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Maintained bone density at advanced ages after long term treatment with low dose oestradiol implants

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ABSTRACT

Objective To investigate whether the bone preserving effect of low dose oestrogen replacement therapy (20 mg oestradiol implanted subcutaneously every six months) persists during continuous long term treatment through advanced ages.

Design Cross sectional clinical study of postmenopausal women treated with oestradiol implants as compared with nonusers matched for age.

Setting Outpatient research unit at a university hospital.

Subjects Thirty-five women with a mean age of 67 years (range 47–83 years) at the time of investigation who, after a prior hysterectomy, had been treated with oestradiol implants for climacteric symptoms for a mean period of 16 years (range 5·5–31 years). The results were compared with those in women matched for age and without any diseases or medications known to affect the bone metabolism.

Main outcome measures Bone mineral densities (BMD) in the distal forearm, vertebrae and hip analysed by study group, age and duration of treatment.

Results Implant users had a median serum oestradiol concentration in the luteal range, 313 (range 126–1711) pmol/l, and premenopausal levels of follicle stimulating hormone (FSH). All women except one who were given the standard dose at the standard intervals had serum oestradiol levels below 650 pmol/l. Compared with nonusers, women treated with oestradiol implants had 20 to 25% higher BMD at all measurement sites: distal radius ($P<0·0001$), lumbar vertebrae ($P<0·0002$) and femoral neck ($P<0·0001$). These differences also remained after adjustment for potential confounders (height, age at menarche, parity, smoking habits, physical exercise and education) ($P\leq 0·01$ at all sites). In a multiple regression analysis the negative effect of advancing age was more than compensated by the positive effect of increasing treatment duration with a higher BMD at all measurement sites in women with a longer as compared with shorter, duration of treatment; the regression coefficients were significant ($P<0·05$) in the spine and hip measurements.

Conclusions Continuous long term treatment with low dose oestradiol implants yielding physiological levels of serum oestradiol preserves both compact and cancellous bone and the effect seems to persist into advanced ages without any inevitable age related bone loss.

The effect of oestrogen replacement therapy (ERT) in preventing bone loss and fragility fractures is well established mainly for the immediate postmenopausal period and up to an age of about 70 years (Lindsay *et al.* 1980; Weiss *et al.* 1980; Ettinger *et al.* 1985; Kiel *et al.* 1987; Quigley *et al.* 1987; Naessén *et al.* 1990). Oestrogens also prevent further bone loss in osteoporotic women who have already had a fracture (Christiansen & Riis 1990; Lindsay & Tohme 1990). Whether the effect of hormone replacement therapy on the bone mass will persist after a long duration of treatment and into advanced ages when most hip fractures occur is less well known (Quigley *et al.* 1987; Melton *et al.* 1990). It has been postulated that an inevitable age related bone loss might ultimately supersede and diminish the bone preserving effect of oestrogens (Lindsay *et al.* 1980; Quigley *et al.* 1987; Melton *et al.* 1990), but there have been few long term studies on the outcome of continuous oestrogen treatment. ERT given parenterally, as compared with orally, has less effect on the liver metabolism, yields more physiological levels of

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serum oestradiol and a physiological oestrone to oestradiol ratio (Magos & Studd 1990).

The aim of the present study was to compare the bone mineral density (BMD) in long term users of oestradiol implants with that in age matched nonusers, in order to assess the bone preserving effect of continuous ERT into advanced ages.

Subjects and methods

All women had been treated with oestradiol implants (Organon Laboratories, UK) for more than five years after a preceding hysterectomy. Among 42 women fulfilling this criteria, seven women were excluded: one because of hypothyroidism, one because of malignancy of the urinary bladder, one whose address could not be traced and four who refused to participate because of lack of time. The remaining 35 women, residents in the Uppsala community, with a mean age of 67 years (range 47–83 years), were investigated. The mean duration of treatment with oestradiol implants was 15·5 years (range 5·5–31 years). In 77% the hysterectomies had been combined with bilateral oophorectomy. The indications for the hysterectomy were usually bleeding problems and/or fibromyomata. Oestradiol implants were given for prevention of climacteric symptoms in women who had undergone bilateral oophorectomy or for treatment of already existing vasomotor symptoms. The administered dose of oestradiol was usually 20 mg implanted subcutaneously in pellets every six months. In a few women the dose was individually adjusted on the basis of climacteric symptoms. Thus, two were given 40 mg during most of their treatment periods; in three (including the two given the higher dose) the interval was shorter than six months and in another three the interval was longer.

