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Increase in bone mass after one year of percutaneous oestradiol and testosterone implants in post-menopausal women who have previously received long-term oral oestrogens

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ABSTRACT

Objective To determine the effect on the bone density of the skeleton after changing from oral oestrogen to subcutaneous oestradiol and testosterone replacement.

Design Prospective non-randomized single centre study.

Subjects Twenty women who were receiving long-term oral oestrogen replacement. Ten changed to oestradiol and testosterone implants; the remaining ten continued with oral oestrogens.

Main outcome measures Bone density was measured using dual photon absorptiometry at the lumbar spine and neck of femur at the start of the study and after one year.

Results The bone density increased significantly by 5·7% at the spine and by 5·2% at the neck of femur in those women who changed to implant therapy but remained unchanged in those women who continued with oral therapy.

Conclusion Subcutaneous oestradiol and testosterone implants will result in an increase in bone mass even after many years of oral oestrogen replacement therapy.

Hormone replacement therapy is effective in alleviating climacteric symptoms (Greenblatt & Studd 1977), preventing osteoporosis (Lindsay *et al.* 1976) and has been shown to reduce significantly the mortality from ischaemic heart disease and cerebrovascular accidents (Ross *et al.* 1981; Paganini-Hill 1988). Oestrogen may be given orally or parentally in the form of creams, transdermal patches or subcutaneous implants (Drife & Studd 1991). The parenteral routes have a number of advantages in that gastrointestinal side effects are avoided and by obviating the first-pass effect through the liver a physiological ratio of oestradiol to oestrone is achieved.

The hormonal profiles of women receiving oral oestrogen replacement often remain in the post-menopausal range whereas the serum oestradiol and FSH levels are within the premenopausal range following long-term hormone implants (Studd & Whitehead 1989). We have reported previously that the higher serum oestradiol levels achieved with long-term subcutaneous implants are associated with a greater bone density than found in women receiving long-term oral oestrogen replacement (Savvas *et al.* 1988). Subcutaneous hormone implants result in a substantial increase in bone density and we have demonstrated that the increase in bone density following hormonal implants correlated significantly with serum oestradiol but showed no correlation with serum testosterone (Studd *et al.* 1990). This indicates that the superiority of this mode of therapy is due to the higher oestradiol levels achieved. A number of women do not obtain satisfactory symptomatic relief with conventional oral hormonal therapy as the FSH levels remain high and the plasma oestradiol levels are inadequate. The present study was designed to investigate the effect on bone density when women change from oral oestrogen replacement therapy to subcutaneous hormone implants.

We recruited 10 women who had received oral hormone therapy for a number of years but were still troubled by climacteric symptoms and were requesting hormone replacement therapy with subcutaneous implants. These were compared with 10 women who remained on oral hormone replacement therapy.

Subjects and methods

Twenty women receiving long-term oral oestrogen replacement were recruited for this study. Ten women (Group I) were happy to continue with oral hormone replacement but 10 (Group II) were changed to subcutaneous implants as they were complaining of problems with depression, loss of energy and loss of libido although the vasomotor symptoms were controlled.

There was no statistically significant difference in the age,

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Table 1. Initial hormone profiles and bone densities in 10 women receiving long-term oral hormone replacement therapy and values, after a further year of oral therapy.

Variable	Initial	After a further year of oral therapy
Age (years)	60 (50–67)	
Years from menopause	8 (6–15)	
Duration of treatment with oral oestrogens (years)	8 (2–14)	
Serum FSH (iu/l)	40·5 (0·9–61)	37 (25–45)
Serum estradiol (pmol/l	176 (64–351)	201 (125–448)
Serum testosterone (nmol/l)		
Bone density (gHa/cm^2)	0·85 (0·4–1·1)	0·5 (0·4–0·6)
Vertebral	0·92 (0·09)	0·92 (0·1)
Femoral	0·78 (0·08)	0·80 (0·1)

Results are median (range) or mean (SD) values as appropriate.

number of years past the menopause, duration of treatment with oral therapy, initial hormonal profile and initial bone density between the two groups (Table 1).

The women in Group I had received oral oestrogen replacement in the form Prempak C 1·25 mg (Ayerst, 1·25 mg conjugated oestrogen daily and 150 μg norgestrel for 12 days a month) for a median of 8 years (range 2–14). The women in Group II had received Prempak C at the same dose for a similar length of time (median 5 years, range 2–18) before changing to subcutaneous hormone implants with oestradiol 75 mg and testosterone 100 mg. The implant was repeated at 6 monthly intervals.

