found that decreased levels of activity are associated with increased rates of loss.

METHODS

Measurement of bone mineral. A Norland-Cameron bone mineral analyzer (Norland Associates, Inc., Ft. Atkinson, Wisc.) was utilized to measure bone mineral content (BMC) [1] in grams per centimeter of the right radius at the midshaft site as previously described (6). A plaster form-fitting forearm cast was used for repositioning (11). The instrument was standardized with a known phantom before and after each subject was scanned. Four scans were performed at each site on each visit.

Statistical analyses. A detailed description of the statistical methods has been published (6). Briefly, the rate of mineral loss of an individual is computed as the regression coefficient of the mean BMC at each visit against time. This regression has been determined to be linear for this population over the span of time covered, but there is significant heterogeneity among individual regression coefficients (6). The average rate of loss used for a group is the pooled within-subject regression coefficient. To compare average rates from two different groups, the approximate t test with approximate degrees of freedom (df) (12) was used with variation among individual regression coefficients in each group as the error variance.

Selection of subjects. All subjects were Caucasian females aged 50 yr or older and at least 1 yr post-menopausal at the start of the study. The sources and age distribution of the 530 women used for cross-sectional data have previously been described (4). At least 30% of this group had complete history and physical examinations, hemoglobin, white blood count, urinalysis, Serum Multiple Analysis-12 (SMA-12), and X rays of the chest, thoracic, and lumbar spine as screening procedures. All of the 71 women included in the longitudinal study had received the screening procedures. Of these, 33 were from a private gynecology clinic population who were returning for annual examinations and had a mean age of 57 yr (range 51–65). 38 were from a home for the aged and had a mean age of 81 yr (range 70–91).

Subjects with organic bone disease other than osteoporosis were excluded. Also subjects with chronic liver disease, renal disease, or diseases known to affect bone metabolism were excluded. In addition, subjects receiving estrogens and cortisone were excluded.

Determination of activity status. The disabilities of subjects were recorded as negative scores modified from the Northwestern University Disability Scale (13). This scale grades disabilities according to the difficulty subjects have in performing activities such as mobility, dressing, eating, feeding, and hygiene, as negative scores. Positive scores for activity were graded in areas of activity of daily living (such as cooking and cleaning), occupational, and athletic-recreational activities. The grades for these are shown in the Appendix.

RESULTS

Estimates of rates of loss from a cross-sectional study. Regression analysis was performed on the midshaft BMC values of 530 women, aged 50 yr and older (mean 70.5, range 50–96), against age using both linear and quadratic functions. It was found that a quadratic function was significantly ($P < 0.005$) better fit for the data. The test for this was the variance ratio (F-ratio) of the mean square for the quadratic term divided by the mean square for deviation about the quadratic regression ($F = 0.166335/0.018819 = 8.839$, $df = 1,527$). The regression equation derived from this analysis was:

$$\text{Predicted BMC} = 1.92026 - (0.02672)\ (\text{Age}) + (0.000136)\ (\text{Age}^2).$$

The regression curve for this equation is shown in Fig. 1. The curve indicates that there is a slowing or deceleration of the rate of mineral loss in late post-menopausal years.

The data on this sample was also used to derive an exponential equation with the general formula: $y = a + br^x$ or $y = a + be^{-x}$ where y = predicted BMC, x = age − 50, and a, b, and r are constants to be estimated. The equation derived from the data was:

$$y = 0.5324 + (0.4003)\ (0.9614)^x$$

or

$$y = 0.5324 + 0.4003e^{-0.0394x}.$$

The closeness of fit (multiple R^2) for this data to the exponential was 0.3587 and to the quadratic was 0.3846. Thus the exponential or the quadratic function appear to fit the data equally well. The quadratic has the disadvantage of predicting an increase in BMC (minimum value of 0.608 g/cm at 98.2 yr) in ages beyond this study when an increase in BMC would not be anticipated. The exponential approaches a value of 0.534 g/cm asymptotically. The rate of loss predicted at any specific age from the quadratic is only dependent upon age, whereas the rate predicted from the exponential is directly proportional to the level of BMC above the asymptote at that age. This feature of the exponential would be more compatible with the model of bone loss presented in the Discussion.