All treated women had been followed up at the same hospital during the entire period of their treatment. Information concerning durations of, exposure to, and doses of oestradiol implants, oral contraceptives and to other exogenous hormones were obtained from their medical records. Additional information on covariates, (i.e. potential confounding factors such as age of menarche, parity, smoking habits, physical activity and educational level), was obtained through an interview and a short questionnaire completed both by implant users and nonusers at the time of examination.

Women without a history of hysterectomy or oophorectomy, ERT or other medications known to affect the bone metabolism served as controls, and 35 women thus were selected from the population registry in the same municipality as the treated women, matched for age (± 1 year), and recruited through a mailed invitation. Selection according to age at menopause was not possible because the time of the true menopause could not be ascertained in the hysterectomised women. Among the invited controls, five women declined because of lack of time and were replaced by others.

Blood samples were collected between 8 and 10 a.m. after a 12 h fast and kept at −20°C. The concentration of serum oestradiol was assayed in batches by a kit, Amerlite oestradiol-60 assay (Amersham, UK). Follicle stimulating hormone (FSH) in serum was measured consecutively as clinical routine by Delfia hFSH (Pharmacia-Wallac Oy, Finland).

Bone mineral density was measured in the distal part of the nondominant forearm by single photon absorptiometry (SPA), using a Bone Density Scanner 1100 (Nuclear Data, Schaumberg, Illinois, USA) and an I^{125} source. SPA values in the forearm are reported to correlate well with the bone mineral content at other sites and with total body calcium (Christiansen & Rödbro 1975). Measurements were made at two sites in the distal forearm, a distal (BMD_{dist}) and a proximal (BMD_{prox}) site, which have a relative trabecular bone content of about 55% and 13%, respectively (Nilas & Christiansen 1987). The results are given in arbitrary units. The estimated long term precision of the method in our hands is about 1·0% to 1·3% (Naessén 1992). Dual energy X-ray absorptiometry (DEXA) (Lunar DPX-L) was used to measure the bone density in the lumbar spine (L2–4) and hip. The method has a long term precision of about 1% (Lilley *et al.* 1991).

Statistical methods

Comparisons between the two study groups regarding quantitative variables were made by both paired and unpaired *t* tests. The within-pair correlation was very small, which meant that the results of the two approaches were very similar. Results of the paired tests are given. Comparisons between groups regarding categorical variables were made by McNemars' test. For comparisons between groups with respect to bone density variables after adjustment for other variables, multiple regression analysis was made (Kleinbaum *et al.* 1988). The variables included in this analysis were height, age at menarche, parity, smoking habits, physical exercise and level of education.

The regression models included as explanatory variables: study group, dummy variables representing the different pairs and the confounding variables in original continuous form (height, age at menarche, parity) or represented by suitably chosen dummy variables (smoking, physical exercise and level of education). In this way it was possible to estimate the group difference after adjustment for possibly confounding variables and also accounting for the matched data collection procedure.

The relationship between age and bone density was analysed separately in the two groups by standard regression analysis. In the treatment group a multivariate analysis was performed in which bone density (BMD) was related to both age (AGE) and treatment duration (TD), using the model: $BMD = \alpha + \beta\,(AGE - 50) + \gamma TD + \varepsilon$. By this model the effect of age can be estimated after adjustment for the effect of treatment duration, and vice versa. The parameter α shows the bone density at age 50 and with a treatment duration of 0, the parameter β shows the effect of each extra year of age given a certain values of treatment duration, and γ shows the effect of each extra year of treatment duration given a certain age. The value for β plus γ gives the net effect on the bone density when both age and treatment duration increase by one year.

Table 1. Descriptive variables, potential confounders and bone mineral density (BMD) at various skeletal sites in 35 users of oestradiol implants and 35 nonusers. Values are shown as mean (standard deviation) or numbers of women (n). ns = nonsignificant, $P>0.05$.

