

Changes in forearm bone mass and bone size after menopause – A mean 24-year prospective study

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Abstract

Objective: Bone loss and periosteal expansion is found after menopause. The accelerated early postmenopausal bone loss is not permanent but if the same accounts for the periosteal expansion is unknown. **Methods:** Bone mineral density (BMD) and skeletal structure of the distal forearm were followed from menopause and on average 24 years (range 18-28) by single-photon absorptiometry at 12 occasions in a population-based sample of 81 Caucasian women with no medication or disease affecting bone metabolism. A Strength Index based on areal BMD and bone structure was calculated. Postmenopausal serum-estradiol levels and incident distal radius fractures were registered. Data are presented as means with 95% confidence interval (95% CI). **Results:** The annual BMD loss in three periods, 0-8, 8-16 and 16-28 years after menopause, was 2.0% (1.6, 2.4), 1.0% (0.6, 1.4) and 1.0% (0.7, 1.3), respectively. The annual periosteal expansion was 1.0% (0.8, 1.3), 0.0% (-0.3, 0.3) and 0.0% (-0.2, 0.2), respectively. Mean post-menopausal oestrogen levels correlated moderately with annual loss in aBMD ($r=0.51$, $p<0.001$) but less with the annual changes in bone width ($r=-0.22$, $p=0.06$). **Conclusion:** Postmenopausal periosteal expansion in the distal forearm seems to occur only in the first postmenopausal decade.

Keywords: Bone Loss, Bone Mineral Density, Bone Size, Postmenopausal, Oestrogen

Introduction

Post-menopausal bone loss follows a pattern with an early oestrogen-dependent phase of rapid decline in bone mass followed by an age-related bone loss at a constant, slower rate throughout ageing^{1,2}. Our group has previously reported that the early post-menopausal bone loss is associated with an increased bone width in the forearm up to age 67³, and the same phenomenon is shown in the femoral neck, both in cross-sectional⁴⁻⁷ and longitudinal^{8,9} studies. The increase in bone size would in mechanical models partially preserve bone strength through increased resistance to bending forces. Small bone size

has also been independently associated with fractures in both the femoral neck¹⁰ and in vertebrae¹⁰⁻¹². In other words, both material qualities such as the tissue mineral content and strength properties such as the Young's modulus are of importance for the skeletal ability to resist a fracture during a fall¹³. Whether the periosteal expansion exists only in association with the oestrogen-dependent fast bone loss in the early postmenopausal period or continues also into higher ages when fragility fractures become a problem in magnitude is still unknown since most studies on changes in bone width are either cross-sectional⁴⁻⁶ or of too short follow-up^{3,7-9,14,15} for this particular question.

While it is well established that oestrogen suppresses bone resorption^{16,17} and bone turnover¹⁸, bone size in humans has not been shown to be affected by falling oestrogen levels, although the hormone-related post-menopausal bone loss is accompanied by periosteal expansion.

Several reports have forwarded that the skeletal response to external stimuli, such as mechanical load and changes in hormonal status, is most pronounced during periods with high bone turnover such as during growth¹⁹⁻²¹. The early postmenopausal phase is another period in life with accelerated bone turnover^{1,3}. Therefore, periosteal expansion could possi-

The authors have no conflict of interest.

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Edited by: F. Rauch
Accepted 28 September 2012