[1] *Abbreviation used in this paper:* BMC, bone mineral content.

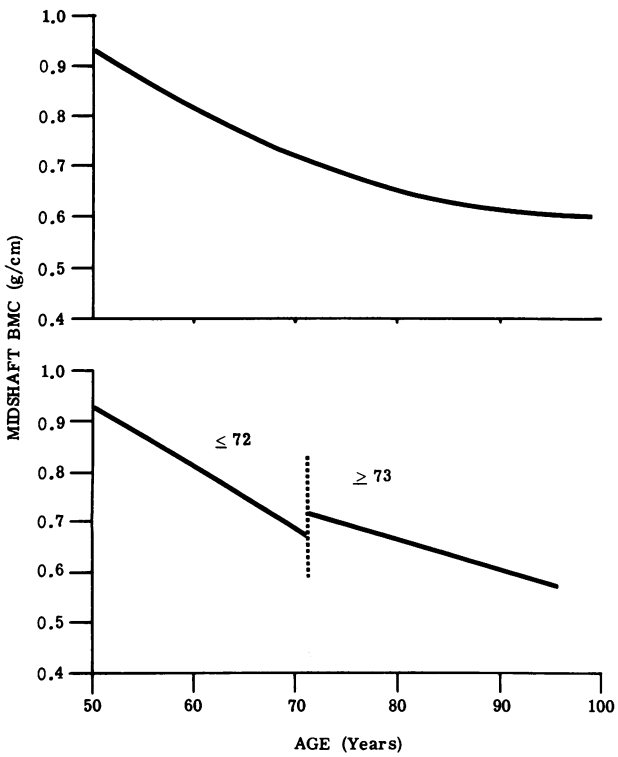

FIGURE 1 Cross-sectional measurements on 530 women. (Top) The regression curve of bone mineral measurements of 530 women aged 50–96 yr. (Bottom) The two regression lines were obtained when the population was divided by age into a younger group, aged 50–72 yr and an older group aged 73–96 yr.

To compare the results of the cross-sectional study with that of the longitudinal study (see below), the sample was divided into two age groups of equal size. The estimated rates of loss were then computed by regression analysis for each group. (The regression coefficient of BMC against age is not a true measure of rate, but serves to estimate the changes of bone mineral with age). As might be expected from the shape of the regression curve for the entire population, a quadratic function was no longer found to be a significantly better fit than a linear function for the subgroups ($F < 0.63$ for both subgroups). Thus the results in Table I which compare the estimated rates in the younger and older groups contain only linear regression coefficients. The regression lines for these data are shown at the bottom of Fig. 1.

The *t*-test for difference between the estimated rates in the younger and older groups (test of significant difference between the two regression coefficients) was

TABLE I

Comparison of Estimated Rates of Mineral Loss from a Cross-Sectional Study of Postmenopausal Women of Differing Ages

	Younger	Older
Mean age, *yr*	57 (50–72)*	81 (73–96)*
No. of subjects	264	266
Estimated rate of loss, *g/cm per yr*	−0.0114	−0.0055
SE	±0.0014	±0.0017

* Numbers in parentheses refer to range.

TABLE II

Comparison of Rates of Mineral Loss from a Longitudinal Study of Postmenopausal Women of Differing Ages

	Younger	Older
Mean age, *yr*	57 (51–65)*	81 (70–91)*
No. of subjects	33	38
Mean follow-up period	4.5 yr	3.8 yr
No. of visits, mean/subject	16	31
Mean rate of loss, *g/cm per yr*	−0.00990	−0.00020
SE	±0.00107	±0.00236

* Numbers in parentheses refer to range.

