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Bone Loss and Bone Size after Menopause

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ABSTRACT

BACKGROUND

Bone loss increases after menopause. However, bone strength also depends on structural characteristics such as bone size. Whether bone size increases as a result of periosteal apposition and whether a strength index accounting for both bone density and bone size might predict the risk of fracture better than bone density alone are unclear.

METHODS

Bone mass and the skeletal structure of the distal radius were evaluated by single-photon absorptiometry every other year in 108 women, all of whom were followed from the time of menopause for a mean period of 15 years. Postmenopausal serum estradiol levels and fractures of the distal radius were noted.

RESULTS

The mean (±SD) annual decrease in bone mineral density was 1.9±0.7 percent. The medullary bone diameter increased annually by 1.1±0.9 percent, and the periosteal diameter by 0.7±0.3 percent; the strength index decreased by 0.7±0.7 percent. The expansion of the medullary diameter and the expansion of the periosteal diameter were correlated with one another ($r=0.54$, $P<0.001$), and women in the highest quartile of medullary expansion had more loss of bone mineral density and greater periosteal apposition than women in the lowest quartile ($P<0.001$ for both comparisons). The postmenopausal serum estradiol level was correlated with changes in the periosteal diameter ($r=-0.25$, $P=0.009$) and with changes in bone mineral density ($r=0.34$, $P<0.001$). A 1-SD decrement in the strength index at base line was associated with a risk ratio for fracture of the distal radius of 3.8 (95 percent confidence interval, 1.8 to 8.0).

CONCLUSIONS

Increased bone loss after menopause is associated with increased periosteal apposition, which partially preserves bone strength. A strength index may be a helpful predictor of the risk of fracture.

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Bone strength depends on material properties, such as tissue mineral content. Certain structural characteristics of the skeleton — for example, size, shape, and the three-dimensional architecture — also affect bone strength. The observed increase in the fragility of bone with age is regarded as predominantly the result of the loss of bone density, but changes in bone structure may also influence skeletal strength. Estrogen deficiency after menopause accelerates the age-related loss of bone.[1,2] Cortical bone loss occurs mainly at the inner (endosteal) surface and partly in the Haversian canals.[3,4] Cross-sectional studies also indicate that bone size increases with age.[5] Such a change might increase bone strength and compensate, at least in part, for the negative effect of decreases in bone density.[6,7] Both bone density and bone structure are clinically important, since fractures due to the fragility of bones are independently associated with both low bone mass[8] and reduced bone size.[9-11]

Age-related periosteal apposition, which increases the width of the bone through the formation of bone at the outer (periosteal) surface, is believed to occur in men[6,12] and, to a lesser extent, in women.[6,13-15] Data supporting this notion are derived primarily from cross-sectional studies. The only published prospective, long-term study reported increases in bone size with age but did not evaluate the endosteal surface.[13] We hypothesized that postmenopausal estrogen deficiency, which reduces bone density, is associated with a periosteal apposition, which increases the resistance of bone to bending.

We undertook a study to determine whether menopause is followed by endosteal resorption and periosteal apposition, and if so, whether geometric changes in bone were associated with the postmenopausal serum estradiol levels. We also asked whether periosteal apposition compensated for the decreased bone strength caused by the decrease in tissue mineral content and whether a strength index that accounts for both tissue density and geometric properties might be a better predictor than bone mineral density alone of future fracture of the distal radius.

METHODS

STUDY PARTICIPANTS

We invited 241 white women who were 48 years of age and living in the city of Malmö, Sweden, to participate in this prospective study.[1,16] Forty-nine were subsequently excluded because they were postmenopausal, were taking medications, or had conditions that are known to interfere with bone metabolism, leaving 192 women eligible to enter the study between 1977 and 1978. Subsequently, 21 women withdrew from the study during the first five years — 17 because of surgically induced menopause or because they moved away and 4 because of technical measurement errors. In addition, 17 women who received estrogen treatment and 8 women who died were also excluded, leaving 146 women who were then followed through their spontaneous menopause. The analyses presented here include the 108 women (74 percent) who continued to participate throughout the study period (19 years). The last premenopausal measurements, obtained no more than two years before the onset of menopause, were defined as the measurements at menopause and were used as the base-line measurements. The 10th and final measurement was obtained at 67 years of age. Since menopause began at different ages in the 108 women who were followed throughout the study period, the postmenopausal follow-up period varied; the mean (±SD) period was 15.4±2.1 years.