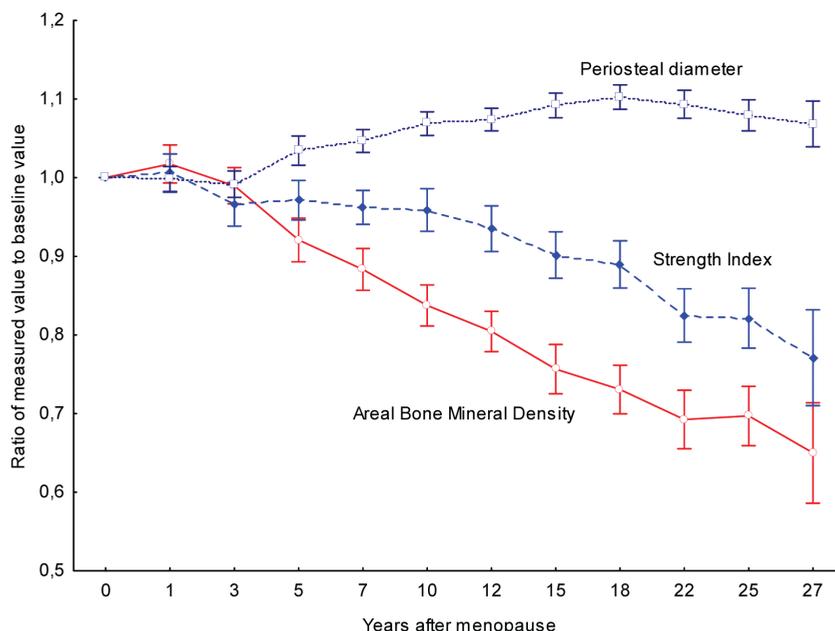


Figure 1. Mean relative changes in periosteal diameter, areal bone mineral density (aBMD) and Strength Index at the cortical site of the distal radius in 81 women followed from menopause and for a mean 24 years (range 18 to 28). In comparison with baseline values, aBMD became significantly lower 5 years after menopause, periosteal diameter significant wider 5 years after menopause while Strength Index did not become significantly lower until 12 years after menopause. Data are presented as means with standard errors.

bly be more pronounced in the early than in the remote postmenopausal period.

With this background, we extended our previous report³ for another decade with the following aims: (i) to evaluate if periosteal expansion is more pronounced in the early postmenopausal period with a fast loss in BMD than in a long-term perspective; (ii) to investigate whether the skeletal changes are primarily associated with the postmenopausal levels of oestrogen or the peri-menopausal decline in oestrogen levels; and (iii) as the study was not powered to include fracture as endpoint variable, report incident fractures in relation to quartiles of BMD and Strength Index only as descriptive data.

Methods

In 1977 we invited a population-based sample of 48-year-old Caucasian women ($n=241$) to participate in this prospective study that aimed to follow women who were non-menopausal at baseline^{1,22}. Forty-nine women were excluded at baseline because they were peri- or postmenopausal or had conditions or medications interfering with bone metabolism, leaving 192 women with cyclic menstrual bleedings eligible to enter at study start 1977-1978. During the first 5 years, 17 withdrew because of surgically induced menopause or relocation, 4 were omitted because of baseline technical measurement errors, 17 owing to menopausal oestrogen treatment and 8 died, resulting in 146 remaining women who were followed through their spontaneous menopause. BMD was measured on 12 occasions,

initially every second year and thereafter at intervals of 3 to 5 years. The average attendance rate was 11.4 (range 7-12) measurements. During the total 28-year follow-up period, another 22 died, 5 relocated, 7 received corticosteroids or anti-resorptive osteoporosis therapy, 29 declined participation for personal reasons or diseases and 7 had to be excluded due to technical measurement errors at the 12th and last measurement at age 76. In sum, 81 women were followed throughout the entire study period, constituting the cohort of this report. Since menopause occurred at different ages with an average menopausal age of 52 (range 48-57), the postmenopausal follow-up period was a mean 24 years (range 19-28).

Menopause was estimated according to the criteria established by the World Health Organization²³, i.e. permanent cessation of menstruation due to the loss of ovarian follicular activity. The onset of menopause was therefore determined retrospectively when 12 months of spontaneous amenorrhoea was reported, in conjunction with elevated serum levels of follicle-stimulating hormone. Follicle-stimulating hormone was analysed by double-antibody radioimmunoassay^{24,25} every three months during the first year, then every six months until one year after menopause, and then yearly. Serum level of estradiol was also determined after ether extraction every year until 8 years after menopause as described previously²⁴. As serum levels of estradiol in this cohort decreased during the first 3 postmenopausal years, but not after this²⁴, the postmenopausal estradiol level was defined as the mean value from 3 to 8 years postmenopausal. The duration of amenorrhoea and general

