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Evolution of Spinal Bone Loss and Biochemical Markers of Bone Remodeling After Menopause in Normal Women

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Abstract. The main objective of this study was to describe longitudinal patterns of spinal bone loss in normal women who undergo a natural menopause. The second objective was to determine if a proportion of women suffer excessively rapid postmenopausal bone loss from the spine. If this was the case it was the aim to devise a means of predicting the woman at excess risk; but if all women lost bone at similar rates, the aim was to document changing loss rates over the first 5–8 postmenopausal years. Responding women in six suburban general practices recalled for cervical smears who had their last menstrual period 9–36 months previously were invited to participate in a longitudinal study of bone loss and the biochemical markers plasma osteocalcin and urinary hydroxyproline. Sixty-four subjects agreed to participate, a response rate of 80%. In the ensuing 5 years, six received hormone replacement therapy and are not reported on. The main outcome measures were rates of spinal bone loss over 5 years, measured by dual photon absorptiometry, and radial bone loss over the first 2 years measured to quantitative computed tomography. Spinal bone loss was similar between individuals, with 94% of the variability in the data being accounted for by a statistical model that assumed parallel rates of bone loss. A less restrictive model allowing women to have different rates of spinal bone loss accounted for 12% more of the remaining variance in the data than the previous model. However, rates of radial bone loss were more dissimilar between women than rates of spinal loss. The results of the biochemical data collected serially showed that the plasma osteocalcin rose slowly to a plateau at 5 years postmenopause; in contrast, the hydroxyproline fell progressively with time over the whole period of study. These results were interpreted as being consistent with diminishing rates of bone destruction which gradually reequilibrated with bone formation as time passed after menopause.

Key words: Menopause — Bone loss — Osteoporosis — Bone densitometry — Biochemical markers.

Two decades or more after menopause, bone mass is an important risk factor for osteoporotic fractures [1–5]. This is particularly true of vertebral [1] and hip [5] fractures where for each decline of one standard deviation in bone mass there is a 1.5–2.6 fold increase in susceptibility to future fracture [1–5].

Before the menopause, normal women have a range of measured bone mass indices in the spine and hip which covers a range of about ±20% (2 SDs) of the normal mean. It has been suggested that peak bone mass may be the most easily identified determinant of the susceptibility to future fractures. Early menopause is also a significant risk factor for fragility fractures under the age of 70 [6]. This has suggested that postmenopausal bone loss could contribute substantially to fracture risk and might account for differences in fracture rates between men and women. Hansen et al. [7] showed in a 12-year longitudinal study that women have different rates of radial bone loss in the forearm in the early postmenopause, suggesting that the fast bone loser could be significantly more vulnerable than the slow loser whose initial density value was identical [7]. They suggested that fast bone losers could be identified by means of biochemical markers [7, 8].

There have been many cross-sectional studies of bone density measurements in populations, some of substantial size [9–12], but for the purpose of establishing rates of bone loss, cross-sectional studies are vulnerable to cohort effects (e.g., different life-styles between generations affecting bone mass). Also, differences in loss rates between individuals cannot be studied by this approach. In addition to that of Hansen et al. [7], there has been a moderate number of longitudinal studies of peripheral bone loss rates in individuals such as those of Ross et al. [13] and Hui et al. [14]. The former showed that estimates of rates of change in bone mass are strongly dependent on study duration whereas Hui's study showed that bone loss rates could change in either direction with time and there was a weak positive relationship between rate of bone loss and initial bone mass. The important study of Falch and Sandvik [15] found that forearm bone loss in the individual was closely linked to the cessation of menses.

A key question is that of study length. Ross et al. [13] found that follow-up duration affected the apparent normal range for individual loss rates for up to 4 years after the start of measurements. No data of equivalent duration have been published with respect to bone loss rates from the spine, although two large studies, those of Harris and Dawson-Hughes [16] and Pouilles et al. [17], have followed axial skel-

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etal bone loss in postmenopausal women for 2 years. In the mid-1980s we began a prospective study to descriptively examine changes in bone mass in the lumbar vertebrae and radii of normal women in the immediate postmenopause, together with biochemical markers of bone remodeling [18]. The results of our first 5 years of observations are presented here.