Hormonal profiles were measured in all women at the beginning of the study and a year later which usually coincided with the visit for the third implant. Bone density measurements were performed in all women using dual photon absorptiometry at the lumbar spine and neck of femur. A Novo 22A BMC-LAB absorptiometer utilizing a Gadolinium-153 source was used. The precision was determined by repeated measurement in 10 subjects at both sites at 12 weekly intervals, giving a precision of 2·0% at the lumbar spine and 2·2% at the femoral neck.

Table 2. Initial hormone profiles and bone densities in 10 women receiving long-term oral hormone replacement therapy and values after a year of subcutaneous oestrogen implants.

Variable	Initial	After one year of implants
Age (years)	52 (47–64)	
Years from the menopause	7 (2–16)	
Duration of treatment with oral oestrogens (years)	5 (2–18)	
Serum FSH (iu/l)	45 (11–70)	10 (1·6–22)*
Serum oestradiol (pmol/l	164 (88–372)	437 (312–519)*
Serum testosterone (nmol/l)		
Bone density (gHa/cm^2)	0·7 (0·4–2·2)	2·0 (0·6–3·0)*
Vertebral	0·87 (0·11)	0·92 (0·1)**
Femoral	0·76 (0·1)	0·80 (0·12)**

* $P<0·01$ Mann Whitney U-test.
** $P<0·01$ paired t-test.
Results are median (range) or mean (SD) values as appropriate.

Statistical analysis

The changes in bone density were analysed using the paired t-test; the hormonal data were analysed using the Mann Whitney U test.

Results

The initial median hormonal profiles were in the post-menopausal range in both groups of women and remained in this range after a further year of oral oestrogen in Group I (Table I). In Group II (Table 2) the serum oestradiol level increased significantly from a median of 164 pmol/l (range 88–372) to 437 pmol/l (range 312–519, $P<0·01$) and the serum FSH was reduced significantly from 45 iu/l to 10·0 iu/l ($P<0·01$) after one year of subcutaneous hormonal therapy.

The bone density at the lumbar vertebrae and femoral neck was unchanged in the group that continued with oral oestrogen (Table 1). However, in the group that converted to implant therapy the bone density increased by 5·7% from 0·87 gHa/cm^2 to 0·92 gHa/cm^2 at the spine ($P<0·001$). The bone density at the femoral neck increased by 5·2% from 0·76 gHa/cm^2 to 0·80 gHa/cm^2 (Table 2). The individual changes in bone density in the women in the study are illustrated in Figs 1 and 2.

Discussion

Numerous studies have demonstrated the efficacy of oral oestrogens in the prevention of further postmenopausal bone loss (Lindsay *et al.* 1976). These studies suggest that if oestrogen therapy is started soon after the cessation of periods before significant loss of bone mass has occurred, osteoporosis can be prevented. However, the hormonal profiles of women receiving long-term oral oestrogens often remain in the post-menopausal range. This may be due to first-pass liver metabolism or poor patient compliance. Various studies have shown that up to 70% of women do not take the prescribed oestrogens at all or fail to take them on a regular basis (Ravnikar 1987; Hahn 1989). Subcutaneous implants avoid both problems and

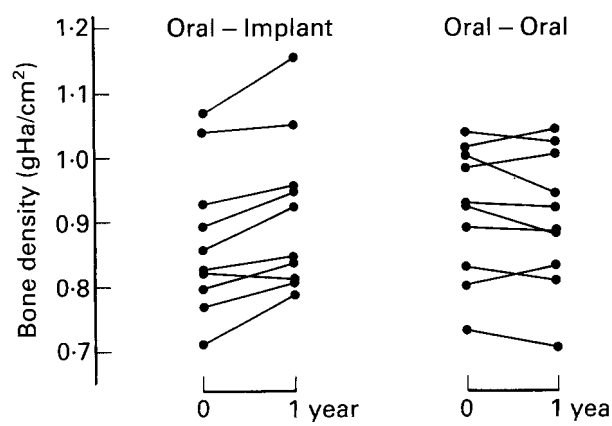

Fig. 1. Changes in bone density of the spine over 1 year in 10 women who continued Prempak 1·25 mg and in 10 women who changed to implants of oestradiol 75 mg and testosterone 100 mg.

