Osteoporosis Int (1996) 6:320–324

Osteoporosis International

Original Article

Variability of Vertebral and Femoral Postmenopausal Bone Loss: A Longitudinal Study

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Abstract. The rate of postmenopausal bone loss varies considerably between individuals and it has been suggested that about 1 in 3 women loses significant amount of bone mineral in the forearm. The rate of vertebral and femoral bone loss was determined by dual-energy X-ray absorptiometry throughout two consecutive 22-month periods, in 93 healthy women who had passed a natural menopause 6–60 months earlier. In all cases the bone changes were normally distributed, ranging from −6.9% to +2.8% per year in the spine and from −7% to +4.8% per year in the femur. No significant relationship was found between the two fractional rates of bone loss. When the women were stratified into three groups according to their individual rate of bone loss, we found that only 20%–47% retained their first classification during the second period of follow-up. In particular, less than 10% of the women showed a rapid rate of bone loss throughout the study. We conclude that spontaneous vertebral and femoral bone loss exhibit a great variability within the first postmenopausal years and that only a small minority of women sustain a fast rate of bone loss over several years. These results raise the question as to whether the evaluation of individual rates of bone loss at menopause might be useful in the identification of women at higher risk of osteoporosis.

Keywords: Menopause; Osteoporosis; Rate of bone loss

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Introduction

It is generally recognized that menopause induces a phase of accelerated bone loss which has been observed in virtually all parts of the skeleton. Several prospective studies have reported that the rate of postmenopausal bone loss varies considerably between individuals [1–4]. It has been suggested that a rapid rate of bone loss is observed in about 1 in 3 women within the early postmenopausal years, which has led to the characterization of a so-called 'fast losers' group [5]. This group, theoretically, should be at higher risk for developing osteoporosis, insofar as rapid bone loss is capable of continuing over several years. This issue is, however, still debated since there is some disagreement in the literature regarding the relationship between the rate of postmenopausal bone loss and the subsequent risk of osteoporosis. Hansen et al. [6] found a fair correlation between the rate of bone loss within the first 2 years of a longitudinal follow-up and that estimated 12 years later in the same group. Accordingly, at the end of the study, the women who had been classified as 'fast losers' had lost 10% more bone mineral and had experienced significantly more fractures than the rest of the group [7]. On the other hand, in an extended longitudinal study, Hui et al. [2] showed that the rate of bone loss was not stable after the menopause, thus making hazardous an identification of long-term 'fast losers'. From a practical point of view, it appears of particular interest to determine whether the rate of bone loss is likely to influence fracture risk. If so, it should emphasize the need for estimating the individual pattern of postmenopausal bone loss (through repeated bone mass measurements or biochemical markers) to screen women at higher risk for osteoporosis [8]. However, to date most of the data available have been limited to peripheral bone mass measurements.

We present here the results from a longitudinal study of vertebral and femoral bone loss in early postmenopausal women. We sought to determine whether a subgroup of fast bone losers could be identified at these particular skeletal sites and whether the rate of bone loss for each individual was stable over time.

Materials and Methods

Population

Ninety-three healthy Caucasian postmenopausal women, selected from those regularly attending our menopause clinic, were investigated. All these women gave their informed consent to undergo serial bone mass measurements. Normality was assessed through interview and after extensive physical and biochemical examination according to a procedure previously reported [9]. None of the women had a history of disease known to affect bone metabolism, took part in regular exercise, smoked, or had documented alcoholism. None of the women was taking or had taken estrogen replacement therapy or others drugs known to influence bone metabolism.

At the beginning of the study, the subjects were aged 43–63 years and had passed a natural menopause 6–60 months earlier. Menopause was defined as an amenorrhea of at least 6 months' duration and was confirmed by measurements of plasma 17β-estradiol concentrations below 20 pg/ml and plasma LH levels about 30 IU/l.

Bone Mass Measurements

Bone mineral density (BMD) of the lumbar spine (L2–4) was determined using dual-energy X-ray absorptiometry (DPX, Lunar, Madison, WI), following conventional procedures as previously described [10]. Additionally, 59 women also had a measurement of the right hip femoral neck (FN) BMD. The in vivo precision assessed in our laboratory has a long-term (1-year) coefficient of variation of 1% (0.010 g/cm^2) for L2–4 and 1.7% (0.018 g/cm^2) for FN [10].

All the women had three measurements over a mean time period of 42 ± 8 months. The mean interval between two measurements was 22 ± 6 months. The stability of the instrument over time was controlled by means of an aluminum standard (provided by the manufacturer) scanned regularly during the study period. All the scans were performed and analyzed by the same person with software version 1.3.