Variable	Implant users		Non-users		*P* value* (after adjustment)	
Age (years)	66·6	(7·0)	66·4	(7·3)	ns	
Age at menarche (years)	13·6	(1·7)	13·4	(1·3)	ns	
Number of births	1·7	(1·0)	2·1	(1·3)	ns	
Age at 1st birth (years)	24·5	(5·0)	26·6	(5·2)	ns	
Height (cm)	162·3	(6·4)	161·7	(5·3)	ns	
Weight (kg)	72·6	(12·9)	68·9	(12·7)	ns	
Oral contraceptive use (*n*)					ns**	
Never	27		27			
Ever	8		8			
Smoking (*n*)					ns**	
Never	20		20			
Ex-smoker	8		8			
Current	7		7			
Outdoor walking (*n*)					<0·05**	
Seldom	2		0			
On average one time a week	3		0			
Several times a week	11		7			
Daily walking	19		28			
Education (*n*)					ns**	
<8 years	23		19			
8–10 years	5		5			
High school	2		6			
University	5		5			
S-Oestradiol (pmol/l)†	387	(294)	71	(49)	0·0001	
S-FSH (μg/l)	2·54	(2·5)	13·34	(5·3)	0·0001	
Forearm BMD_{dist}‡	0·97	(0·17)	0·81	(0·18)	0·0002	(0·022)§
Forearm BMD_{prox}‡	1·33	(0·19)	1·11	(0·21)	0·0001	(0·002)
BMD L 2–4 (g/cm²)	1·316	(0·28)	1·080	(0·16)	0·0001	(0·008)
BMD fem neck (g/cm²)	0·967	(0·15)	0·815	(0·12)	0·0001	(0·002)
BMD Ward's triangle (g/cm²)	0·881	(0·20)	0·701	(0·15)	0·0001	(0·007)
BMD troch. region (g/cm²)	0·887	(0·17)	0·743	(0·12)	0·0001	(0·012)

*Student's *t*-test for paired samples for continuous variables.
**McNemars' test on the distribution between categories.
†Postmenopausal range 5–30 μg/l.
‡Arbitrary units.
§After adjustment for height, age at menarche, parity, smoking category, physical exercise and education.

Results

Implant users and nonusers were similar with regard to age (matching variable) and a number of potential confounders, including smoking habits (Table 1). Women not exposed to ERT reported greater physical activity. Implant users had luteal levels of serum oestradiol, mean 387 (median 313 and range 126–1711) pmol/l, and premenopausal levels of FHS as compared with postmenopausal values in nonusers. All women except one with the standard dose of 20 mg implanted every six months had serum oestradiol levels below 650 pmol/l. Higher values were otherwise confined to the three women who were given a higher dose (40 mg) and/or had an interval shorter than six months between the implantations (not shown).

The bone densities were, on average, 20 to 25% higher in implant users than in nonusers and the differences were highly significant at all measurement sites, which included both axial and appendicular parts of the skeleton. These differences also remained after adjustment for a number

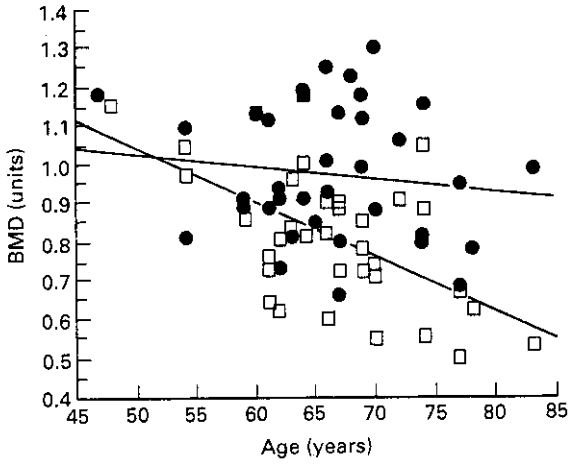

Fig. 1. Bone mineral density (BMD) in the distal forearm by age in implant users (●) and nonusers (□). Best fit regression lines are shown.