Subjects and Methods

As part of a campaign in early 1984 to enhance protection against cervical cancer, all women between the ages of 45 and 55 who were overdue for a routine 3-year cervical smear examination were recalled in six local National Health Service General (Family) Practices, covering a total population of some 45,000 patients. All those women who answered were asked about the date of their last menstrual period, and those who were in good general health, as determined from their medical records, and were between 9 and 36 months of their last menstrual period were assessed by additional cytology of their vaginal cells [19]. All those showing parabasal cells, which are a marker of diminished ovarian hormone stimulation, and a random 50% of those not showing parabasal cells were invited to join the study of postmenopausal bone loss. Sixty-four accepted, giving an 80% response rate. Over the ensuing 5 years, 58 did not receive hormone replacement therapy at any stage. None had cervical cancer. The daily calcium intakes of these women were comparatively stable and ranged from 466 to 1882 mg/day (median 916) [20]. At the conclusion of these measurements, the subjects were an average age of 57.0 years (SD 2.4, median 57.4, range 49.3–60.5).

Bone Densitometry

Six-monthly measurements of the lumbar spine over the first 2 years with further measurements at 3.5 years and in the majority of women at 5 years were made using the Novo BMC Lab 22[a] dual photon absorptiometer (DPA) [21]. Five-year measurements on 15 of the patients were made using a Hologic QDR-1000 which replaced the Novo BMC Lab 22a [22]. Prior to this change, paired measurements on the Novo and QDR had been made on each of these patients so that individual conversion factors could be used to convert QDR bone mineral density (BMD) values into DPA BMD values.

Spine density data from the Novo and Hologic densitometers were expressed in g/cm^2. At the time of transfer from the Novo to the Hologic, individual conversion factors were calculated from the ratios of the paired measurements to allow in individual's Hologic data as well as her Novo data to be expressed in g/cm^2 (Novo units). For the purposes of the present paper, this was necessary only for the data from the last 15 of the 58 patients whose 5-year data were collected on the Hologic machine alone.

For the first 2 years of the study, measurements were also made on the midshaft of the radius by quantitative computed tomography (QCT), using a special-purpose tomographic densitometer employing an ^{125}I source [23]. At the same times as DPA measurements were made, trabecular bone density in the distal radius (8% from the ulnar styloid) and radial midshaft bone mineral content (33% site) were assessed using the peripheral QCT equipment. The trabecular bone density (TBD), adjusted to exclude a soft tissue component, was obtained from the linear attenuation coefficient of the central 50% of the bone cross-section using the following conversion equation [24]:

$$\text{TBD (g.cm}^{-3}) = \rho\text{CB}\,\frac{\text{TBD (unadjusted)} - \mu\text{M}}{\mu\text{CB} - \mu\text{M}}$$

where ρCB is the physical density of cortical bone (2.00 g.cm^{-3}) and μCB and μM are the mean linear attenuation coefficients of cortical loss and yellow marrow, respectively, at the mean energy of the photons emitted by the ^{125}I source. This equipment became terminally nonfunctional after the 2-year measurements because of a failure of computer disc-writing hardware which could not be replaced as its manufacturer had gone out of business.

Analysis of Densitometry

The bone density data were plotted against time and fitted by means of linear regression analysis. Because in some previous studies rates of bone loss were found to be related to initial bone mass and also because equipment manufacturers routinely present data on bone loss as a percentage of initial values, bone density values were log-transformed before analysis. However, to see the effect of this transformation, the data were also analyzed untransformed. To allow for the differences in initial bone density values between individuals, covariance analysis was applied. Tests were then applied to see if the data were better fitted by allowing individual rates of bone loss to differ. A further analysis was performed in which bone loss was allowed to be curvilinear. This was achieved by fitting the data to the two independent variables, time and time squared. Again, a test was performed to see if the data were better fitted by allowing the individual patients to have different rates of bone loss as well as different initial bone density starting values.