At the start of the study in 1977, no permission from the institutional review board and no consent form were required; the women were asked to provide oral informed consent. However, later in the course of the study, in 1999, written permission was granted by the ethics committee of the University of Lund, the parent organization of both Malmö University Hospital and Lund University Hospital.

DEFINITION OF MENOPAUSE

We used the definition of menopause published by the World Health Organization[17]: the permanent cessation of menstruation due to the loss of ovarian follicular activity. Thus, the onset of menopause was determined retrospectively, on the basis of spontaneous amenorrhea for 12 months, along with elevated serum levels of follicle-stimulating hormone.

LABORATORY MEASUREMENTS AND CLINICAL VARIABLES

Follicle-stimulating hormone was analyzed by double-antibody radioimmunoassay, as described previously,[18,19] every three months during the first year, then every six months until one year after menopause, and then yearly. Serum estradiol levels

were also determined yearly according to the protocol until eight years after menopause, as described previously. Since the serum estradiol levels in this cohort decreased during the first three years after menopause but not thereafter,[19] the postmenopausal serum estradiol level was defined as the mean value obtained between three and eight years after menopause. The duration of amenorrhea and general health were reported on a questionnaire and by means of a personal interview conducted by the same research nurse at the time of each measurement.

Bone mineral content (in milligrams per centimeter of bone length) and bone mineral density (in milligrams per square centimeter) in the forearm were measured at a site 6 cm proximal to the styloid process of the ulna every other year by single-photon absorptiometry. The mean (±SD) number of measurements performed in each woman was 7.8±1.1. A rectilinear scan across the radius and ulna, with a radiation source (^{241}Americium) and a detector moving simultaneously, was used according to the method of Nauclér et al.[20] Both the right arm and the left arm were scanned, and all results are reported as the averages of the values for the two forearms. The same densitometer was used throughout the study, and no long-term drift, determined by measurement of a standardized phantom every other week, was observed during the study period.[1] Because of the replacement of the radiation source in 1980, all measurements thereafter were adjusted with the use of the data from the phantom. The precision (as a coefficient of variation) of the measurements on single-photon absorptiometry was 1 to 2 percent with the standardized phantom and 4 percent as determined by repeated measurement after the repositioning of each subject.[20]

The periosteal diameter, the medullary diameter, and the cortical thickness of the distal radius were calculated from the graph of the scan.[20] The total cross-sectional area, the medullary area, and the cortical area were calculated on the assumption that the bone was cylindrical (area=diameter$^2\times\pi/4$). A key geometric variable called the "cross-sectional moment of inertia" was calculated according to the following formula: ([periosteal diameter/2]^4–[medullary diameter/2]^4)$\times\pi/4$. Another variable, called the "section modulus," is an estimate of the ability of the distal radius to withstand bending forces and was calculated as the cross-sectional moment of inertia divided by half the periosteal diameter.[21] Previous studies in cadavers have verified that the cross-sectional moment of inertia in this region is highly correlated with the strength of the distal radius.[22] The tissue mineral content, expressed as the bone mineral apparent density (in milligrams per cubic centimeter), was calculated as the bone mineral content divided by the cortical area. The strength index, which takes both the bone mass and the structural appearance into account, was calculated as the product of the section modulus and the bone mineral apparent density.[21] A similar strength index has previously been shown to correlate very

Table 1. Skeletal Structure, Bone Mass, and Skeletal Strength at the Cortical Site of the Distal Radius.*

