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Original Article

Long-Term Effects of Transdermal and Oral Hormone Replacement Therapy on Postmenopausal Bone Loss

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Abstract. Transdermal hormone replacement therapy (HRT) is now an accepted form of treatment, but the long-term skeletal effects have not been assessed. Sixty-six early postmenopausal women were randomized to receive either transdermal HRT (continuous 17β-oestradiol 0.05 mg/day, with 0.25 mg/day of norethisterone acetate added for 14 days of each 28-day cycle) or oral HRT (continuous conjugated equine oestrogens 0.625 mg/day, with 0.15 mg/day dl-norgestrel added for 12 days of each 28-day cycle). Treatment was given for 3 years and 30 matched untreated women were studied concurrently as a control group. Bone density was measured in the lumbar spine and proximal femur by dual-photon absorptiometry at 6-monthly intervals. Bone turnover was assessed by measurement of biochemical markers. At 3 years bone density had declined by 4% in the lumbar spine and by more than 5% in the femoral neck in the untreated group. By comparison bone density increased in both treatment groups at both sites (p <0.001 vs. untreated) and biochemical measurements indicated a significant reduction in bone turnover. There were no significant differences between the treatment groups. Twelve per cent of women on transdermal or oral treatments lost a significant amount of bone from the femoral neck by 3 years despite adequate compliance. Women taking therapy primarily for hip fracture prevention may require a follow-up bone density measurement to establish the efficacy of treatment.

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Introduction

The prevention of postmenopausal bone loss [1–6] and the subsequent reduction in the fracture rate [7,8] by oestrogens alone or oestrogen and progestogen combinations is one of the major benefits of hormone replacement therapy (HRT). However, there are few published prospective data beyond 2 years of the effects of oestrogens on the femoral neck, which is clinically the most important site of osteoporotic fracture [9]. Transdermal administration is now an established alternative route for HRT [10,11] and we have previously shown short-term benefits of the skeleton [5].

We now report the long-term results of a prospective controlled comparison of the effects of oral and transdermal HRT on bone loss in the lumbar spine and proximal femur.

Materials and Methods

Full details of the patients and methods have been published [5]. In summary, we studied 96 apparently healthy Caucasian women. All were between 6 months and 7 years postmenopausal or, in the hysterectomized women, since the onset of typical menopausal symptoms. Postmenopausal status was always confirmed by serum gonadotrophin measurement (FSH

>40 IU/l). All women were within 20% of their ideal body weight, were not taking any drugs known to affect bone metabolism and did not use cigarettes (>20/day) or alcohol (>300 g/week) excessively. Written informed consent was obtained from each patient and Ethics Committee approval was granted at both centres.

Sixty-six women seeking HRT were randomized to receive either oral or transdermal therapy. Both were prescribed continuously in 28-day cycles. Oral therapy consisted of conjugated equine oestrogens 0.625 mg/day with dl-norgestrel 0.15 mg/day added for the last 12 days of each 28-day cycle (Prempak-C, Wyeth-Ayerst, Maidenhead, UK). Transdermal therapy comprised 17β-oestradiol 0.05 mg/day (Estraderm TTS 50, Ciba-Geigy, Basel, Switzerland) for the first 14 days of the cycle and 17β-oestradiol 0.05 mg/day plus 0.25 mg/day norethisterone acetate (Estragest, Ciba-Geigy, Basel, Switzerland) for the second 14 days. All patches were applied to the skin below the waist and were changed twice weekly. All patients recorded the taking of tablets or changing of patches and the occurrence of any vaginal bleeding or side-effects. Ethics Committee approval was not granted for a long-term (3-year) study with a placebo group. Therefore, we recruited 30 matched women concurrently to serve as an untreated control group.

Thyroid and parathyroid disease, oesteomalacia and occult renal and hepatic conditions were excluded by appropriate measurements. We recorded height, weight, blood pressure, cigarette and alcohol consumption. We assessed physical exercise by a modified questionnaire [12] and dietary calcium intake from dairy produce intake. At each visit a venous blood sample was taken from a 12-h overnight fast for the measurement of plasma oestradiol, oestrone and follicle stimulating hormone (FSH), serum calcium, albumin, phosphate and alkaline phosphatase. Serum calcium was corrected for serum albumin levels. A fasting urine sample was collected for the measurement of urinary calcium, creatinine and hydroxyproline. These results were expressed as calcium/creatinine (Ca/Cr) and hydroxyproline/creatinine (OHPr/Cr) ratios [5]. Total and high-density lipoprotein (HDL) cholesterol and triglyceride levels were measured by enzymatic methods and low-density lipoprotein (LDL) cholesterol was measured by preparative ultracentrifugation [11].