The precision of the estimate of the rate of bone loss was obtained by calculating the 95% confidence interval for the rate of loss. Whenever models with individual rates of loss were fitted, the 95% confidence interval was based on the average of the standard errors for the individual rates of loss.

Predictions of spinal bone density values at the end of the study were compared in a Receiver Operator Characteristics (ROC) analysis.

The conversion of Hologic-acquired data to Novo-equivalent units, though individualized, was considered as a possible source of bias as the software for the two systems differ substantially. Therefore, to check that bias was not introduced, the 43 subjects measured only on the Novo were analyzed as a subgroup and the differences with the whole group analyses were explored statistically.

Plasma and Urine Biochemistry

Serum osteocalcin (Incstar (UK) Ltd, Wokingham, UK) was measured at yearly intervals for 2 years, then at each densitometry visit. Urine was collected at 6-month intervals after 24 hours of a gel-free diet for the first 2 years and then again at 3.5 and 5 years postrecruitment. Urinary hydroxyproline [25] was measured in a fasting early morning urine specimen after discarding the first voiding of the morning. The ratio of hydroxyproline to creatinine was calculated. Changes in the biochemical data were examined by the same statistical regression techniques as those employed with the spinal bone densitometry data. The osteocalcin [26] and hydroxyproline [25] assays, as performed in our laboratory, were previously compared with reference methods for measuring whole body bone formation and bone resorption using ^{85}Sr as a tracer for calcium and making corrections for long-term exchange of radio-tracer. A single measurement of osteocalcin predicted bone formation with a coefficient of variation of ±30% (equivalent to a bone formation rate of 1 mmol calcium/day, n = 58 [26]) and hydroxyproline predicted bone resorption with a similar coefficient of variation when measured repeatedly and averaged [25, 26]. However, the coefficient of variation of the mean of 18 successive hydroxyproline estimations was 5% compared with an estimated 21% for a single estimation at an excretion rate typical for a normal postmenopausal woman [25], so the predicted coefficient of variation in estimating bone resorption from a single hydroxyproline estimation in the present study was 36% of a typical subject's average value in the population studied, equivalent to 1.2 mmol/day.

Results

Comparison of Subject Groups

A comparison was made between the groups with normal premenopausal vaginal cell histology at baseline and those showing parabasal cells. The two groups had very similar

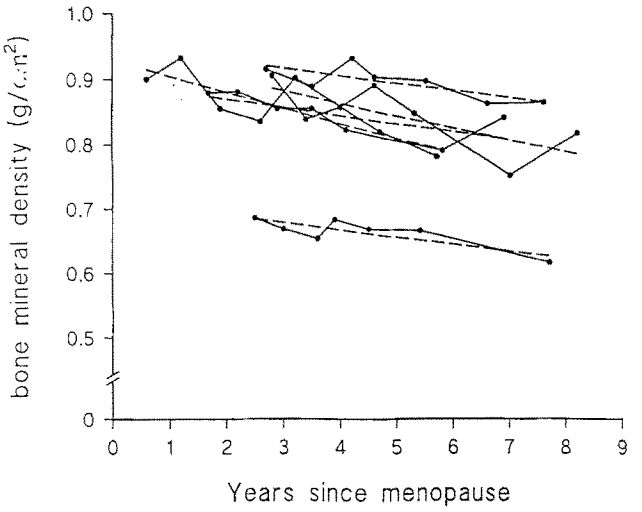

Fig. 1. Spinal bone density results from five women typically showing bone loss with the passage of time after menopause. Solid lines connect individual measured values. Dashed lines show individual linear regressions against time obtained after logarithmic transformation of the data.