Variable	At Menopause	At 67 Yr	Annual Percent Change
Skeletal structure			
Periosteal diameter (mm)	13.0±1.1	14.1±1.2	0.7±0.3
Medullary diameter (mm)	6.8±1.3	7.7±1.3	1.1±0.9
Cortical thickness (mm)	6.2±0.7	6.4±0.7	0.4±0.8
Total area (cm^2)	1.34±0.23	1.58±0.27	1.4±0.8
Medullary area (cm^2)	0.38±0.15	0.48±0.16	2.4±2.2
Cortical area (cm^2)	0.97±0.13	1.10±0.15	1.2±0.9
Bone mass			
Bone mineral content (mg/cm)	729±81	591±104	–1.3±0.7
Bone mineral density (mg/cm^2)	560±55	419±74	–1.9±0.7
Bone mineral apparent density (mg/cm^3)	762±83	540±92	–2.2±0.7
Skeletal strength			
Cross-sectional moment of inertia (cm^4)	0.13±0.04	0.18±0.06	3.1±1.9
Section modulus (cm^3)	0.20±0.05	0.26±0.06	2.1±1.3
Strength index	153±30	136±29	–0.7±0.7

* The cortical site of the distal radius is the site 6 cm proximal to the styloid process of the ulna, which was measured by single-photon absorptiometry at the onset of menopause and at 67 years of age in 108 women. The bone mineral apparent density was calculated as the bone mineral content divided by the cortical area. The cross-sectional moment of inertia was calculated as follows: ([periosteal diameter/2]–[medullary diameter/2]^4)$\times\pi/4$. The section modulus is an estimate of the ability of the distal radius to withstand bending forces and was calculated as the cross-sectional moment of inertia divided by half the periosteal diameter. The strength index, which takes both the bone mass and the structural appearance into account, was calculated as the product of the section modulus and the bone mineral apparent density. Plus–minus values are means ±SD. The annual percent changes were calculated for each woman as the ratio of the slope fitted to that woman's repeated measurements divided by her base-line value. P<0.001 for all annual percent changes.

well with mechanical strength in the long bones of rats.[23]

DATA ON FRACTURES

All fractures of the distal radius that were sustained after a fall from no higher than the standing position and that occurred in the time between the performance of the base-line measurements and 2001 were identified from patient questionnaires and through the examination of hospital charts. Malmö University Hospital has the only emergency department in Malmö, and virtually all patients with a fracture are seen in its trauma unit.[24] Women who had fractures sustained outside of Malmö were subsequently referred to the orthopedic department for a follow-up visit at which the fracture was classified in order to ensure complete ascertainment of cases.

