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An age-related medullary expansion can have implications for the long-term fixation of hip prostheses

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Background **Diaphyseal bone loss occurs mainly at the endosteal surface in the medullary cavity. Since the menopause is followed by an increase in bone loss, the size of the medullary cavity should theoretically increase during the postmenopausal period. If so, this might affect the long-term fixation of hip prostheses.**

Patients and methods **This 19-year prospective study evaluated bone loss and geometrical changes in 112 women, all premenopausal at baseline. Bone mineral density (BMD) and skeletal geometry, with special reference to the size of the medullary cavity, were estimated every other year by single-photon absorptiometry at the cortical site of the distal radius.**

Results **After menopause, a decrease of 1.7 (95% CI 1.6–1.8)% occurred in the BMD every year, while an increase of 0.9 (0.8-1.0)% in the medullary width (endosteal width) too place every year. The annual change in BMD was inversely correlated with the annual change in the medullary width ($r = –0.5$, $p < 0.001$). The quartile of women with the largest BMD loss had a greater medullary expansion than the quartile of women with the least BMD loss ($p < 0.001$).**

Interpretation **If the age-related expansion of the radial medullary cavity is a general phenomenon, this may have implications for the long-term fixation of hip prostheses.**

Estrogen deficiency, after the menopause, accelerates the age-related bone loss (Riggs et al. 1986, Ahlborg et al. 2001). Since the bone loss of the diaphyseal bones occurs mainly at the endosteal surface of the cortex (the inner surface of the cortex) and partly in the Haversian canals (Frost 1999), the medullary cavity should, hypothetically, increase in size after the menopause. Most studies evaluating the age-related structural changes include bone size alone, but, not changes in the endosteal and subperiosteal surfaces separately, and mainly in cadaveric and cross-sectional studies, with the risk of selection bias and cohort effects, which may confound the conclusions (Ruff and Hayes 1988, Bouxsein et al. 1994, Heaney et al. 1997, Mosekilde 1990). Case-control and cross-sectional studies, which suggest that the medullary cavity expands with age, have been published (Poss et al. 1987, Hofmann et al. 1989, Robinson et al. 1994), but if this could be verified in prospective studies, it would further strengthen the findings. If the medullary cavity increases in size with age, this might have implications for the long-term fixation of hip prostheses.

With this background, we hypothesized that the postmenopausal bone loss of the diaphyseal bones expands the medullary cavity and posed the questions: (i) is the BMD loss after the menopause associated with medullary expansion? (ii) do women with a high rate of BMD loss after menopause also have a greater expansion of the medullary cavity than women with a less significant BMD loss?

Patients and methods

We invited 241 Caucasian women aged 48 from Malmo, Sweden to this prospective study (Johnell and Nilsson 1984, Ahlborg et al. 2001). 49 were

excluded before baseline, as all participants in the study had to be premenopausal and without medication or disease known to interfere with bone metabolism, Therefore 192 women were included in the study in 1977–1978. A further 17 persons were excluded, since they left the study during the first 5 years because of surgical menopause or relocation, 4 had errors in technical measurements, 17 had received estrogen treatment and 15 died, leaving 139 women to be followed through menopause. This report includes 112 women (81%) who participated throughout the entire 23 years. Prospective 16-year data as regards bone loss and bone strength have been reported elsewhere (Ahlborg et al. 2001, 2003).

The last premenopausal measurement, made 2 years at most before the menopause, was defined as menopause and therefore the baseline measurement. The last measurement was done at 72 years of age, but as the women had their menopause at various ages, the mean postmenopausal follow-up period was 19 (14–23) years. Menopause was defined using the definitions of the WHO (1981) —i.e., the permanent cessation of menstruation due to the loss of ovarian follicular activity. Therefore the onset of the menopause was determined retrospectively, after 12 months of spontaneous amenorrhea together with elevated serum levels of follicle-stimulating hormone. This hormone was analyzed by double antibody radio immunoassays every 3 months during the first year, every 6 months until one year after the menopause and then once a year (Rannevik et al. 1995).

Bone mineral density (BMD, mg/cm^2) of the distal radius was measured 6 cm proximal to the ulnar styloid process, on the average, every other year, by single-photon absorptiometry (SPA), a total of 11 times. A rectilinear scan across the radius and ulna, with a radiation source (^{241}Am) and a detector moving simultaneously, was taken using Nauclér et al.'s method (1974). Both forearms were scanned and all traits presented below are the average value of the right and left forearms. The bone size (subperiosteal width), the medullary width (endosteal width) and the cortical width of the distal radius were calculated from the graph of the scan (Nauclér et al. 1974).