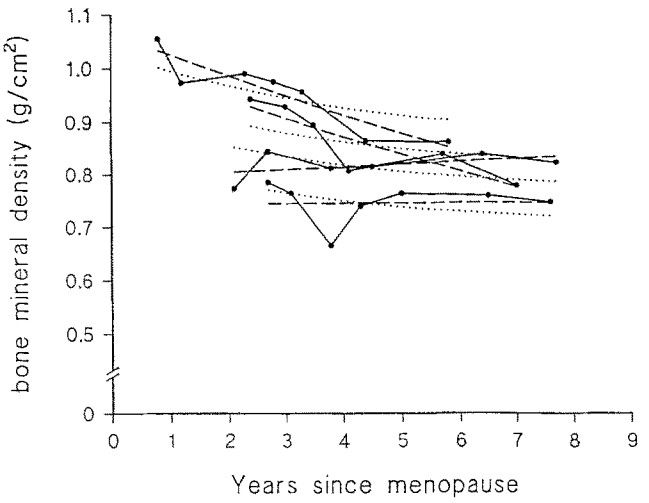

Fig. 2. Spinal bone density results from two women showing high and two women showing low rates of loss, who were at the extremes of the distribution of loss rates in the individual loss rated model. Dashed and solid lines as for Figure 1. The dotted lines show the fits to these data of the parallel loss rate model.

initial values for BMC of the lumbar spine, 0.872 and 0.861 ($P = 0.75$) g/cm^2, respectively. Over the following 5 years, both groups lost spinal bone similarly: when analyzed by the log-linear individual loss rate model, the two groups lost at mean rates of 1.54 and 1.76% per annum respectively ($P = 0.69$). Therefore, the data from both vaginal cytology groups were combined in the analyses described below.

Bone Loss from the Spine and Radius

In comparing the models using, respectively, the bone density data with and without log transformation, the percentages of the variances explained by the equivalent models was in each case remarkably similar, being within 1% of each other. The results of the models using the log-transformed data are described below.

The best statistical model for the changes in spinal BMD (g/cm^2) allowed the logarithm of BMD to change linearly with time at a rate that was different for each individual woman (Fig. 1). This accounted for 95% of the variance in the data. The mean rate of loss was 1.6% annually (95% confidence interval (CI) for the individual −0.1 to 3.2% lost annually). However, a model that was curvilinear with the log of BMD declining in each woman at the same diminishing rate as time passed after menopause provided almost as good a fit (94% of variance accounted for). This model made the assumption that there were no differences between women in their tendency to lose spinal bone after menopause. The curved fit to the data gave different rates of loss with time since menopause. At 1 year, loss was calculated to be 2.9% annually (95% CI for an individual woman 1.9 to 3.9%). At 6 years, annual loss was 1.0% (95% CI—from a gain of 0.9 to a loss of 2.9% annually for an individual woman). These models were both significantly better than a model assuming constant rates of loss which were the same in each woman ($P < 0.001$ for both).

The slightly better fit achieved by the individual loss rates model was attributable to better fits obtained in subjects at the extremes of the apparent distribution of loss rates (Fig. 2).

When the 43 subjects with data derived only from the Novo were analyzed separately, the results were essentially not changed in a way that was statistically significant. The two models (parallel loss rates and individual loss rates) accounted for 1% less of the variance in the data than the whole group analyses in both cases, and analyses of variance showed no significant differences in fit ($P > 0.7$ and 0.9, respectively). With the parallel loss rate model it was still necessary to add a term in (years since menopause)^2 ($P < 0.003$).

The forearm measurements obtained at the beginning of the study were analyzed similarly. In comparison with a parallel, constant loss rate model for radial trabecular bone, the individual loss rate model gave a significantly better fit to the data ($P < 0.001$). Figure 3 shows the calculated distributions of loss rates at the trabecular sites in the radius; the mean loss rate was 4.7% p.a. (95% CI −0.5 to 9.6% p.a. for the individual). Though it was possible that variations between yellow marrow composition in individuals could have affected this analysis, this is not such a serious concern in forearm as it is in spinal densitometry in adults as red marrow is never found in the distal radius. The data for cortical bone were best fitted by a parallel loss rate model (mean loss = 0.6% p.a.; 95% CI, 0.1 to 1.6%). These fits accounted for 98% and 95% of the variance in the data for distal trabecular and midshaft cortical bone, respectively.