Variable	At menopause	At age 76 years	Annual changes during the entire study period	Annual changes 0-8 years after menopause	Annual changes 8-16 years after menopause	Annual changes 16-28 years after menopause
Bone structure						
Periosteal diameter (mm)	13.0 (12.8, 13.3)	14.3 (14.0, 14.5)	0.4% (0.4, 0.4)	1.0% (0.8, 1.3)	0.0% (-0.3, 0.3)	0.0% (-0.2, 0.2)
Medullary diameter (mm)	6.8 (6.5, 7.1)	7.7 (7.5, 8.0)	0.7% (0.6, 0.8)	1.2% (0.8, 1.6)	0.3% (-0.3, 0.9)	0.4% (-0.2, 1.1)
Cortical thickness (mm)	6.3 (6.1, 6.4)	6.6 (6.4, 6.7)	0.2% (0.1, 0.3)	1.0% (0.5, 1.4)	-0.3% (-0.8, 0.1)	-0.3% (-0.9, 0.2)
Bone mass						
Bone mineral content (mg/cm)	727 (709, 744)	521 (498, 545)	-1.1% (-1.2, -1.0)	-1.1% (-1.5, -0.8)	-1.1% (-1.5, -0.7)	-1.0% (-1.3, -0.8)
Areal bone mineral density (mg/cm ²)	558 (547, 570)	366 (350, 383)	-1.4% (-1.5, -1.3)	-2.0% (-2.4, -1.6)	-1.0% (-1.4, -0.6)	-1.0% (-1.3, -0.7)
Bone mineral apparent density (mg/cm ³)	758 (737, 778)	467 (446, 488)	-1.5% (-1.6, -1.4)	-2.7% (-3.3, -2.2)	-0.7% (-1.3, -0.2)	-0.7% (-1.1, -0.4)
Bone strength						
Cross-sectional moment of inertia	0.14 (0.13, 0.14)	0.19 (0.18, 0.21)	1.8% (1.6, 2.0)	4.7% (3.4, 6.0)	-0.1% (-1.6, 1.3)	0.2 (-1.4, 1.8)
Section modulus (cm ³)	0.20 (0.19, 0.21)	0.26 (0.25, 0.28)	1.3% (1.1, 1.4)	3.3% (2.4, 4.2)	-0.1% (-1.1, 0.9)	0.0 (-1.0, 1.1)
Strength index	152 (145, 159)	120 (115, 127)	-0.7% (-0.8, -0.6)	-0.2% (-0.6, 0.3)	-1.1% (-1.6, -0.6)	-1.0 (-1.4, -0.4)

Table 1. Skeletal structure, bone mass and bone strength at the cortical site of the distal radius in 81 women who were followed through their spontaneous menopause with repeated measurements with a mean postmenopausal follow-up period of 24 years (range 18–28). Data are presented as means with 95% confidence interval (95% CI) and at baseline (menopause) and follow-up (age 76 years) in absolute values and as annual changes in per cent in relation to the menopausal values.

health were reported through a questionnaire and personal interviews conducted by the department's research nurses.

Bone mineral content (BMC, g) and areal bone mineral density (aBMD, g/cm²) in the forearm were measured at a cortical site 6 cm proximal to the styloid process of the ulna every other year by single-photon absorptiometry (SPA), according to the method described by Nauc ler et al.^{1,3,26}. The tissue mineral content, expressed as the bone mineral apparent density (in milligrams per cubic centimetre), was calculated as the bone mineral content divided by the cortical area³. The radii and ulnae of both right and left forearm were scanned and one average value for all four bones was calculated for both aBMD and bone width. The same densitometer was used throughout the study, and no long-term drift was detected at measurements of a standardized phantom every other week^{1,3}. Since the radiation source was replaced in 1980, all measurements thereafter were adjusted with the use of the data from the phantom. The coefficient of variation of the bone mass measurements on single-photon absorptiometry was 1.7% with the standard phantom and 4% *in vivo* determined by repeated measurements after repositioning of the measured subjects. The co-efficient of variation for bone width was 1.6%, estimated by the phantom data²⁷. The cortical thickness calculated as the difference between the periosteal diameter (bone width) and the medullary diameters which were estimated from the graphical representations of the scan, has been found to have a coefficient of variation of 8%²⁶.