Statistical Methods

Statistical analyses were performed using the Statview 512 statistical package. Results were expressed as mean ± SD and comparisons between groups were performed by analysis of variance and Student's *t*-test for paired data. For each subject, two fractional rates of bone loss were calculated for the two 22-months intervals of follow-up (a first rate between the first and second measurement and a second rate between the second and third measurement). All the results were normalized for a 1-year period and calculated in g/cm^2 and in percentage of baseline value. Since these two expressions were highly correlated ($r = 0.98$), we chose to compare the results in percentage per year for simplicity. The relationship between these pairs of rates was assessed by routine linear regression.

The study population was arbitrarily stratified into three groups according to the rate of bone loss. 'Fast losers' were defined by the first quartile of the distribution; 'intermediate losers' by the second and third quartiles; and 'slow losers' by the fourth quartile.

Results

The physical characteristics of the population are presented in Table 1. The women had a mean (±SD) age of 53 (±4) years with a mean (±SD) interval since menopause of 20 (±14) months. The annual rates of bone change in vertebral and femoral BMD during the two intervals of follow-up are shown in Fig. 1. In all cases, the histograms indicated a normal distribution. The annual rate of changes in vertebral BMD ranged from +2.6% to −6.9% (mean: −1.46%) within the first and from +2.8% to −5.3% (mean: −1.28%) within the second time interval. At the femoral level, it ranged from +4.8% to −6.8% (mean: −1.41%) within the first and from +1.8% to −7.0% (mean: −1.35%) within the second time interval. For all bone measurements, mean BMD values were significantly decreased at the end of the study (spine: 0.971 ± 0.11 g/cm^2 vs 1.016 ± 0.11 g/cm^2, $p<0.0001$; femoral neck: 0.808 ± 0.10 g/cm^2 vs 0.850 ± 0.10 g/cm^2, $p<0.0001$). No significant relationship was found between the fractional rates of bone loss calculated for the two time intervals (spine: $r = -0.18$, $p = 0.17$; femoral neck: $r = 0.04$, $p = 0.77$). A weak correlation ($r = 0.17$–0.20; $p<0.05$) was found between initial BMD and the subsequent rate of vertebral or femoral bone loss.

The women were then classified into three groups

Table 1. Main physical characteristics of the 93 women at the beginning of the study

	Mean ± SD	Range
Age (years)	53 ± 4	43– 63
Time since menopause (months)	20 ±14	6– 60
Weight (kg)	55.5± 6	42– 74
Height (cm)	160 ± 6	148–175
BMI (kg/m^2)	21.7± 2	18– 26

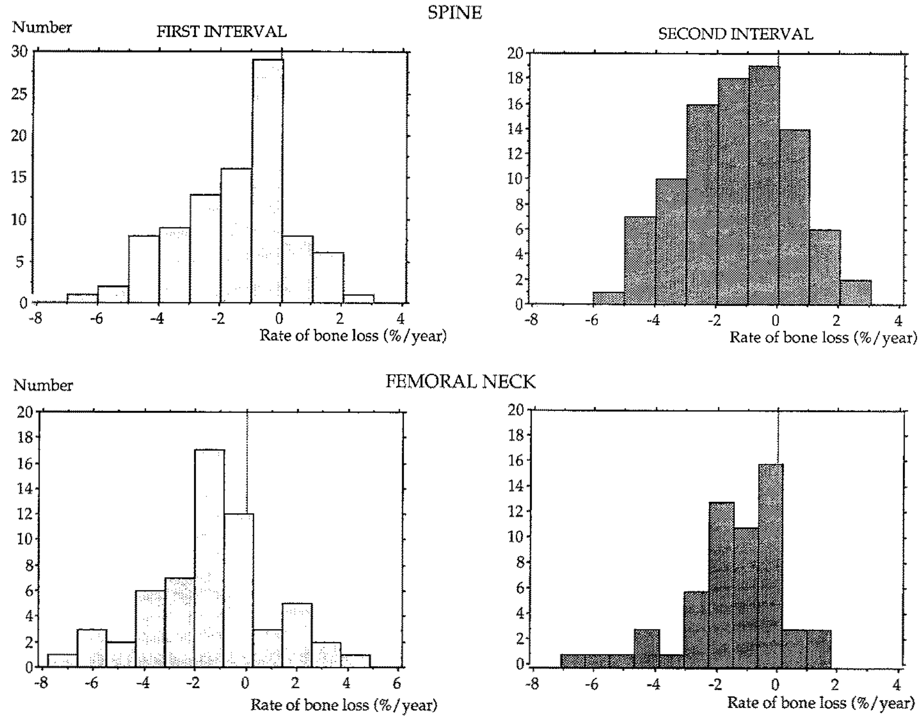

Fig. 1. Histograms of the rates of vertebral and femoral bone changes assessed in 93 early postmenopausal women during two consecutive 22-month periods.