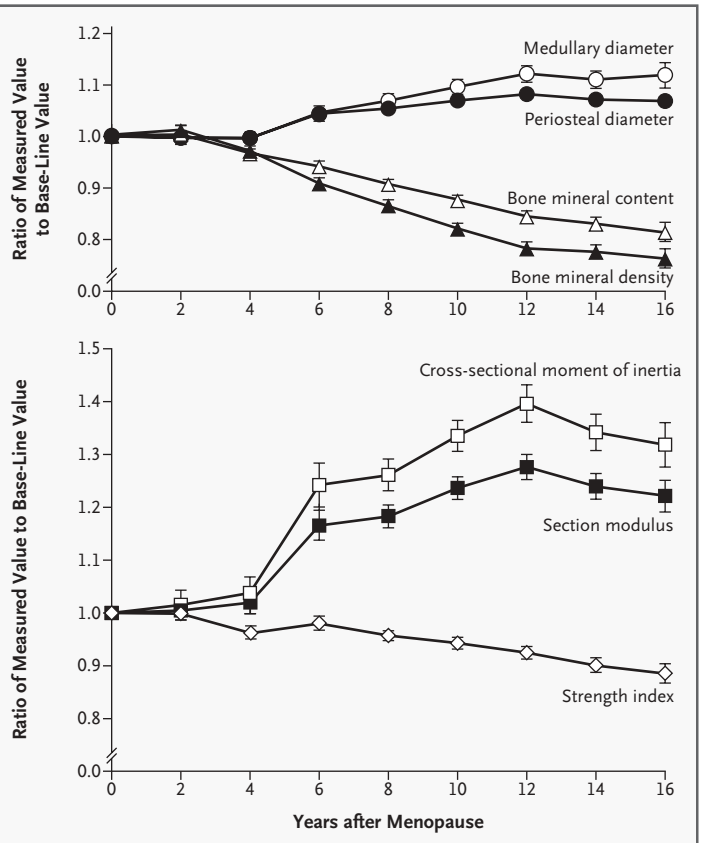

Figure 1. Mean Relative Changes from Menopause in the Medullary and Periosteal Diameters, Bone Mineral Content, Bone Mineral Density, Cross-Sectional Moment of Inertia, Section Modulus, and Strength Index at the Cortical Site of the Distal Radius in 108 Women Followed from Menopause.

I bars represent standard errors. The change from menopause became significant at 6 years for the periosteal diameter, bone mineral content, bone mineral density, cross-sectional moment of inertia, and section modulus; at 8 years for the medullary diameter; and at 14 years for the strength index.

STATISTICAL ANALYSIS

We present overall data for all 108 women who participated in the study and data for the women divided into quartiles according to the rate of expansion of the medullary cavity, since postmenopausal bone loss in long bones occurs predominantly at the endosteal surface. The annual percentage change was calculated for each woman as the ratio of the slope fitted to that woman's repeated measurements divided by the base-line value.

Analysis of variance for repeated measurements was used to evaluate significance, and a post hoc comparison with the Tukey honestly-significant-difference test was then used to further evaluate whether the specific measurements differed from those obtained at base line. Student's t-test was used to compare the mean values among women in the highest quartile of medullary expansion with the mean values among those in the lowest quartile, and bone size at base line was adjusted for by analysis of covariance. Linear regression was used to examine the association between medullary and periosteal changes, with adjustment for bone size at base line by analysis of covariance, and to examine the association between postmenopausal estradiol levels and changes in periosteal size, medullary size, and bone mineral density. We adjusted for bone size and the body-mass index (the weight in kilograms divided by the square of the height in meters) at base line with the use of analysis of covariance. A Cox proportional-hazards regression model with adjustment for age at the onset of menopause was used to calculate the risk ratio for a fracture of the distal radius.

RESULTS

BONE MEASUREMENTS

Bone mineral density decreased annually by a mean of 1.9 percent (95 percent confidence interval, 1.7 to 2.0), and bone mineral content decreased by a mean of 1.3 percent (95 percent confidence interval, 1.2 to 1.5) from menopause to 67 years of age (Table 1 and Fig. 1). The medullary diameter increased annually by 1.1 percent (95 percent confidence interval, 0.9 to 1.3), the periosteal diameter by 0.7 percent (95 percent confidence interval, 0.6 to 0.7), the cross-sectional moment of inertia by 3.1 percent (95 percent confidence interval, 2.7 to 3.4), and the

section modulus by 2.1 percent (95 percent confidence interval, 1.9 to 2.4) (Table 1 and Fig. 1). The strength index, which accounts for both bone mass and skeletal structure, decreased annually by 0.7 percent (95 percent confidence interval, 0.5 to 0.8) during the study period (Table 1 and Fig. 1). Bone mineral density had decreased significantly by six years after menopause, the periosteal diameter had increased significantly by six years, and the medullary diameter had increased significantly by eight years. However, the strength index did not decrease significantly until 14 years after menopause (Fig. 1).

ANALYSIS ACCORDING TO QUARTILE OF MEDULLARY EXPANSION

Among women in the quartile with the greatest expansion of the medullary cavity, the medullary diameter increased annually by 1.6 to 4.5 percent (median, 2.2), whereas in the women in the quartile with the least medullary expansion, the annual change in medullary diameter ranged from a decrease of 0.5 percent to an increase of 0.4 percent (median, an increase of 0.1 percent). The corresponding annual losses in bone mineral content in the two quartiles were 1.7 percent (95 percent confidence interval, 1.4 to 2.0) and 1.0 percent (95 percent confidence interval, 0.7 to 1.2), respectively, and the annual losses in bone mineral density were 2.3 percent (95 percent confidence interval, 2.0 to 2.6) and 1.4 percent (95 percent confidence interval, 1.1 to 1.6), respectively ($P<0.001$ for the comparison between the two quartiles).