The reproducibility was 4% (coefficient of variation) in vivo, determined by duplicate measurements in 20 persons measured twice at intervals of weeks or months apart. The estimate of cortical thickness from the graph of the scan had a reproducibility of 8% (coefficient of variation) and was found to be proportional to the cortical thickness on x-rays from the same site (Nauclér et al. 1974). In this study the same densitometer was used throughout the study and, during follow-up, repeated measurements of a standardized phantom were taken every other week. To determine whether long-term drift of the densitometer occurred during follow-up, all phantom data were analyzed, using a linear regression equation. This analysis showed no significant long-term drift of the equipment, either in BMD or skeletal width estimates (0.1%/year (95% CI –0.2–0.4) and 0.08%/year (95% CI –0.01–0.17), respectively). Due to a replacement of the radiation source in 1980, all the following BMD measurements were adjusted by using the phantom data.

The data are given for all 112 participants and have been divided into quartiles according to the annual relative changes in BMD. The annual percentage change was calculated for each woman as the ratio of the slope fitted to each woman's repeated measurements divided by the baseline value. Figure 1 shows the relative change as the ratio of the value observed at each time as compared to each woman's baseline value. A linear regression equation was used to determine the association between annual change of BMD and medullary width. Student's t-test between means was used to compare women within the highest and the lowest quartiles of BMD loss, with adjustment for menopausal age by analysis of covariance. The data are presented as the mean, with a 95% confidence interval (95% CI). The study was approved by the local ethics committee.

Results

The BMD declined annually by 1.7 (95% CI 1.6–1.8)% while the medullary width increased by 0.9 (0.8–1.0)% and the bone size by 0.6 (0.6–0.7)% during the two decades after menopause (Table 1, Figure 1). The absolute changes in BMD and the absolute changes in medullary width were correlated ($r = –0.6$, $p < 0.001$), as also were the relative changes ($r = –0.5$, $p < 0.001$) (Figure 2).

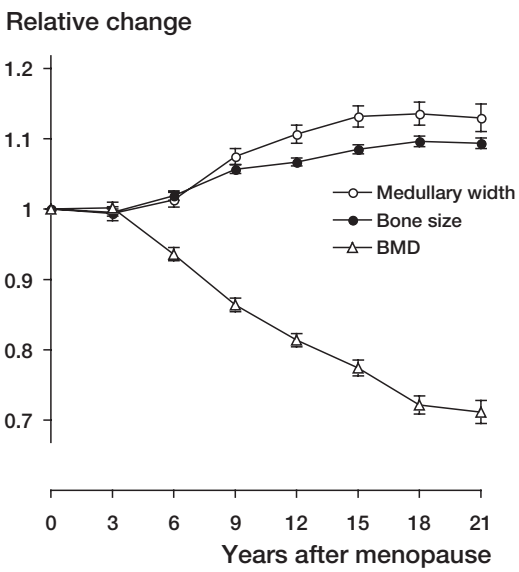

Figure 1. Relative changes since menopause of medullary width (endosteal width), bone size (subperiosteal width) and in bone mineral density (BMD) at the cortical site of the distal radius, in 112 women (mean ± SEM).

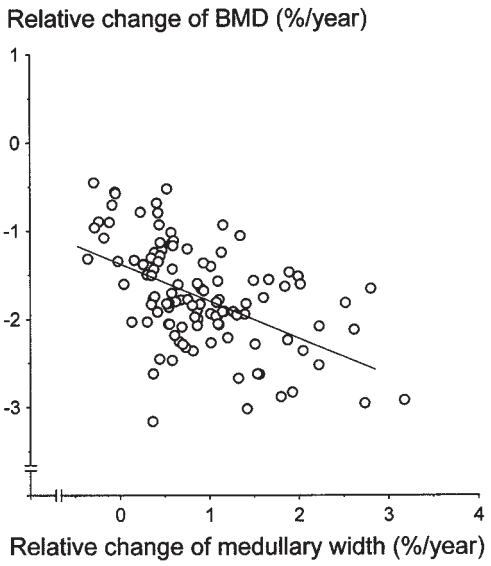

Figure 2. Relation between annual relative changes in medullary width (endosteal width) and annual relative changes in bone mineral density (BMD) at the cortical site of the distal radius, in 112 women, followed from menopause to age 72 ($r = –0.5$, $p < 0.001$).