Biochemical Markers of Bone Formation and Resorption

Both the hydroxyproline:creatinine data and the osteocalcin data differed significantly between individuals and were statistically strongly dependent on time since menopause ($P < 0.001$ for both markers). The hydroxyproline:creatinine ratio data were fitted on a linear scale by individual, parallel rates of decline with 42% of the variance accounted for overall, leaving a residual SD of 7.6 μmol/mmol creatinine. The fit to the data suggested that over 5 years hydroxyproline excretion reduced on average by 7.7 μmol/mmol urinary creatinine (95% CI 5.2 to 10.2) from an average value at 1 year postmenopause of 25.5 (range 15.3 to 39.5) μmol/mmol. In

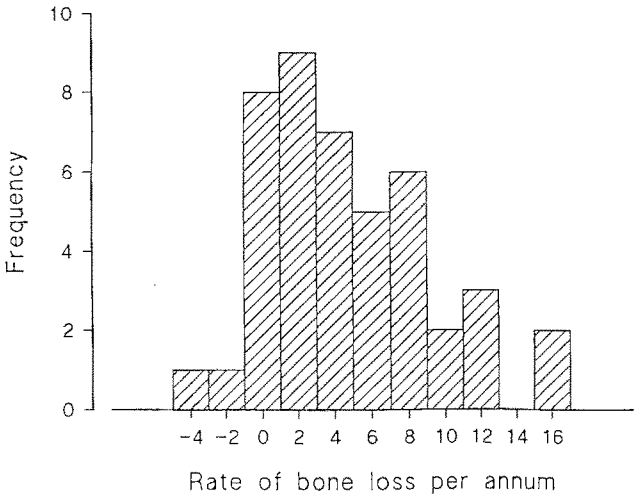

Fig. 3. Distribution of loss rates from the trabecular (cancellous) bone of the distal radius expressed as a histogram.

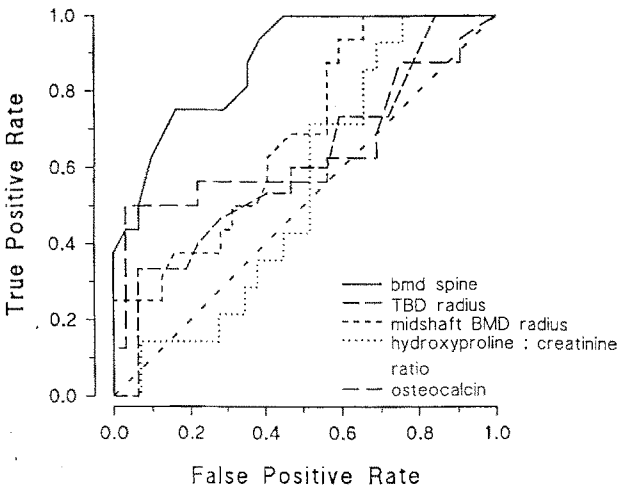

Fig. 4. Received operator characteristic (ROC) analysis of the power of five indices measured at baseline to predict low bone mass in the spine 5 years later. The nearer the individual curve rises vertically to 1.0 from the origin, the more accurate the prediction.

contrast, the plasma osteocalcin data were best fitted by a quadratic regression model indicating a rise from a mean of 2.84 ng/ml 1 year after menopause, by 0.5 ng/ml over the ensuing 12 months. The rise appeared then to taper off, reaching a mean peak of 4.13 ng/ml at 5 years postmenopause and was followed by a small fall of 0.05 ng/ml between years 5 and 6. There was also considerable variation between individuals with this model, accounting for 48% of the variance in the data (residual SD 1.04 ng/ml). Likewise, the 95% CI for the year-on-year changes in osteocalcin were wide: from −0.16 to +1.29 ng/ml over years 1–2 and from −0.75 to + 0.64 for years 5–6. Assumptions regarding interindividual normality and equality of variances were fulfilled for osteocalcin, but for hydroxyproline the variances were unequal, consistent with greater fluctuations in excretion rate in some women than in others. If no account was taken of changes in hydroxyproline and osteocalcin with time after menopause, differences between individual mean values accounted for only 34% and 40% of the variance in the data, respectively.