The corresponding annual periosteal expansion was 0.92 percent (95 percent confidence interval, 0.78 to 1.05) in the quartile with the greatest medullary expansion and 0.47 percent (95 percent confidence interval, 0.37 to 0.57) in the quartile with the least medullary expansion ($P<0.001$). The difference between these two quartiles in the annual change in periosteal diameter (0.45 percentage point [95 percent confidence interval, 0.29 to 0.61]) remained significant after adjustment for bone size at base line (0.38 percentage point [95 percent confidence interval, 0.21 to 0.56]). That is, the quartile of women whose medullary diameter increased the most also lost the most bone mass and had the greatest increase in skeletal size. This finding is demonstrated in Figure 2, which shows a correlation between the average annual changes in the medullary and periosteal diameters ($r=0.54$, $P<0.001$) when all 108 women who were followed throughout the study are included in the analysis. The correlation remained significant after adjustment for the bone size at base line ($r=0.47$, $P<0.001$).

SERUM ESTRADIOL LEVELS

The mean serum estradiol level three to eight years after menopause was 23.7±6.7 pg per milliliter (86.8±25.5 pmol per liter). The postmenopausal serum estradiol level correlated with both the average annual change in the periosteal diameter ($r=-0.25$, $P=0.009$) and the average annual change in bone mineral density ($r=0.34$, $P<0.001$) (Fig. 3). The correlations remained significant after adjustment for bone size and the body-mass index at base line ($r=-0.20$, $P=0.03$, and $r=0.33$, $P<0.001$, respectively). There was no significant correlation between the postmenopausal serum estradiol level and the average annual change in the medullary diameter ($r=-0.16$, $P=0.11$).

RISK OF FRACTURE AND STRENGTH INDEX

Thirteen women sustained a fragility-related fracture of the distal radius. A 1-SD decrement in bone mineral density at base line was associated with a risk ratio for a fracture of the distal radius of 1.5 (95 percent confidence interval, 0.9 to 2.6); a 1-SD decrement in the cross-sectional moment of inertia was associated with a risk ratio of 3.8 (95 percent confi-

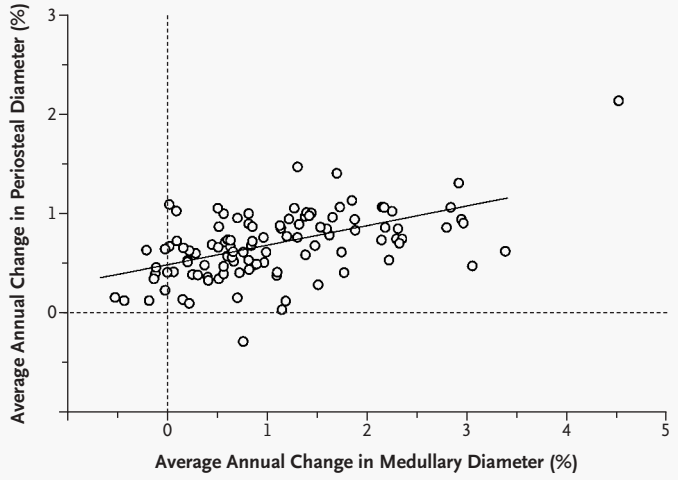

Figure 2. Relation between Average Annual Changes in Medullary and Periosteal Diameters at the Cortical Site of the Distal Radius in 108 Women Followed from Menopause to 67 Years of Age.

The correlation coefficient was 0.54 ($P<0.001$).