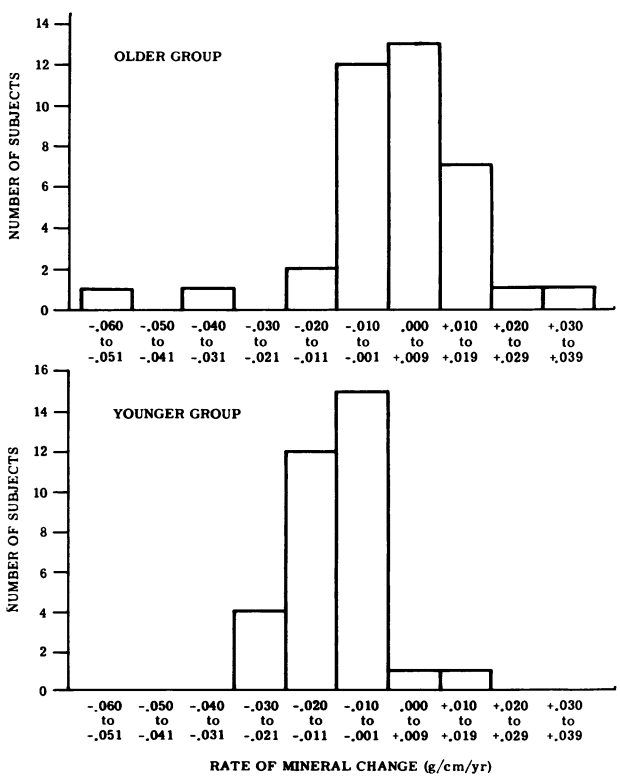

FIGURE 2 The distribution of individual rates of mineral loss obtained in the longitudinal study.

significant, $P < 0.001$. This would indicate that the older group was losing mineral at a significantly slower rate.

Rates of loss determined from a longitudinal study. The data for this study are shown in Table II. The *t*-test for differences between mean rates in the younger and older groups (12) was significant, $P < 0.01$. The magnitude of these mean rates is close to that estimated from the cross-sectional study (Table I) and demonstrates a slower rate in the older group. The standard error for the mean rate of mineral loss of the older group in Table II is larger than that for the younger group. This difference is due both to the differences between the two groups in average length of follow-up period and to the variances among the individual rates of loss in the two groups. The variances among the individual rates of loss in the two groups were found to be significantly different ($F = 5.463$, df = 37,32, $P < 0.005$). The distribution of individual rates is shown in Fig. 2, and demonstrates that although the mean rates of the two groups are significantly different, there is overlap of individual values between the two groups.

The initial BMC value for each subject was computed as the intercept of the regression line at time zero (time started in the study). The mean initial BMC of the older group was significantly smaller ($P < 0.001$) than the mean initial BMC of the younger group: older group, 0.63±0.12 (SD) g/cm; younger, 0.79±0.11 g/cm. For comparison of rates in this study to other methods of measuring bone mineral, the individual rates were computed as a percentage of the individual's initial BMC. The mean percent rate of loss for the older group was −0.02±2.36 (SD)/yr compared to −1.32± 0.86/yr for the younger group. Using the rates expressed as a percent there was also a significant ($P < 0.01$) difference between the group mean rates by *t* test (12).

Within both groups there were sets of individuals with significantly different rates. Thus, by testing for significant differences between individual regression coefficients (14), within the younger group, a set of five rapid and another set of five slow losers could be identified, and within the older group, a set of 11 rapid and another set of 11 slow losers could be identified as having significantly different rates (6). The investigation of sets of individuals with significantly different rates will provide a unique approach to determining variables related to rates of mineral loss.

Relationship of activity status to rates of mineral loss. There were no subjects in the younger group with any of the disabilities measured (see Methods section). There were no subjects in the older group with positive occupational or athletic recreational scores (see Appendex). A total individual activity score was computed as the sum of each subject's activity scores observed for all areas. The scatter diagram of individual rates plotted against the individual total activity scores is shown in Fig. 3. As can be seen, the two groups have significantly different activity scores with no overlap of values. The older group exhibited a significantly slower average rate of mineral loss as well as significantly less activity. The relationship between activity status and rate of loss was found to be negative by Spearman rank correlation ($r = -0.427$, $P < 0.001$). Thus factors other than decreased activity appear to have a greater influence on the higher rate of mineral loss in early postmenopausal years.