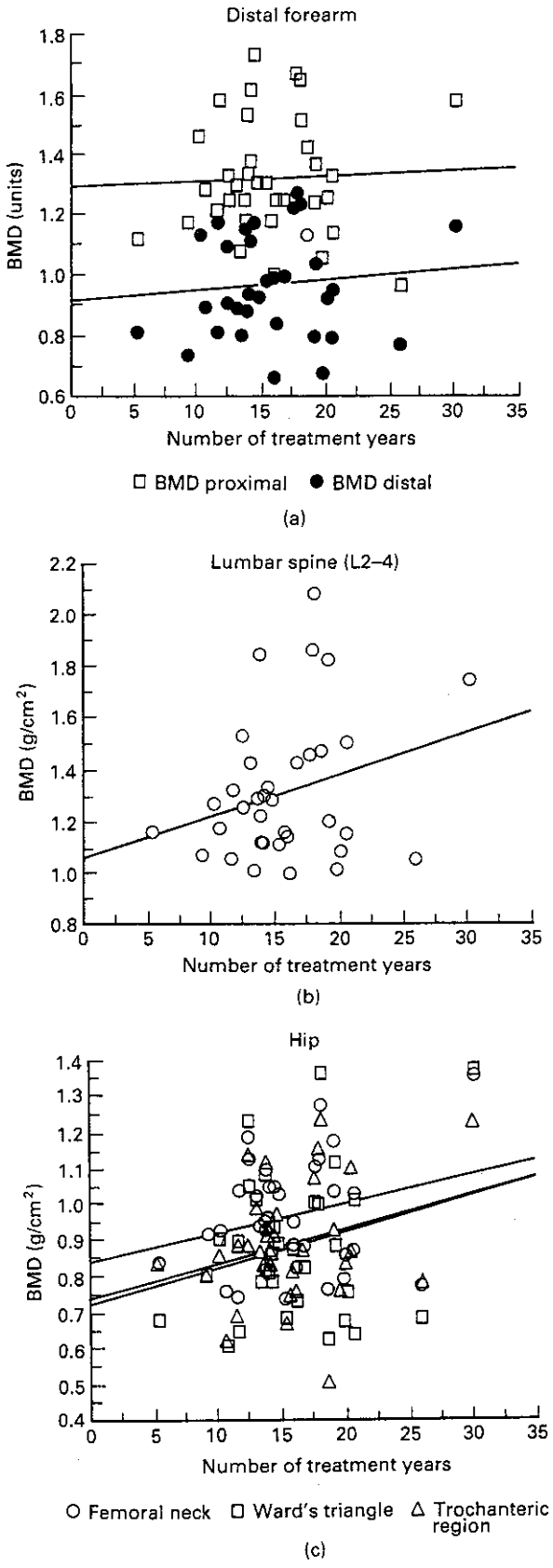

Fig. 2. Bone mineral density (BMD), by duration of treatment (years), in the distal forearm (a), spine (b) and hip (c) in women treated with oestradiol implants. Best fit regression lines are shown.

of covariates (Table 1). Addition of weight to the adjustment procedure was also tested and yielded similar results (data not shown). The values for forearm bone density in implant uses were very similar to those found in a study of perimenopausal women from the same population (mean age 51 years, BMD_{dist} 0·97 and BMD_{prox} 1·31) (Naessén *et al.* 1992). Serum levels of oestradiol correlated with bone density at all measurement sites (r = 0·38–0·53, $P<0·001$) and the highest correlation was found at the proximal measurement site in the forearm among controls (r = 0·53, $P<0·001$).

Among implant users, regression analysis did not reveal any significant association between age and bone density (Fig. 1). In contrast, the analysis of the BMD values among nonusers of ERT showed significantly decreasing values with advancing age ($P<0·05$) at all measurement sites (Fig. 1), except in the spine (data not shown). The slope of the regression line in the forearm measurement indicted that on average the bone density at the age of 80 was 40% lower than at 50 years (Fig. 1).

A multivariate regression analysis in the treatment group with both age and treatment duration in all cases showed a negative effect of advancing age and a positive effect of increasing treatment duration. The treatment duration parameter was always numerically larger than the age parameter, indicating that the negative effect of advancing age was more than compensated by positive treatment effects (Fig. 2, Table 2). This was consistently found at all measurement sites. The treatment effect was significant ($P<0·05$) for BMD in the spine and in the hip (Table 2).

Discussion

This study suggests that the bone preserving effect of low

Table 2. The effect of age and duration of treatment on bone mineral density (BMD) in users of 17β-oestradiol implants. Regression model $y = \alpha + \beta$ (age −50) + γ (treatment years) + residual. α shows the value for a 50 year old with 0 treatment years. β shows the effect of each extra year of age and γ the effect of each extra treatment year. $\beta + \gamma$ gives the net effect on bone density when both age and treatment years increase by one year. Standard error in parenthesis. *$P<0·05$.