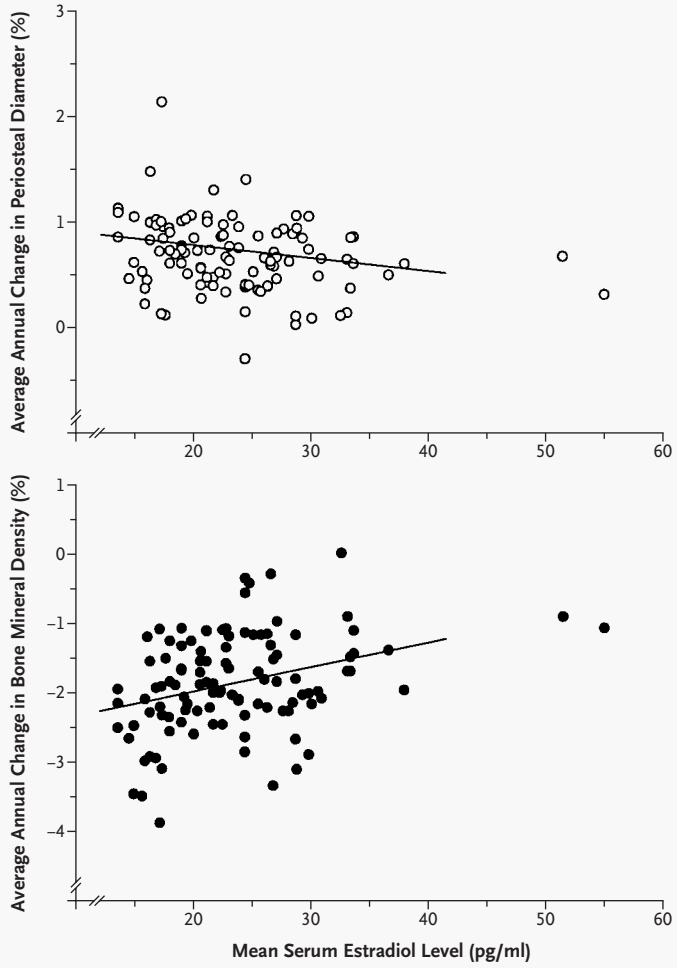

Figure 3. Relation between Mean Serum Estradiol Levels Three to Eight Years after the Onset of Menopause and Average Annual Changes in Periosteal Diameter and Bone Mineral Density at the Cortical Site of the Distal Radius in 108 Women Followed from Menopause to 67 Years of Age.

For the correlation with the periosteal diameter, r=–0.25 (P=0.009); for the correlation with bone mineral density, r=0.34 (P<0.001). To convert the values for serum estradiol to picomoles per liter, multiply by 3.67.

dence interval, 1.6 to 9.1); a 1-SD decrement in the section modulus was associated with a risk ratio of 3.6 (95 percent confidence interval, 1.6 to 7.9); and a 1-SD decrement in the strength index was associated with a risk ratio of 3.8 (95 percent confidence interval, 1.8 to 8.0). The numbers of women with a fracture of the distal radius and the rates of fracture per 1000 person-years, according to the quartiles of bone mineral density, section modulus, and strength index at base line, are shown in Table 2.

DISCUSSION

The results of our prospective study indicate that after menopause, the medullary cavity expands and bone size increases, periosteal apposition is inversely associated with postmenopausal estradiol levels, and periosteal apposition compensates in part for the decreased bone strength caused by the postmenopausal bone loss. In addition, a strength index that accounts for both bone density and bone size appears to predict the risk of future fragility-related fractures of the distal radius.

A postmenopausal increase in bone loss due to estrogen deficiency, mediated mainly through endosteal resorption and resulting in reduced bone strength, has been well documented.[3,25] However, bone strength depends not only on the material properties but also on the structural characteristics of the skeleton. Endosteal resorption leads to a decrease in bone mass, thereby decreasing bone strength. One effective way to compensate for diminished bone density is through periosteal bone apposition, which increases bone size. If the cortical shell is placed farther away from the long axis of the bone, the resistance of bone to bending and torsional forces should improve, resulting in a reduced risk of fracture that is independent of the changes in bone mass. In our study, the section modulus, a measure of the ability of the distal radius to withstand bending forces, increased by about 30 percent during follow-up. If no periosteal apposition had occurred, the section modulus would instead have decreased by 5 percent because of the medullary expansion. This consideration is of clinical relevance, since bone mineral density, bone size, and the skeletal architecture all independently predict the risk of fracture.[8-11]

Our study suggests that women not only lose bone density after menopause but also have an increase in skeletal size as a result of periosteal apposition. There are at least two plausible reasons for periosteal apposition in postmenopausal women. The reduction in estrogen levels after menopause may result not only in the loss of bone mineral density, but also in periosteal apposition, since estrogen is known to inhibit periosteal bone formation, on the basis of data from experiments in rats.[26] Another possibility is that bone is lost on the endocortical surface, so mechanical stresses in the bone tissue are increased, thus stimulating periosteal bone formation.