Predicting Spinal Bone Mass at the End of the Sixth Decade

When the initial and 5-year spinal bone density data were grouped in tertiles, there was a high sensitivity and specificity of the baseline spinal bone density data for the 5-year results (75% and 84%, respectively), giving a positive predictive value of 71%. Other potential predictors of low spinal bone mass at the 5-year measurement were compared with baseline spinal bone mass in a ROC analysis (Fig. 4) but none was comparable in predictive power to the initial bone density measurement, which subtended an area equal to 74% of the maximum possible.

Discussion

There have been few published observations in which longitudinal studies of loss of both axial and peripheral bone in normal women after a natural menopause followed for as long as 5 years, and none as far as we are aware that have been combined with serial measurements of biochemical markers over the same period. The results demonstrate that in healthy women, after a natural menopause, individual spinal bone loss rates are sufficiently similar that we found it difficult to discriminate with our equipment between loss rates in individuals. The practical usefulness of determining individual bone loss rates, as a public health measure, in an unselected population of women in the early menopause [e.g., by repeated dual x-ray absorptiometry (DXA) measurement], therefore remains uncertain. In determining bone density just before the seventh decade, the starting value immediately after menopause, when combined with the length of time that has elapsed since menopause, was of far greater statistical importance than the individual rate of loss. Though these spine data have not generally shown substantial differences in rates of bone loss between individuals, a contrast has been established with the forearm data of ourselves and others in which rates vary between individuals [5, 7, 8, 27]

Extending these data with further measurements may answer definitively whether the model in which rates of spinal bone loss are constant over time but vary between individuals is realistic. Pouilles et al. [17] have recently shown, in a large DPA study of 2 years' duration, that compared with women who passed through the menopause up to 3 years beforehand, women whose menopause had been experienced earlier showed progressively slower rates of spinal bone loss. The interpretation by Pouilles et al. of their own data is more consistent with our parallel loss rate model, with declining rates of loss as time elapses after menopause.

As is inevitable wtih most longitudinal studies, technical advances occurred during this study's progress. We began the study with what is now outmoded equipment, giving what now seems only a modest precision of a single spine measurement—about 3.2% of the measured value (equivalent to about 0.03 $g.cm^{-2}$), which is nearly three times higher than the precisions usually quoted for all types of DXA equipment. Nevertheless, due to the number and spacing of measurements, the precision of estimation of loss rates for an individual over the 5 years of the study was more satisfactory giving a standard deviation for an individual loss rate equivalent to 1% of the initial value/year (about 0.01

$g.cm^{-2}$ $year^{-1}$). The cross-calibration procedure from the Novo DPA to the Hologic DXA machine was made necessary by the obsolescence of the former as well as the high cost of replacing its source of radioactivity for measurements on the last 15 women recruited. The assumptions required to accept this cross-calibration are modest and statistical analyses performed to test these assumptions suggest that they did not materially affect the results. These assumptions are that both machines behave linearly with respect to bone density changes (in g/cm^2) and that the plot of bone density (apparent) versus bone density (true) should pass through the origin for each woman, as has routinely been claimed by all commercial manufacturers of DPA and DXA equipment. These considerations suggest that the study was capable of detecting a distribution of loss rate such as that reported for the forearm by Christiansen et al. [8].

One possible reason why interindividual variability in rates of loss should be relatively hard to detect in our 5-year spine data but was more evident in our forearm data, is that the variability in averaged rates of loss declines with the length of the period of observation, as noted for peripheral bone data by Hui et al. [14] and He et al. [28]. QCT, which allowed a complete separation of cortical and trabecular bone (whereas single photon absorptiometry [7, 8] does not) has allowed us to pinpoint the source of forearm interindividual variability to the cancellous bone of the distal forearm. However, He et al. [28] have questioned the long-term importance of rapid bone loss measured over only 2 years for bone mass a decade or more later.

One possible cause of above average bone loss, a very low dietary calcium intake, was not examined in our study in which the lowest intake was 466 mg/day [20]. Dawson-Hughes et al. [29] have shown that women later in the menopause on very low intakes respond to calcium supplements by conserving bone.

