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.

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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 progestogen (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-

TABLE I—*Characteristics of 114 women in study*

	Controls	Women receiving: Oral oestrogen	Women receiving: 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)