It has previously been shown that a measurement

Table 2. Incidence of Distal-Radius Fractures during Follow-up.*

Variable	No. of Women with a Fracture	Rate of Fractures per 1000 Person-Yr
Bone mineral density		
Quartile 1	4	8.3
Quartile 2	4	7.7
Quartile 3	5	11.3
Quartile 4	0	0
Section modulus		
Quartile 1	8	18.3
Quartile 2	3	6.7
Quartile 3	1	1.9
Quartile 4	1	1.9
Strength index		
Quartile 1	8	18.4
Quartile 2	3	6.2
Quartile 3	1	1.9
Quartile 4	1	1.9

* Quartile 1 had the lowest values for the particular measure, and quartile 4 had the highest values. The section modulus is an estimation of the ability of the distal radius to withstand bending forces and was calculated as the cross-sectional moment of inertia divided by half the periosteal diameter. The strength index, which takes both the bone mass and the structural appearance into account, was calculated as the product of the section modulus and the bone mineral apparent density. There were 27 women in each quartile for each variable. Because the time to fracture and the follow-up time were variable, the total number of person-years varied among quartiles.

of bone mineral density is the best predictor of the risk of fracture at the measured site.[27] It is probable that geometric estimates of the risk of fracture are also site-specific. For this reason, we included only fractures of the distal radius in our analysis. Since both bone mass and bone size are independently associated with fractures due to fragility[8-11] and since both traits contribute to bone strength, we combined the tissue-level strength, expressed as the bone mineral apparent density, with the skeleton's resistance to bending and torsion, expressed as the section modulus, into a strength index. The relative decrease in the strength index with age was smaller than the relative decrease in bone mineral density. The strength index was significantly lower 14 years after menopause, corresponding to the period when the incidence of fractures of the distal radius in women increases exponentially.[28] The strength index may be a clinically important tool for the prediction of fractures. The predictive value of the strength index was, in absolute terms, more than double that of the bone mineral density; however, because of the small sample of women with fractures in our study, we cannot be sure that the strength index is a better predictor than bone mineral density of the risk of fragility-related fractures of the distal radius.

Our study has several advantages. The subjects were from a well-defined population of white women, were all 48 years old at base line, and were living in the same city. The system for the ascertainment of fractures included virtually all fractures, allowing us to define the type and cause of the fracture. The estimated date of the onset of menopause was accurate, and the women had a high rate of clinic attendance and had neither conditions nor treatments that were known to interfere with the normal skeletal metabolism. Furthermore, the measurements obtained by single-photon absorptiometry and all the analyses were performed by one technician using one densitometer. A similar study could not be conducted today, since bisphosphonates and selective estrogen-receptor modulators are now used for the prevention of osteoporosis.[29-31] In addition, given that the intrapersonal variation in bone shape is known to be large,[13,14] a longitudinal study design is preferable in studies involving geometric variables. Contradictory observations in previous studies may be the result of secular effects, since these studies were cross-sectional and different measuring techniques were used.[5,6,13-15]

The limitations of our study are the small number of observed fractures and the use of single-photon absorptiometry, which is now an outdated technique. A technique for three-dimensional measurement such as computed tomography would have made it possible to obtain geometric measurements at the ultradistal radius as well as at the distal radius, which might have improved the predictive value of a strength index, since the ultradistal radius includes mainly trabecular bone and is often the site of the fracture. After menopause, the distal radius undergoes endosteal resorption and periosteal apposition, which partially preserves bone strength.

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