The biochemical data provide the first longitudinal description over 5 years of the evolution of two important markers of bone formation and resorption after a natural menopause. Stepan et al. [30] showed that after a surgical menopause, urinary hydroxyproline excretion approximately doubled. Stepan et al. [30] also found that urinary hydroxyproline excretion rates and presumably bone resorption rates decline with time after a surgical menopause, and our results confirm this for a natural menopause. In contrast, the plasma osteocalcin, which has been identified as a statistical risk factor for low bone mass in older subjects [31], increased slowly to a peak at 5 years or later.

In previous work we have shown that a single measurement of osteocalcin, using this assay, predicts radioisotopic measured bone formation with an SE of 1.0 mmol/day after correction for long-term exchange [26]. The purpose of following changes in biochemical indices in this study was to interpret them in relation to bone remodeling. Therefore, it is appropriate to consider the derived precision of estimating bone formation and resorption in different individuals when interpreting our results. For unknown reasons, both for hydroxyproline and osteocalcin, these precisions were equivalent to CVs that were about double the interassay coefficients of variation, perhaps because both measurements reflect other processes besides bone formation and bone resorption. That only about 50% of the variability in the biochemical data was fitted by the two best statistical models is not surprising in view of the rather high levels of imprecision these assays have for estimating the processes of interest, when measured on only a single occasion. Nevertheless, in view of previous evidence that osteocalcin correlates with bone formation measured histologically [32], the evidence suggests that after a period of disequilibrium immediately after menopause, reequilibration of bone remodeling occurs through a gradual increase in bone formation as well as a gradual fall in bone resorption.

These women had not yet passed their 61st birthdays and therefore were younger than most subjects in previously published prospective studies that have associated bone mass measurements with insufficiency fractures [1–5, 31]. Nevertheless, if present trends continue and are unconfounded by the development of osteoarthritis [12], it is clear that a spinal measurement made near the menopause will be a good predictor of bone mass at later times when the population risk of fracture has increased substantially and bone mass measurements are known to predict fracture [1–5]. To allow us to interpret future data that might be affected by newly developing arthritis, we performed QCT of the trabecular bone of the lumbar spine at 3½ years and this will be repeated 5 or more years later.

If patients with spinal osteoporosis form a subgroup with accelerated bone loss before fracture, this study has failed to convincingly identify such a subgroup. Eastell [33], in a recent review, has concluded that the evidence for the existence of a substantial subgroup with fast bone loss after menopause is unconvincing. Other studies, such as those by Hansen et al. [7] and Mole et al. [34,35], which showed variations in loss rates between subjects, could have been affected by differences in menopausal age at recruitment. An alternative hypothesis for the development of clinical osteoporosis is that low premenopausal bone mass is a prerequisite for the development of nontraumatic spinal fractures. To examine the full spectrum of patterns by which women develop spinal osteoporosis will require longitudinal studies of considerably greater power than the present one.

Alone among the measurements performed, spinal bone densitometry after menopause proved useful for identifying the woman who will have low spinal bone mass as she approaches her seventh decade. These results are also useful in establishing the range of loss rates within which new studies, employing more precise techniques such as DXA, should seek to establish individual or collective rates of bone loss at different times after menopause. Further longitudinal studies are justified to resolve the question of whether bone densitometry could usefully contribute to the assessment of future risk in the individual, or whether resources would be more effectively directed to a population-based approach to the reduction of risk [36, 37]. It is possible that our future results will identify a large subgroup who develop rapid bone loss beginning more than 5 years after menopause. If this proves not to be so, spinal bone densitometry undertaken at menopause may prove useful in population screening aimed at identifying the woman at future risk of a spinal fragility fracture. An alternative possibility is that extremely rapid spinal bone loss leading eventually to multiple fractures of the spine occurs in a rather small subgroup not represented in our study, in which case identifying the at risk woman prior to fracture could be a suitable objective for potentially cheaper technologies such as biochemical screening.

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