The quartile of women with the largest BMD loss (> 2.1% a year, n = 28) had, as compared to the quartile of women with the least BMD loss (< 1.3% a year, n = 28) a greater annual medullary expansion (1.0 (0.7–1.4)%, $p < 0.001$) and a greater annual bone size expansion (0.3 (0.2–0.4), $p < 0.001$) (Table 2). After adjustment for baseline differences in age at menopause, the findings were the same (1.0 (0.7–1.4)% and 0.3 (0.2–0.5)%, respectively). That is, the women with the greatest BMD loss had the greatest medullary expansion and the greatest gain in bone size (Figure 3).

Table 1. Skeletal structure and bone mass in the distal radius, measured 6 cm proximal to the styloid process of the ulna by single photon absorptiometry (SPA), and anthropometric data at menopause (MP) with the absolute and relative changes a year estimated by individual regression slopes until the age of 72 years

	Measurement at menopause (n = 112) mean	95% CI	Absolute change a year (n = 112) mean	95% CI	Relative change a year (%) (n = 112) mean	95% CI
Skeletal structure						
Bone size (mm)	13.0	12.8 to 13.2	0.08	0.07 to 0.08 [a]	0.60	0.55 to 0.65 [a]
Medullary width (mm)	6.8	6.5 to 7.0	0.06	0.05 to 0.06 [a]	0.89	0.76 to 1.02 [a]
Cortical width (mm)	6.2	6.1 to 6.4	0.02	0.01 to 0.03 [a]	0.37	0.26 to 0.48 [a]
Bone mass						
BMD (mg/cm^2)	559	549 to 570	–9.7	–10 to –9.0 [a]	–1.73	–1.84 to –1.62 [a]
Anthropometrics						
Height (cm)	164	163 to 165	–0.1	–0.1 to –0.1 [a]	–0.07	–0.08 to –0.06 [a]
Weight (kg)	64	62 to 66	0.3	0.2 to 0.3 [a]	0.40	0.30 to 0.51 [a]
Age at MP	52	52 to 53				

[a] $p < 0.001$, when significantly different from zero

Table 2. Skeletal structure and bone mass in the distal radius, measured 6 cm proximal to the styloid process of the ulna by single photon absorptiometry (SPA), and anthropometric data at menopause (MP), with absolute and relative changes a year estimated by individual regression slopes until the age of 72 years in the quartile of women with the largest BMD loss (> 2.1%/year) and in the quartile of women with the least BMD loss (< 1.3%/year)

	Measurememt at menopause		Absolute change in BMD loss per year		Relative change in BMD loss per year (%)	
	Largest BMD loss (n = 28) mean 95% CI	Least BMD loss (n = 28) mean 95% CI	Largest BMD loss (n = 28) mean 95% CI	Least BMD loss (n = 28) mean 95% CI	Largest BMD loss (n = 28) mean 95% CI	Least BMD loss (n = 28) mean 95% CI
Skeletal structure						
Bone size (mm)	13.1	12.8	0.09	0.05 [b]	0.73	0.43 [b]
	12.7 to 13.6	12.4 to 13.3	0.08 to 0.11	0.05 to 0.06	0.60 to 0.86	0.35 to 0.51
Medullary width (mm)	7.0	6.6	0.09	0.02 [b]	1.36	0.33 [b]
	6.5 to 7.5	6.1 to 7.0	0.07 to 0.11	0.01 to 0.03	1.06 to 1.66	0.16 to 0.51
Cortical width (mm)	6.1	6.3	0.004	0.03 [b]	0.08	0.59 [b]
	5.9 to 6.3	6.0 to 6.6	–0.01 to 0.02	0.02 to 0.05	–0.14 to 0.31	0.41 to 0.77
Bone mass						
BMD (mg/cm^2)	552	563	–13.6	–5.5 [b]	–2.46	–0.98 [b]
	528 to 575	541 to 586	–14.5 to –12.6	–6.2 to –4.9	–2.59 to –2.34	–1.09 to –0.88
Anthropometrics						
Height (cm)	165	163	–0.1	–0.1	–0.07	–0.06
	163 to 166	161 to 165	–0.2 to –0.1	–0.1 to –0.1	–0.10 to –0.05	–0.08 to –0.04
Weight (kg)	66	67	0.3	0.3	0.45	0.40
	61 to 71	62 to 72	0.1 to 0.5	0.1 to 0.4	0.18 to 0.71	0.20 to 0.61
Age at MP	53	51 [a]				
	52 to 54	51 to 52				