Variable	α	β	γ
Forearm BMD_{dist}	0·925	−0·0072 (0·0049)	0·0106 (0·0078)
Forearm BMD_{prox}	1·311	−0·0095 (0·0056)	0·0112 (0·0089)
Spinal BMD (L2–4)	1·075	−0·0100 (0·0077)	0·0256* (0·0123)
Hip BMD			
Femoral neck	0·852	−0·0094* (0·0041)	0·0170* (0·0065)
Ward's triangle	0·734	−0·0105 (0·0054)	0·0202* (0.0086)
Trochanteric region	0·744	−0·0060 (0·0046)	0·0152* (0·0074)

dose oestrogen implants persists during long term treatment through advanced ages because bone density values remained high with advancing age and increased with increasing duration of treatment. Thus, our findings challenge the hypothesis that the bone preserving effect of oestrogens will ultimately decline as a result of an inevitable age-related bone loss (Lindsay *et al.* 1980; Quigley *et al.* 1987). The present study, together with a recent report (Richelson *et al.* 1984), also raises doubts about whether there are two distinct pathogenetic types of osteoporosis, one oestrogen-dependent (type I) and one more age-dependent (type II) (Riggs & Melton 1983). Our findings support the view that oestrogen deficiency, rather than age per se, is the predominant cause of bone loss after the menopause (Richelson *et al.* 1984).

The results were observed after a long duration of treatment with almost complete compliance by virtue of the route of administration. In the interpretation of these data, the influence of confounding, especially selection bias, must be considered. All women who were treated with oestradiol implants had a duration of treatment of five years, or more, and all had undergone hysterectomy, in most cases because of bleeding or fibromyomata. High average levels of endogenous oestrogens have been found in women with such problems (Studd & Thom 1981), which could entail confounding by indication in the present study through higher bone densities at the time of the start of treatment. However, differences in bone density between the study groups in the perimenopausal period could hardly explain the marked group differences observed at high ages. Further, these differences also remained after adjustment for a number of covariates. The cross sectional design of our study precludes any definite conclusion. However, the increased bone density with increasing duration of treatment indicates that the bone preserving effect of implant replacement therapy persists even after a long duration of treatment.

Weight has been found to have a positive association with bone mineral density in women not given ERT (Dawson–Hughes *et al.* 1987). Addition of weight, measured at the time of the investigation, to the potential confounders in the adjustment model did not, however, alter the results. We chose to exclude weight from the adjustment procedure for the reason that any difference in weight between treated and untreated women was probably an effect of the long term oestrogen replacement therapy in the treated group on account of preserved bone (Fig. 1) and muscle mass (Jensen *et al.* 1986). The estimated 30% reduction of the bone mass up to the age of 70 (Fig. 1) would alone almost account for the difference in mean weight between the study groups.

Adjustment for differences in age at the menopause between women with and without ERT was not possible because this age could not be ascertained in the hysterectomised women. However, given the high mean age at examination, the effect of any differences in age at the menopause would probably have been attenuated and negligible, as the effect of age at menopause on bone density diminishes with increasing time after the menopause (Seeman *et al.* 1988).

A number of the women in the treatment group had a history of medications that are known to cause a decrease in the bone mass: four of them were being or had been treated with corticosteroids, and five were taking 1-thyroxine. None of the control women had such a history. The control women also reported a higher level of physical activity. These differences would rather be expected to have the effect of diminishing any true difference between the study groups.

Our finding of a maintained effect on bone density during long term ERT, in contrast to most earlier reports, may be explained by the particular characteristics of exposure regarding compliance, route of administration and doses. The oestradiol levels found in implant users were higher than those reported after oral administration of oestrogens (Savvas *et al.* 1988; Magos & Studd 1990). Parenteral administration of oestrogen has also been found to be more effective in preventing osteoporosis than oral therapy (Savvas *et al.* 1988). There is evidence that such higher serum levels of oestradiol can also increase the bone formation in addition to their antiresorptive effect (Studd *et al.* 1990; Turner 1991). Oestradiol implants have usually been administered in doses of 50 to 100 mg (Barlow *et al.* 1986; Savvas *et al.* 1988; Garnett *et al.* 1990; Studd *et al.* 1990; Garnett *et al.* 1991). In the present study with a very long mean duration of treatment, a comparatively low oestradiol dose of 20 mg given every six months seemed to preserve and, perhaps, even increase the bone density. Judged from the plasma level of serum oestradiol, there did not seem to be any accumulation of oestradiol to supraphysiological levels as has been found in some (Barlow *et al.* 1986; Garnett *et al.* 1990) but not all (Cardozo *et al.* 1984) earlier studies on oestradiol implants. From our data and others (Garnett *et al.* 1990; Studd *et al.* 1990) an interval of six months between implantations would seem appropriate to achieve bone mass preservation without reaching unnecessarily high levels of serum oestradiol.

We conclude that low dose oestradiol implants, yielding physiological levels of serum oestradiol, preserves the bone density during long term treatment through advanced ages, and that this effect does not seem to be diminished by any inevitable age related bone loss.

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