Table 2. Cross-classification of the population according to their rate of spinal and femoral bone loss measured during two intervals of follow-up

(a) *Spine*

Second interval	First interval			
	Fast (−6.9 to −2.8%/yr)	Intermediate (−2.6 to −2%/yr)	Slow (0 to +2.6%/yr)	
Fast (−5.3 to −2.5%/yr)	5	13	7	n = 25
Intermediate (−2.2 to −0.2%/yr)	12	17	13	n = 42
Slow (0 to +2.8%/yr)	7	14	5	n = 26
	n = 24	*n* = 44	*n* = 25	

(b) *Femoral neck*[a]

Second interval	First interval			
	Fast (−6.8 to −3.1%/yr)	Intermediate (−2.9 to −0.4%/yr)	Slow (0 to +4.8%/yr)	
Fast (−7 to −2.1%/yr)	4	8	5	n = 17
Intermediate (−2 to −0.1%/yr)	7	12	8	n = 27
Slow (0 to +1.8%/yr)	3	6	6	n = 15
	n = 14	*n* = 26	*n* = 19	

[a] *n* = 59.

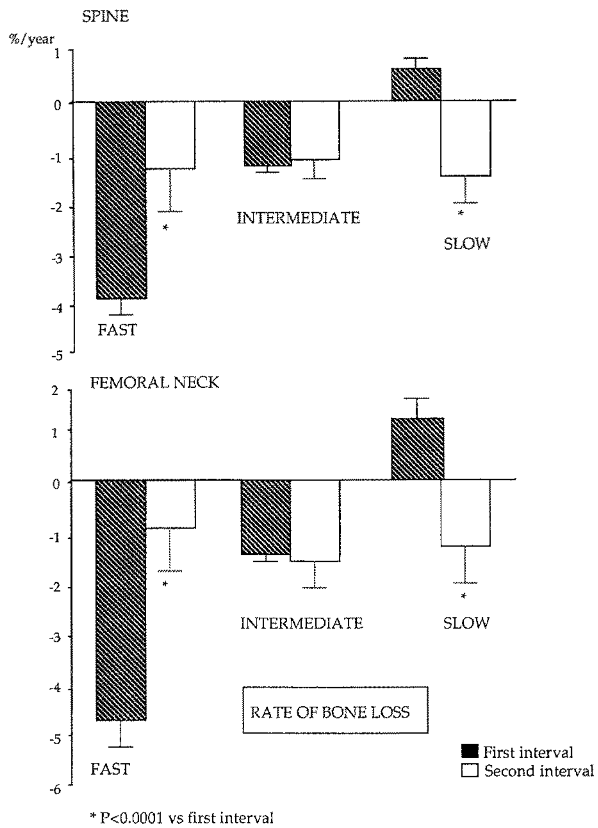

Fig. 2. Comparison of the rates of vertebral and femoral bone loss assessed during two consecutive intervals of 22 months in 93 early postmenopausal women stratified into three groups according to their individual rate of bone loss throughout the first interval (see Statistical Methods).

according to their first fractional rate of bone loss (see Statistical Methods) and cross-classified according to their rate of bone loss within the second interval of follow-up (Table 2). At the spine level, only 20%–30% of the women retained their classification throughout the study. Of the 24 women classified as 'fast losers' at the end of the first period of follow-up, 5 women remained 'fast losers', 12 had to be reclassified as 'intermediate losers' and 7 as 'slow losers' at the end of the second 22-month period of time. In this original subgroup of 'fast losers', the mean (± SD) annual rate of bone loss decreased significantly from −3.9% (±1%) to −1.3% (±1.8%), ($p<0.0001$) between the two time intervals (Fig. 2). On the other hand, an increase in the annual rate of bone loss during the second interval of follow-up was observed in the women who were originally classified as 'slow losers' (+0.63 ± 0.7% vs −1.49 ± 1.6%, $p<0.0001$). The same pattern of bone loss was seen at the femoral neck (Fig. 2) and only 28%–47% of the women retained their first classification (Table 2). When compared with the rest of the group, the women who exhibited an accelerated bone loss during the first period of follow-up were characterized by a slight but significantly shorter interval since menopause (spine: 12 vs 22 months, femur: 13 vs 22 months, $p<0.05$).