Two strict mechanical calculations, cross-sectional moment of inertia and the section modulus, and one Strength Index tak-

Variable	No. of women with distal radius fracture	Fracture rate per 1000 person-years
aBMD		
Quartile 1	4	7.4
Quartile 2	3	5.1
Quartile 3	4	8.0
Quartile 4	2	3.6
Strength Index		
Quartile 1	7	14.3
Quartile 2	2	3.6
Quartile 3	3	5.3
Quartile 4	1	1.7

Table 2. Number of women with distal radius fractures during the mean 30-year (range 25-34) follow-up period in relation to quartiles of areal bone mineral density (aBMD) and Strength Index at menopause. Quartile 1 represents the quartile with lowest values.

ing both bone tissue density and bone structure into account, were calculated as reported in our previous publication³. In mechanical terms, the section modulus represents the bone's resistance to static bending forces.

Distal radius fractures sustained after a fall from no higher than the standing position between menopause and 2011, a follow-up period of mean 30 years (25-34), were identified from patient questionnaires and the hospital archives and databases. In our city there is one hospital, so virtually all fracture patients

attend the emergency unit, and the classification system has been used in epidemiological studies for decades and is well validated, as reports have shown that less than 3% of fractures are missed^{28,29}.

At study start, no permission from the institutional review board and no consent form were required, but the women were informed and gave oral consent. Written permission was granted by the ethics committee of Lund University in 1999, when written informed consent was also obtained from each individual. The study has been conducted in accordance with the norms of the Helsinki Declaration. Statistical processing has been carried out using STATISTICA software version 7.1 (StatSoft). Data are presented as means with 95% confidence interval (95% CI). In order to compare changes in bone parameters during different phases of the postmenopausal period, the follow-up period was divided into three separate intervals, 0-8, 8-16 and 16-28 (mean follow-up 24) years after menopause. The last measurement before menopause, performed 0-2 years pre-menopause, was denoted as the baseline measurement. 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 baseline value. In Figure 1, the relative change represents the ratio of the observed value at each time point relative to each individual's baseline value. Student's *t*-test was used to determine at what point the specific measurements differed significantly from baseline. Linear regression equations were used to examine the association between decline in oestrogen from pre- to postmenopausal levels and the postmenopausal oestrogen levels with aBMD and periosteal and medullary changes. Incident distal radius fractures are only presented in relation to baseline quartiles of aBMD and Strength Index.

Results

Bone traits at menopause, at age 76, and annual changes during the total follow-up period and in the periods 0-8, 8-16 and 16-28 years after menopause are presented in Table 1 and Figure 1. In comparison with baseline, BMD became significantly lower 5 years after menopause, periosteal diameter significantly wider 5 years after menopause while the Strength Index only became significantly lower 12 years after menopause (Figure 1). The annual loss in aBMD during the periods 0-8 years, 8-16 years and 16-28 years after menopause was 2.0% (1.6, 2.4), 1.0% (0.6, 1.4) and 1.0% (0.7, 1.3), respectively, and the annual periosteal expansion 1.0% (0.8, 1.3), 0.0% (-0.3, 0.3) and 0.0% (-0.2, 0.2), respectively. As a result, the Strength Index was virtually unchanged during the period 0-8 years, with an annual decrease of 0.2% (-0.3, 0.6), after which there was a significant decrease in period 8-16 years by 1.1% (0.6, 1.6) and in period 16-28 years by 1.0% (0.4, 1.4) (Table 1).

Serum estradiol levels were stable around the mean value of 88.3 pmol/L (95% CI 82.8 to 93.8, SD 24.1) 3 to 8 years after menopause and correlated moderately in period 0-8 years with the annual change in aBMD ($r=0.51$, $p<0.001$) but to a

lesser degree with the periosteal diameter ($r=-0.22$, $p=0.06$) (Figure 2). There was no correlation between the decline from pre- to postmenopausal oestrogen levels and the annual change in periosteal diameter ($r=0.17$, $p=0.18$) and a weaker correlation with annual changes in aBMD ($r=-0.37$, $p<0.01$). There was no correlation between postmenopausal serum estradiol levels or the decline in oestrogen levels and annual change of medullary diameter.