[a] p = 0.03
[b] p < 0.001, when comparing the two quartiles

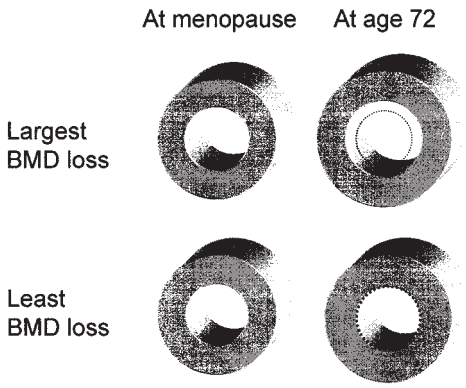

Figure 3. Estimated mean cross-sectional geometry of the cortical site of the distal radius at menopause and at the age of 72 years, in the quartile of women with the largest BMD loss (>2.1%/year) and in the quartile of women with the least BMD loss (<1.3%/year). Dotted line indicates the inner cortical surface at menopause.

Discussion

In this prospective study, we report (i) that the BMD loss following menopause is associated with a medullary expansion and (ii) that women with a large loss risk a large expansion. This study has several advantages: (i) a well-defined, female, Caucasian population was followed, (ii) all were 48 years of age at baseline, (iii) all lived in the same city, (iv) the estimate of the menopause was accurate, (v) the high attendance rate was maintained throughout the 23 years, (vi) no diseases or medication interfered with the normal skeletal development and confounded the data, (vii) repeated SPA measurements were done by the same technician, using the same densitometer, and (viii) all the analyses were done by the same technician. To perform a similar study today would be almost impossible, because of the present use of bisphosphonates and selective estrogen receptor modulators (SERMS) (Black et al. 1996, Ettinger et al. 1999, McClung et al. 2001). Due to, with the large intra-individual variations in the shape of the bone and the documented changes in skeletal geometry with aging (Bouxsein et al. 1994, Heaney et al. 1997), a pro-

spective study design is preferable for studying the age-related, geometrical changes. Since the study was originally designed to follow changes in bone density of the distal radius, its weakness is that only one diaphyseal bone was evaluated. We can therefore assume only that the skeletal remodeling observed is a general phenomenon found in all diaphyseal bones. Earlier human cross-sectional and cadaveric studies of the femur shaft support this view since they found an age-related increase in medullary width and bone size (Smith and Walker 1964, Ruff and Hayes 1988).

Some reports indicate that loosening of hip prostheses may be associated with an expansion of the medullary cavity (Poss et al. 1987, Hofmann et al. 1989, Robinson et al. 1994). Hofmann et al. (1989) found, in a case-control study including 60 persons with total hip arthroplasty (THA), a four times higher medullary expansion of the femur in the group with aseptic femoral stem loosening than in a group with stable hip prostheses. Radiostereometric studies have shown that most of the motion between the femur and the implant takes place at the cement-implant interface during the first two postoperative years (Nivbrant et al. 1999), but also to some extent at the bone-cement interface. The motion at this interface seems to occur whether or not the implant is designed to adhere to the cement or has a tapered form with smooth surface designed to move inside the cement mantle (Alfaro-Adrian et al. 1999, Nivbrant 1999). Long-term retrieval studies have shown that implants which have functioned well for many years have signs of trabecular bone in direct contact with the cement mantle, and radiolucent lines at the bone-cement interface. This phenomenon has been attributed to endosteal remodeling (Schmalzried et al. 1993). Our hypothesis is that late loosening, as opposed to early loosening, may, to some extent, be due to medullary expansion.

Moreover, as bone loss occurs mainly at the endosteal surface, it is not surprising to find a larger medullary expansion in those with a high loss of BMD. Treatment with bisphosphonates would then reduce not only the resorption of trabecular bone, but theoretically also the medullary expansion by inhibiting osteoclastic activity. As a result, this might reduce the effect at the bone-cement interface (Hilding et al. 2000, Åstrand and Aspenberg 2002). Some short-term data support this view by suggesting that early migration of the tibial component after total knee replacement can be inhibited by anti-resorptive drugs (Hilding et al. 2000).

The mean age of menopause in Sweden is 52 years, as in this study, while the mean age of women undergoing THA is generally higher. Since the BMD loss and the medullary expansion in the current study seem to occur preferably during the first 15 years after menopause, it is possible that the consequences of medullary expansion as regards THA are confined to women undergoing surgery before or shortly after this. Future studies in the field should therefore include women undergoing surgery before the age of 60 years.

No competing interests declared.

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