Discussion

In agreement with other studies using peripheral bone mass measurements [1–4], we found that the rate of both vertebral and femoral bone loss varies considerably between early postmenopausal women. This variability has been attributed either to physiological fluctuations in the rate of postmenopausal bone loss over time, or to technical reasons such as measurement errors [11]. The contribution of instrument precision decreases with increasing the follow-up duration [11]. In this study, bone mass measurements were performed using DXA with a precision ranging from 1% at the spine to 1.7% at the femur and the rates of bone loss were calculated within two periods of about 22 months each. In this regard, it seems likely that a part of the great variability observed in our study (especially in the femur) is related to the measurement error [12]. Moreover, the fact that the variability tended to decrease within the second interval of follow-up could be explained by the increasing time after menopause, as previously reported [9].

The bone changes were nearly symmetrically distributed for all measurements and we could not detect a subpopulation of fast losers. These results confirm previous findings showing a gaussian distribution in the rates of bone loss for spine, radius or calcaneus [2,4,13]. Furthermore, we found that the individual rate of bone loss was not stable over time. Most of the women originally classified as 'fast losers' tended to slow down their rate of bone loss at the second evaluation, whereas those originally classified as 'slow losers' increased it. Altogether, less than 10% of the population maintained a fast rate of vertebral or femoral bone loss over the duration of the follow-up. Conversely, 50%–70% of the women changed their first classification during the second interval of follow-up. Accordingly, we did not find any significant correlation between the two fractional rates of bone loss either at the spine or at the femur. Hui et al. [2] also showed that only a small number of early postmenopausal women (4/47) sustained a fast rate of bone loss at the midshaft radius over a 10-year follow-up. Furthermore, they did not find any significant correlation between the two fractional rates of bone loss measured at 5-year intervals, which is in agreement with our current findings [2]. On the other hand, Hansen et al. [6] reported a high correlation (r = 0.7) between the rate of bone loss measured within the first 2 years of their follow-up and that estimated 12 years later. Moreover, the 'fast losers' had still a higher bone turnover 12 years postmenopause than the women in the rest of the group. The reasons for such discrepancies are not clear. It is likely that a part of the correlation found in Hansen's study arises from an overlapping period of the two first years of the follow-up. Moreover, these studies differ in terms of methodology, measurement sites and/or study population. The duration follow-up was shorter than that in Hansen's study; we did not measure radial but vertebral and femoral bone mass; and finally our population was recruited following a different procedure. Therefore, we cannot completely eliminate the possibility that a (hypothetical) subgroup of women undergoing rapid and prolonged bone loss after menopause might have been underrepresented in our population. It can also be noted that the women in our group of 'fast losers' had a mean interval since menopause of about 10 months shorter than in the rest of the group, which is consistent with our previously published studies [9,14] where we have shown, in different populations, that the accelerated phase of vertebral or femoral bone loss was limited to the first years after menopause.

He et al. [11] have emphasized the strong dependence between the variability in the rate of bone loss and the length of follow-up. They showed that the more extreme rates of bone mass changes observed over a short period of time were not sustained over a longer period of time. These results agree with the hypothesis of a self-regulation in the rate of bone loss according to the initial level of bone mass as suggested by Smith et al. [15], 20 years ago. Several longitudinal studies including ours [2,9,16,17], have reported a weak negative correlation between initial bone mass and the rate of bone loss (the higher the bone mass, the greater the bone loss). This would explain why the variance in BMD values in the population does not increase with aging in spite of different rates of bone loss [2,16,18]. However, in our study, we cannot fully eliminate the possibility that the dependence of the rate of bone loss on initial value may represent regression toward the mean as already discussed by others groups [3,16]. Finally, this true biological variability in long-term rates of bone loss is probably influenced by other factors besides the absolute amount of bone mass, such as body weight, diet or physical activity, which are likely to vary over time [19].

In summary, we found that only a small minority of early postmenopausal women sustained a fast rate of vertebral and femoral bone loss over several years. Those results raise the question as to whether the evaluation of individual rate of bone loss at menopause might be useful in the identification of women at higher risk of osteoporosis. Further longitudinal studies are thus still needed to address the issue of long-term variability in the individual rate of postmenopausal bone loss and its relative contribution to the subsequent risk of fracture.

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Received for publication 4 January 1996
Accepted in revised form 22 April 1996