Skeletal effects of oral oestrogen compared with subcutaneous oestrogen and testosterone in postmenopausal women

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Structured Abstract

Study objective—To compare oral and implanted oestrogens for their effects in preventing postmenopausal osteoporosis.

Design—Non-randomised cohort study of postmenopausal women treated with oral or depot oestrogens and postmenopausal controls.

Setting—Gynaecological endocrine clinic in tertiary referral centre.

Patients—Oral treatment group of 37 postmenopausal women (mean age 57.5 years, median 8.75 years from last menstrual period), compared with 41 women given oestrogen implants (mean age 56.2 years, median 9.5 years from last menstrual period) and 36 controls (mean age 51.8 years, median 2.0 years from last menstrual period). Weight was not significantly different among the groups.

Interventions—Oral treatment group was given continuous treatment with cyclic oestrogen and progesterone preparations (Prempak C or Cyclo-progynova) for a median of 8.0 years. Implant group was given subcutaneous implants of oestradiol 50 mg combined with testosterone 100 mg, on average six monthly for a median of 8.5 years. Controls were not treated.

End point—Significant increase in bone density.

Measurements and main results—Bone density measured by dual beam photon absorptiometry was 1.02 (SD 0.13) g hydroxyapatite/cm² in implant group versus 0.89 (0.11) in oral group ($p < 0.01$) and 0.87 (0.14) in controls ($p < 0.01$). Serum oestradiol concentration in implant group was (median) 725 pmol/l versus 170 pmol/l in oral group ($p < 0.01$) and 99 pmol/l in controls ($p < 0.01$). Serum follicular stimulating hormone was median 1 IU/l (range 1-11) in implant group (equivalent to premenopausal values) versus 43 (4-94) IU/l in oral group ($p < 0.01$) and 72 (28-99) IU/l in controls ($p < 0.01$).

Conclusions—Subcutaneous oestrogen is more effective than oral oestrogen in preventing osteoporosis, probably owing to the more physiological (premenopausal) serum oestradiol concentrations achieved. It also avoids problems of compliance that occur with oral treatment.

Introduction

Peak bone mass is achieved in the fourth decade of life in both men and women, after which it decreases with age. The rate at which bone is lost accelerates in women after the menopause to the extent that they have lost half of their skeletal calcium by the age of 70. This leads to the excess of osteoporotic fractures in women compared with men. Albright *et al* were the first to show the value of oestrogen in preventing

postmenopausal osteoporosis,¹ and several prospective studies have confirmed their results.^{2,4}

Oestrogens may be given orally as tablets or percutaneously as implants, creams, or patches.⁵ Although oral treatment is standard, subcutaneous implantation is a simple technique that can be performed as an outpatient procedure under local anaesthesia.⁶ Subcutaneous administration has several advantages: the enterohepatic circulation is avoided, gastrointestinal symptoms are reduced, and the ratio of oestradiol to oestrone achieved is physiologically appropriate.⁷ Oral treatment results in an abnormal ratio favouring oestrone as a result of conversion of oestradiol to oestrone in the liver. The percutaneous route also has the advantage that it can be used to give testosterone, if indicated, which avoids the hepatotoxic effects of oral methyltestosterone.

We investigated in a cross sectional study the effects of the route of administration of oestrogen in women attending our clinic who had been treated satisfactorily with oestrogen by various routes for many years for various menopausal symptoms. We compared them with a control group of postmenopausal women who had not started treatment with oestrogen and were attending our clinic for the first time.

Patients and methods

Table I shows the characteristics of the 114 women studied. They were postmenopausal as defined by amenorrhoea for at least one year with a serum follicle stimulating hormone concentration of more than 15 IU/l. Bone density was compared in a control group consisting of 36 untreated women (mean age 51.8 years; median time since last menstrual period 2.0 years); 37 women (mean age 57.5 years; median time since last menstrual period 8.5 years) who had been treated with oral oestrogens for a median of 8.0 years; and 41 women (mean age 56.2 years; median time since last menstrual period 9.5 years) who had been treated with subcutaneous implants of oestradiol and testosterone for a median of 8.5 years. The women treated either orally or subcutaneously, depending on their preference, had had amenorrhoea for a median of one year before starting their treatment.

All women with a uterus who were receiving oral oestrogens had their treatment supplemented with cyclic progesterone (either the combined preparation Prempak C, containing 12 days' supply of norgestrel (23 women), or Cyclo-progynova, containing 10 days' supply of levonorgestrel (six)). Women with a uterus receiving hormonal implants were given cyclic norethisterone 5 mg daily for the first seven to 13 days of each calendar month to prevent endometrial disorders.⁸ Hormonal implantation was carried out under local anaesthesia during a routine visit to the clinic, the pellets being inserted into the subcutaneous fat of the anterior abdominal wall. The usual dose was oestradiol 50 mg combined with testosterone 100 mg. Rarely, the oestradiol dose was increased to 75 or 100 mg. Implantation was repeated as symptoms of the climacteric returned, at about six month intervals, and at these visits bone density was measured and hormones assayed.