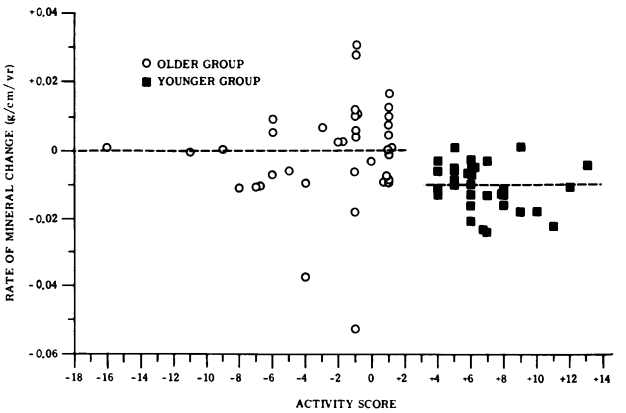

FIGURE 3 The distribution of individual rates of mineral loss plotted against the activity score. The larger (more positive) scores indicate greater activity. The horizontal dotted lines indicate the mean rates of loss for each group.

DISCUSSION

An effect of age on rate of bone mineral loss has not previously been demonstrated by valid statistical techniques. However, some of the population surveys have suggested that the trend of values of bone mineral against age after age 50 yr is not linear and that a slowing of mineral loss may occur (5, 10, 15, 16). Most of the previous longitudinal studies did not relate age with differences in rates of loss (3, 17, 18). Horsman and Simpson (19) have reported data from a longitudinal study with cortical thickness measurements which suggest that the maximal rate of bone mineral loss occurs 3 or 4 yr after menopause and that during the next 3 yr the rate of loss decreases to about one-half its peak value. However, tests of statistical significance of the differences were not reported.

In this study a slower rate of mineral loss was observed in a population which also exhibited markedly reduced activity. It has been shown from longitudinal studies that prolonged bed rest or immobilization (20, 21) produces a loss of bone mineral. In addition there is evidence that isotonic running exercise causes muscle and bone to hypertrophy in the growing rat (22). However, some studies relating other types of activity or inactivity to measurements of bone mineral from popula-

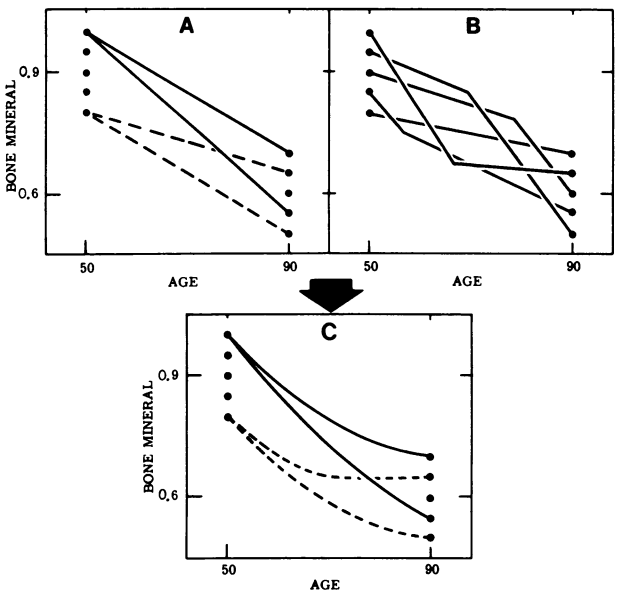

FIGURE 4 Hypothetical models of mineral loss. Models for the development of osteoporosis. The theoretical effect of aging on bone mineral in five individuals with varying amounts of bone mineral at age 50 yr. All three models have restrictions that the variation of bone mineral values in the population remain constant with aging and that individuals have different rates of loss. (A) Rates of loss constant with time and generally related to initial mineral values. (B) Rates of loss not constant with time and not related to initial mineral values (C) Average rate of loss slowing with time and rates of loss generally related to initial mineral values.

tion surveys have not always found this relationship. For example, Meema et al. (23) found that muscle width in females did not begin to decrease until after age 60 yr, whereas mineral mass (roentgenographic technique) began to decrease after age 45–50 yr and there was no correlation between mineral mass and muscle width. Very similar results were found when muscle strength was measured with the use of a strain-gauge tensiometer and dynamometer and when bone mineral was measured by photon absorption (24). That is, no significant correlation was found between age-related loss of bone mineral and age-related change in muscle strength.