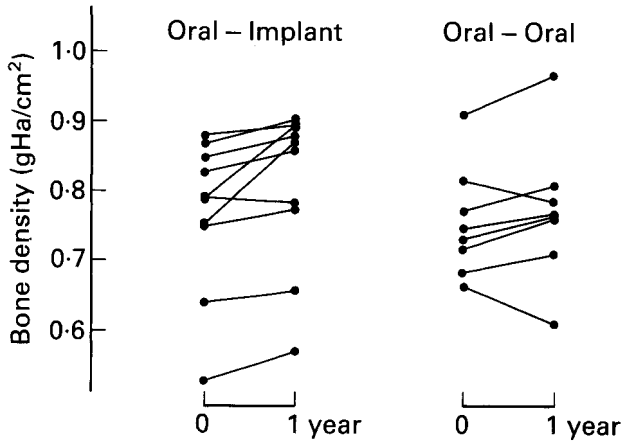

Fig. 2. Changes in bone density of the proximal femur over 1 year in 10 women who continued Prempak 1·25 mg and in 10 women who changed to implants of oestradiol 75 mg and testosterone 100 mg.

achieve a significantly higher serum oestradiol level and lower FSH level.

The two groups in this study were self-selected in that those women who were changed to implant therapy were still experiencing some climacteric symptoms with oral therapy and this may have been due to poor patient compliance. The increase in bone density seen following one year of implants may thus be due to avoiding patient non-compliance. However, there was no significant difference in the initial serum oestradiol and FSH levels between the two groups suggesting that they were well matched in terms of compliance.

We have previously demonstrated that the increase in bone mass seen with subcutaneous oestradiol and testosterone implants correlates significantly with the serum oestradiol level (Studd *et al.* 1990). Our findings suggest that the serum oestradiol levels achieved with oral hormone replacement therapy at the conventional dose may be sub-optimal and that subcutaneous oestradiol and testosterone implants will lead to an increase in bone density by further increasing the serum oestradiol in women who have received long-term oral hormone replacement therapy. The levels achieved with oral therapy in this study are of the same order as those seen in other studies of oral hormone replacement therapy (Powers *et al.* 1985). This supports the suggestion that the improved bone density seen in postmenopausal women receiving implants is due to the rise in serum oestradiol levels. This benefit is not transient as cross-sectional studies have indicated a prolonged improvement in bone density with up to 14 years of hormone implants (Garnett *et al.* 1991). Studies from this unit indicate that addition of testosterone has no significant added effect on bone density (Studd *et al.* 1990).

The concept of increase in bone density following hormone therapy is established in other conditions characterized by a deficiency of sex steroids. Treasure *et al.* (1987) have demonstrated that bone loss associated with anorexia nervosa is reversed when weight is regained and menstruation returns. Osteoporosis seen in men with hyperprolactinaemic hypogonadism is also reversed following either medical or surgical treatment that results in normal circulating levels of sex steroids (Greenspan *et al.* 1986; Finkelstein *et al.* 1989). Loss of vertebral bone mass in amenorrhoeic women athletes is reversed after the resumption of menstruation (Drinkwater *et al.* 1986), and bone loss following the down regulation of the pituitary gonadotrophin secretion with GnRH use is regained after stopping treatment (Matta *et al.* 1988).

This study supports the view that adequate oestrogen therapy which returns serum oestradiol levels to premenopausal values will also reverse postmenopausal bone loss. This suggestion has currently little support because most studies have investigated the effect of oral oestrogen replacement and the consensus of these studies is that such therapy can only prevent further bone loss and cannot reverse significantly any bone loss that may already have occurred. However, Horsman *et al.* (1983) have demonstrated that the skeletal response to oral ethinyloestradiol is dose dependent with 15 μg daily preventing bone loss whereas 25 μg resulted in significant increase in bone mass. Epidemiological studies confirm the value of oral oestrogen replacement in the prevention of fractures with 5-year use being associated with a 50% reduction in overall fracture rates (Mazess *et al.* 1989). Vertebral, forearm and rib fractures are convincingly reduced but there is less protection against the more important femoral neck fractures.

Melton *et al.* (1986) have shown that the risk of fracture is closely related to bone density. It may be that the greater increase in bone density seen with hormone implants is associated with a greater protective effect on fracture incidence, although this will only be confirmed by epidemiological studies and prospective histological studies of bone morphology.

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