Bone density was estimated in the spine at L2-4 and in the neck of the right femur with a Novo 22A BMC-LAB dual photon absorptiometer with gadolinium-153 as the source of radiation.⁹ The ab-

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TABLE I—Characteristics of 114 women in study

	Controls	Women receiving:	
		Oral oestrogen	Oestradiol and testosterone implants
No of women	36	37	41
Mean (SD) age (years)	51.8 (4.1)	57.5 (6.6)	56.2 (7.4)
Mean (SD) weight (kg)	62.5 (6.5)	60.7 (8.0)	63.3 (8.7)
Median (range) years from menopause	2.0 (1-7)	8.5 (2-25)	9.5 (2-18)
Median (range) years of treatment		8 (1-20)	8.5 (1-22)
Median (range) years of amenorrhoea before treatment	2 (1-7)	1 (1-19)	1 (1-19)

sorptiometer was standardised with a solution radio-
logically equivalent to hydroxyapatite, and the results
were expressed as grams of hydroxyapatite per unit
projected area of bone. The precision of this technique
is 1-3% and the accuracy 2-5%.¹⁰

Statistical analysis—Data on the bone density, age,
and weight of the three groups of patients were
normally distributed and were therefore compared by
the non-paired Student's *t* test. All other variables were
analysed with the Mann-Whitney U test as they were
not normally distributed.

Results

The women in the two treatment groups were not
significantly different in terms of their age, weight,
years since the menopause, duration of treatment,
or duration of amenorrhoea before treatment. The
women in the control group were significantly younger
and were fewer years past the menopause ($p < 0.01$).

Table II summarises the measurements of bone
density and plasma concentrations of sex hormones
in the three groups. Bone density was significantly
increased in the women receiving subcutaneous oes-
tradiol and testosterone compared with the two other
groups. In the group receiving oral oestrogens the
median serum oestradiol concentration was slightly
but not significantly increased compared with that in
the control group and the median follicle stimulating
hormone concentration was significantly reduced but
remained within the postmenopausal range. Women
receiving subcutaneous oestrogen and testosterone had
a significantly increased median serum oestradiol
concentration and a significantly decreased follicle
stimulating hormone concentration compared with the
other women.

TABLE II—Bone density and serum concentration of sex hormones in untreated women and women who had been treated with hormones

	Women receiving:		
	Controls	Oral oestrogen	Oestradiol and testosterone implants
Mean (SD) bone density in spine (g hydroxyapatite/cm ²)	0.87 (0.14)	0.89 (0.11)	1.02 (0.13)*†
Mean (SD) bone density in neck of femur (g hydroxyapatite/cm ²)	0.73 (0.10)	0.74 (0.08)	0.80 (0.10)*†
Median (range) serum follicle stimulating hormone (IU/l)	72 (28-99)	43 (4-94)†	1 (1-11)*†
Median (range) serum oestradiol (pmol/l)	99 (44-580)	170 (30-651)	725 (372-2370)*†
Median (range) serum testosterone (nmol/l)	1.00 (0.3-2.7)	0.50 (0.3-2.2)	0.90 (0.4-2.4)

* $p < 0.01$ Compared with controls.

† $p < 0.01$ Compared with women receiving oral oestrogen.

Discussion

This study confirms the value of oestrogen replace-
ment treatment in preventing postmenopausal loss of
bone. The bone density in the spine and neck of the
femur in untreated women was maintained in women
given a median of 8.0 years of oral treatment but was
significantly increased in women who had been treated
for a median of 8.5 years with subcutaneous implants
of oestradiol and testosterone. The difference between
the two treatment groups cannot be explained by a
difference in the duration of amenorrhoea before
treatment. All of the women receiving subcutaneous
oestradiol also received testosterone but at a dosage
that reputedly does not have any significant effect
on bone.¹¹ The effect of androgens is, however, an
important therapeutic variable that needs further
evaluation, which is now being done.

The current recommended dose of oral oestrogen
for relieving menopausal symptoms and protecting
the skeleton is 0.625 mg or 1.25 mg conjugated
equine oestrogens or the equivalent dose of oestradiol
valerate.¹² The serum oestradiol concentration at this
dose will, however, be only slightly raised and the

follicle stimulating hormone concentration will remain
in the postmenopausal range.^{13,14} Several studies have
shown that higher concentrations of oestradiol are
achieved by subcutaneous implantations; the effect
was cumulative when implantation was repeated every
six months.^{11,15} This is due to the metabolic advantages
of the percutaneous route and the elimination of
non-compliance, which is reputed to occur in up to
70% of women prescribed oral oestrogens as replace-
ment treatment.¹⁶ Despite the cumulative effects of
repeated implantation on plasma oestradiol concentra-
tions no harmful effects have been identified on blood
pressure, coagulation of blood, or glucose tolerance.¹⁷
Percutaneous treatment is an efficient route of ad-
ministering oestrogen as many metabolic changes
occurring in the enterohepatic system are avoided and
an appropriate ratio of oestradiol to oestrone of about
2:1 results.^{7,18} We believe that the difference in bone
density between the two treatment groups was due to
the higher serum oestradiol concentrations achieved
with subcutaneous implants of oestrogen (725 *v*
170 pmol/l).