Thirteen women sustained incident fragility-related fractures of the distal radius. Descriptive fracture data in relation to quartiles of baseline aBMD and Strength Index are presented in Table 2.

Discussion

We have previously reported that increased bone loss in the distal forearm following menopause is accompanied by periosteal expansion which partially preserves bone strength³. The present study suggests that the periosteal expansion in the distal forearm is an impermanent phenomenon, found only in the early postmenopausal period in conjunction with the previously reported accelerated postmenopausal bone loss^{1,3} and not in the higher ages when fragility fractures are more frequent. In other words, this structural adaptation of the skeleton could possibly counteract bone loss in the first decade following menopause but not in the remote post-menopausal period.

Changes in bone size have been seen in cross-sectional studies comparing differences between men and women or comparing cohorts stratified according to age, indicating a wider femoral neck⁷ and increased bone size in the tibia^{6,30} in older people. Also longitudinal data support periosteal expansion of the femoral neck with advancing age, as presented by Uusi-Rasi et al in prospective studies of up to 10 years duration^{8,9} where Hip Structure Analyses of DXA measurements⁷ of post-menopausal women was used. The forerunner of the current report presents the longest follow-up, as 112 women were followed with repeated SPA measurements from menopause up to age 67 and found a periosteal expansion of 10% of the distal forearm³. There are also contradictory prospective data as Szulc et al¹⁴ found lower periosteal apposition in the distal radius in post-menopausal than in pre-menopausal women in their seven-year study of 821 women aged 31-89 years. Also Uusi-Rasi et al found no periosteal expansion in the femoral neck in their 9-year prospective study¹⁵. However, the study by Ahlborg is the only one to have analyzed periosteal expansion across and on average 15 years after menopause in a homogeneous cohort, whereas other authors have described general changes in bone structure in post-menopausal women regardless of age, and not related to time passed since menopause. Consequently, when aggregating women from a wide span of ages and with varying number of years passed since menopause, the effects of a temporarily increased periosteal expansion in the early post-menopausal period may be obscured. Furthermore, the intrinsic difficulty of detecting subtle dimensional changes in three-dimensional bones must not be underestimated. All bone measurements methods available today are afflicted with limitations as regards image quality and