There are several possible explanations for these seemingly conflicting reports. Among these are the possibility that there are other factors, such as hormones, diet, heredity, etc., which have greater effects on mineral loss in postmenopausal women than activity. Certainly the decreasing levels of estrogen found in the postmenopausal woman may be important, but this remains to be demonstrated. Another possibility is that the degree of activity or inactivity needed to affect mineral loss is greater than that which has been measured in this study. Or, it may also be possible that it is the change in activity status which affects rate rather than the absolute level of activity. For example, the activity status of women aged 50–65 yr may be decreasing, and they thus have more active rates of loss, whereas women aged 70–90 yr have been at relatively the same activity levels for several years and thus have reached a new equilibrium. Prospective studies in which changes in level of activity are measured will be necessary to validate this possibility. The results found here could also have been explained if subjects with more rapid rates of loss died earlier, thus leaving those with slower rates in the older group. The determination of which of these possibilities best explains the slowing of rates of loss in the elderly, less active population will require further investigation.

We have previously reported that the variance of bone mineral values in the population does not increase with aging (4) and that individuals followed as a function of time exhibit significantly different rates of loss (6). Two models were proposed (4) as illustrated in Figs. 4A and B. These models can now be modified to include the further restriction indicated by the results of this study, i.e., the average rate slows with aging (Fig. 4C). This new model postulates some relationship of rates of loss to initial mass. For example, the slower rates would in general occur in the subjects with lower initial mass. This postulated relationship would explain how individuals can have significantly different rates and yet the variation in bone mineral values does not increase with aging. For example, if there were not relationships to initial mass, that is, if the rates of loss and initial mass are only randomly related, then subjects with low initial bone mineral values and rapid rates of loss and subjects with high initial values and slow rates of loss would produce an increase in variance of bone mineral values with aging in the population. Since the variance of bone mineral values has not been found to increase with aging (4), it can be postulated that there is a relationship of rate of loss to initial bone mineral. This postulate would favor the exponential function described in the Results section.

Further longitudinal studies with measurements of rates of mineral loss in postmenopausal women directed toward the identification of the effect of variables upon rates would improve our understanding of the pathogenesis of osteoporosis.

APPENDIX

Scoring System for Activity Status

Stages of inactivity were scored according to the Northwestern University Disability Scale, except that no disability (normal function) was scored as zero and disabilities were recorded as negative values. Stages of activity were scored according to the system below as zero or positive scores. The total of all scores (positive and negative) was used as the activity level for that subject.

Activity

Occupational activity.

0. Not employed.
1. Part-time employed.
2. Full-time employed.

Participation in athletic recreational activities such as golf, tennis, cycling, skiing, bowling, and dancing.

0. No participation.
1. Occasional participation—once a mo.
2. Seasonal participation—twice a mo.
3. Seasonal participation—once a wk.
4. Seasonal participation—over once a wk.
5. Year-round participation—twice a mo.
6. Year-round participation—once a wk.
7. Year-round participation—over once a wk.

Activities of daily living (Mark 1 if true, 0 if false).

——1. Makes shopping trips of any type at least three times a wk. (Includes window shopping, groceries, meals out, etc.)
——2. Daily involved in either preparing meals or cleaning up afterwards.
——3. Does some yard work of any degree at least once a wk in season.
——4. Some involvement in cleaning, mopping, sweeping, or vacuuming floors at least once a wk.
——5. Some involvement in washing or ironing clothes at least once a wk.
——Total score.

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