The precise mechanism whereby patients receiving
oestrogen implants gain bone is unclear. The higher
serum oestradiol concentrations achieved with implan-
tation may stimulate osteoblasts directly, leading to a
true gain in bone, or may be more effective in
suppressing resorption of bone, thus permitting some
recovery of early postmenopausal loss of bone. All
women had first started treatment on average about
one year after the menopause, a time when rapid
postmenopausal bone loss would be expected and
therefore when most could be gained by inhibiting
resorption of bone and allowing the resulting spaces to
be refilled. The increase in bone mass in the women
receiving subcutaneous implants was greater in the
spine than in the proximal femur, probably because the
vertebral bodies consist predominantly of trabecular
bone, which has a greater surface area and is metaboli-
cally more active than the cortical bone, which predomi-
nates in the femoral neck.¹⁹ Nevertheless, Keil *et al*
suggested that even fairly short exposure to oral
oestrogen within four years after the menopause may
confer long term protection against fracture of the
hip.²⁰

Despite the original suggestions of Albright *et al* that
the collagen of the bone matrix was important,¹ most
recent work on postmenopausal osteoporosis has con-
centrated on calcium and the hormones regulating
calcium, with conflicting results. The generalised loss
of collagen in the body that occurs with decreasing
oestrogen concentrations may be the primary factor
causing postmenopausal osteoporosis. The association
of osteoporosis with thin skin is well recognised, and
we recently showed that there is a 40% decline in
the collagen content and thickness of the skin after
the menopause that cannot only be prevented with
oestrogen but can be corrected to normal values
within nine months after the start of percutaneous
treatment.^{21,22} Decreased skin thickness with reduced
collagen content has been associated with osteoporosis
in anorexia nervosa (Savvas *et al*, unpublished results).
The loss of collagen in the skin has been estimated at
1-3% a year and is similar to the rate at which bone is
lost after the menopause, which suggests that the
collagen in bone may behave similarly to that in skin.²³
After loss of the matrix calcium would be lost as a
secondary effect independent of dietary calcium or
hormones regulating calcium. The observations that
osteoporotic bone has a reduced collagen content²⁴ and
that oestrogen receptors are present on osteoblasts
(F S Kaplan *et al*, unpublished results) support this
concept.

Clearly, the cornerstone of preventing osteoporosis
must now be oestrogen replacement treatment. The
results of our cross sectional study confirm the protec-

tive effect of oral oestrogens and show an apparent increase in bone mass after treatment with subcutaneous oestradiol and testosterone.

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Reversal of renal failure in nephritis associated with antibody to glomerular basement membrane

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Nephritis associated with antibody to glomerular basement membrane generally presents as rapidly progressive renal failure. Histological examination shows crescentic nephritis with linear deposits of IgG on the glomerular basement membrane. Pulmonary haemorrhage may occur. Effective treatment comprises immunosuppression and plasma exchange.¹ Recovery of useful renal function is considered to be unlikely but has been reported in patients dependent on dialysis.² We describe such a case in a patient with acute oliguric renal failure.

Case report

A 35 year old woman was referred in March 1987 with a one month history of tiredness and nausea. She complained of haematuria and oliguria but did not have any respiratory symptoms. She had a history of essential hypertension, which had been treated with a thiazide diuretic. Her renal function had been normal eight months earlier. On examination her blood pressure was normal and she did not have a rash. Radiographic examination of her chest showed no abnormalities. Her haemoglobin concentration was 101 g/l, urine volume 0.4 l, serum creatinine concentration 435 μ mol/l, and creatinine clearance 12 ml/minute. Her urine showed haematuria and red cell casts on microscopy.

Two days later her renal function had deteriorated further (serum creatinine concentration 715 μ mol/l and creatinine clearance 2 ml/minute). She underwent haemodialysis, after which percutaneous renal biopsy

was performed. On histological examination two of the four glomeruli obtained showed florid necrotising crescentic glomerulonephritis; there was an inflammatory reaction around the glomeruli and associated tubulointerstitial tissue. The other two glomeruli showed mild mesangial hypercellularity. No arteriolar lesions were observed. Immunofluorescence showed strongly positive linear deposits of IgG along the surviving capillary walls of the glomeruli. Her serum contained a high titre (80%) of antibody to glomerular basement membrane (normal value <12%) and a transient low titre of antibody to the cytoplasm of neutrophils on radioimmunoassay.

Treatment with 3 mg cyclophosphamide/kg, 60 mg prednisolone, and daily plasma exchange (4 litres) was started. The titre of antibody to glomerular basement membrane decreased to normal values (figure). She

Changes in titre of antibody to glomerular basement membrane and creatinine clearance during treatment with plasma exchange and cyclophosphamide and prednisolone

remained dependent on dialysis for four weeks; subsequently her renal function gradually recovered almost to normal (serum creatinine concentration 140 μ mol/l and creatinine clearance 60 ml/minute). Plasma exchange was stopped after six weeks and cyclophosphamide after eight weeks. Ten months after