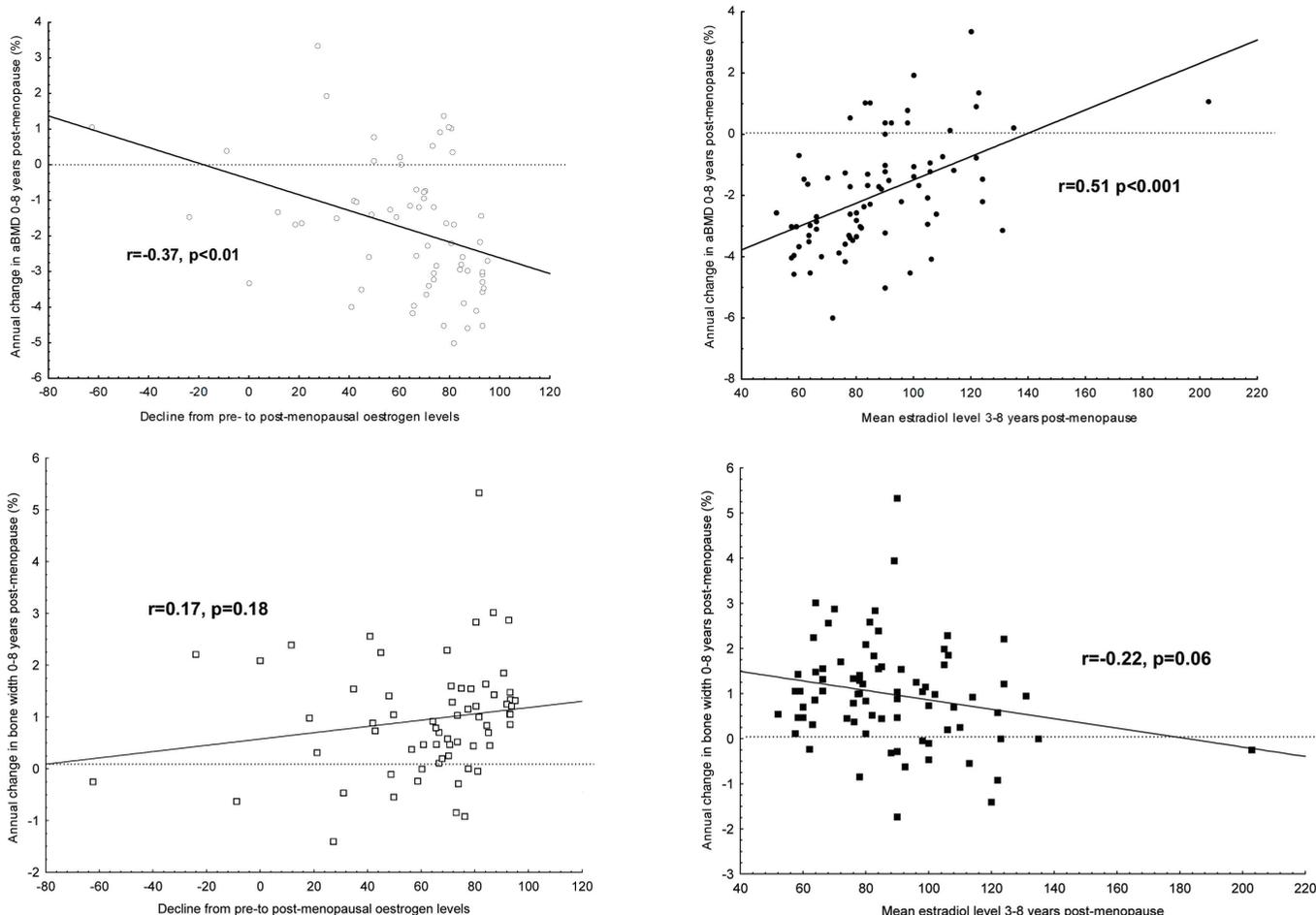


Figure 2. Correlation between post-menopausal decline in serum estradiol and the stable mean estradiol levels 3-8 years post-menopause with annual changes in periosteal diameter and areal bone mineral density (aBMD) at the cortical site of distal radius in 81 women followed from menopause during the period 0 to 8 years after menopause. This period was chosen as the period with significant annual changes in aBMD and periosteal expansion. aBMD correlates moderately with estradiol levels and to a lesser degree with the post-menopausal drop in estradiol levels. Periosteal expansion showed a trend of correlation estradiol levels but not with the postmenopausal drop in estradiol levels.

subject positioning and calculations are based on the assumption that the bone is cylindrical and symmetrical in its thickness.

The fast postmenopausal bone loss in the early post-menopausal period which is associated with a decline in oestrogen and mediated mainly through resorption at the endosteal surface and in Haversian canals^{5,6,14,31-33}, is well documented^{1,34}. However, bone strength depends not only on the material properties but also on the structural characteristics of the skeleton. An increased bone size would counteract a diminished bone density and partially preserve bone strength. If the cortical shell is placed farther away from the long axis of the bone, the resistance of the bone to bending and torsional forces improves. Strict mechanical calculations such as the cross-sectional moment of inertia, which is highly correlated with the strength of the distal radius³⁵, and the section modulus, a measure of the ability to withstand bending and torsional forces³⁶, represent the geometrical contributions of bone

strength. In this study, the section modulus increased by about 30% during the follow-up. Hypothetically, if no periosteal expansion had occurred, the section modulus would instead have decreased because of the medullary expansion following the bone loss. In our material, we found an average annual increase of 3.3% in the section modulus in the first 8-year interval following menopause and thereafter, no significant changes up to age 76. This is somewhat discordant with other authors who have reported that the section modulus in the femoral neck decreases after menopause^{9,15} or is maintained until age 60 and thereafter declines⁷.

Periosteal expansion is probably of clinical relevance, since small bone size has been independently associated with fractures in both the femoral neck¹⁰ and in vertebrae^{10,12}. The Strength Index is an estimate that takes not only bone structure but also bone mass into account and hypothetically could predict fracture risk better than BMD alone³ although there is no

statistical evidence of its usefulness in fracture prediction.

There are several plausible explanations for the periosteal expansion. The reduction in oestrogen levels or the absolute low stable oestrogen levels after menopause may result not only in the loss of BMD, but also in periosteal expansion, since oestrogen has been shown to inhibit periosteal bone formation in experiments in rats³⁷. Our data indicate that there could be an association with oestrogen levels, even if this is speculative since we found only trends in the correlation analyses. Any influence of oestrogen on periosteal expansion must be regarded as low since postmenopausal oestrogen levels only explained 4.8% of the variance in periosteal expansion during the first 8 postmenopausal years. Another possibility is that bone loss on the endocortical surface causes increased mechanical stresses in the bone tissue, in turn stimulating periosteal bone formation; another hypothesis not possible to test by our study design. The complexity of exploring any relationship between changes in the endosteal and periosteal surfaces should not to be underestimated for several reasons. One may be that cortical bone loss occurs by intracortical remodeling throughout the cortex, not only on the inner aspect. If so, it could not be expected that changes in endosteal and periosteal surfaces would correlate. Furthermore, our mechanical calculations are based on the assumption that the distal radial shaft and the medullary cavity are cylindrical, which we know are approximations that could influence our interpretations of changes in medullary and periosteal width. In addition, all bone scanning techniques today have limitations in detecting small differences in bone dimensions, as discussed above more extensively. And finally, one interpretation could be that the events on the endocortical and periosteal surfaces are independent, not codependent.

It has previously been shown that BMD is one of the best predictors of fractures at the measured site³⁸. For this reason, we included only fractures of the distal radius in our analysis, with the knowledge that we measured a cortical region while the reported distal radius fractures occurred in the metaphyseal region. Since both BMD and bone size are independently associated with fractures^{10-12,39} and since both traits contribute to bone strength, we combined the tissue-level strength (BMD) with the skeleton's resistance to bending and torsion (section modulus) into a Strength Index. Our descriptive fracture data also seem to show a more marked preponderance of fractures among women in the lowest quartile of Strength Index than in the lowest quartile of BMD. The Strength Index may thus be a usable tool for the prediction of fractures, although further, larger studies are required for statistical evidence.

The advantages of this study include the follow-up period of on average 24 years, the use of menopause as baseline and the homogeneous population-based cohort of Caucasian women without diseases or medications interfering with the skeleton. The use of menopause as baseline is mandatory when trying to answer our hypotheses and a similar study could hardly be conducted today after the introduction of anti-resorptive osteoporosis therapy. Menopause was determined accurately according to the WHO definition and bone mass and bone structure could then be followed through the spontaneous menopause with the same

scanner with no long-term drift. The mean 11.4 measurements per woman and the long follow-up period enabled us to calculate individual slopes with better precision than delta values.

The limitations include the small sample size which was not powered for evaluating incident fractures and the use of single-photon absorptiometry in the distal forearm instead of modern scanners and measurements of both axial and appendicular regions. However, such scanning techniques were not available at study start. Measurement reservations include difficulties in capturing very small changes, especially if edge detection may be hampered by changes in fat content in the upper extremity and if bone loss occurs with not only resorption at the endosteal surface but also at the outer surface. We cannot rule out the risk of a type two-error, since discrete changes in small sample sizes may be obscured by errors in measurement,

In spite of these limitations, we suggest that periosteal expansion in the distal forearm is not a permanent phenomenon but found only in the first decade after menopause whereas the loss in BMD continues also in the remote postmenopausal period.

Acknowledgements

Gunnar Rannevik and Olof Johnell initiated the longitudinal prospective perimenopausal project and were responsible for the endocrinological aspects.

Financial support for this study was received from the Österlund, the Pålhlsson, the Herman Jernhardt and the Malmo Hospital Foundations.

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