Bone density measurements were performed pretreatment and at 6-monthly intervals by dual-photon absorptiometry using a Lunar DP3 (Lunar, Madison, Wis.). Spinal bone density was measured in the first four lumbar vertebrae and the mean value of the second, third and fourth lumbar vertebrae was taken wherever possible. For longitudinal comparison the same combinations of vertebral measurements were used for each individual throughout the study. Proximal femur bone density was measured in the femoral neck, Ward's triangle and the trochanteric region. Significant bone loss after 3 years of treatment in either spine or hip was defined as that which was more than twice the precision of the measurement. Quality control of bone density measurements was monitored both in vitro and in vivo throughout the study by performing serial measurements of phantoms, cadaveric samples and young volunteers [5,13]. The isotope source was changed four times during the study period.

Compliance was assessed by examination of the diary cards, monitoring bleeding patterns, serial measurements of gonadotrophin and oestradiol levels and by

Table 1. Baseline demographic, bone density and biochemical data

	Untreated (n = 30)[a]	Transdermal (n = 33)	Oral (n = 33)[b]
Age (yr)	53.9 (2.9)*	52.3 (3.6)	51.8 (3.6)
Months since menopause	35.7 (6–72)	24.0 (6–84)	24.4 (8–72)
Ponderal index	23.8 (2.2)	23.7 (2.1)	23.2 (1.4)
Hysterectomy (%)	33	21	27
Bone density (g/cm^2)			
L2–4	1.126 (0.123)	1.178 (0.140)	1.168 (0.161)
Femoral neck	0.885 (0.132)	0.904 (0.119)	0.905 (0.141)
Ward's triangle	0.786 (0.164)	0.800 (0.134)	0.797 (0.169)
Trochanter	0.743 (0.114)	0.781 (0.114)	0.787 (0.122)
Biochemistry			
Serum calcium (mmol/l)	2.23 (0.08)	2.21 (0.08)	2.21 (0.10)
Serum phosphate (mmol/l)	1.27 (0.11)	1.23 (0.15)	1.21 (0.14)
Serum ALP (IU/l)	69.6 (15.9)	70.3 (23.4)	65.0 (13.5)
Urinary Ca/Cr (mmol/mmol)	0.39 (0.02)	0.36 (0.16)	0.38 (0.24)
Urinary OHPr/Cr (mmol/mmol)	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)

[a] n = 29 for femoral neck, Ward's triangle and trochanteric measurements.
[b] n = 31 for femoral neck, Ward's triangle and trochanteric measurements and n = 32 for urinary measurements.
* p <0.05 vs. oral group.
ALP, alkaline phosphatase; Ca/Cr, calcium/creatinine; OHPr/Cr, hydroxyproline/creatinine.

asking patients to return all used medication packs which were counted at each visit.

Statistical Analysis

Bone density and biochemical changes were evaluated as absolute values and as percentage changes from baseline. Time since menopause data and plasma oestradiol levels were not normally distributed and are presented as median and ranges or 95% confidence limits. Two-tailed paired Student's *t*-tests or Wilcoxon matched-pairs ranked-sign tests were used to compare the changes at each time point with the baseline values. Linear regression analysis was also used to confirm bone loss in women whose final bone density indicated significant loss. Differences between the patient groups were assessed by using one-way repeated measures analysis of variance, two-tailed unpaired Student's *t*-test, Kruskal–Wallis one-way analysis or variance, Mann–Whitney *U*-tests, and chi-squared analyses as appropriate.

Results

The baseline measurements for the three groups are shown in Table 1. Women in the untreated control group had less premenopausal exposure to the contraceptive pill than women in the two treatment groups ($p < 0.05$). There were no differences between the groups in any other parameters which might affect bone metabolism [5].

There were 10 (33%) withdrawals from the untreated control group, 7 (21%) from the transdermal group and 7 (21%) from the oral group over the 3 years. Nine patients (5 oral and 4 transdermal) withdrew because of treatment-related side-effects which included pelvic pain, progestogenic effects, weight gain, dysmenorrhoea, dislike of the recurrence of vaginal bleeding, and

Table 2. Changes in biochemical markers

Measurement	Untreated	Transdermal	Oral
Serum calcium (mmol/l)			
12 months	−0.00 (0.09) ($n = 30$)	−0.06 (0.9)** ($n = 31$)	−0.03 (0.09) ($n = 29$)
24 months	−0.00 (0.09) ($n = 25$)	−0.02 (0.11)$^{+}$ ($n = 28$)	−0.03 (0.11) ($n = 27$)
36 months	−0.05 (0.12) ($n = 20$)	−0.02 (0.11)* ($n = 26$)	0.02 (0.11) ($n = 26$)
Serum phosphate (mmol/l)			
12 months	0.00 (0.17) ($n = 30$)	−0.06 (0.16)* ($n = 31$)	−0.14 (0.16)*** ($n = 29$)
24 months	0.05 (0.16) ($n = 25$)	−0.10 (0.14) ($n = 28$)	−0.13 (0.15)$^{+++}$*** ($n = 27$)
36 months	−0.04 (0.15) ($n = 20$)	−0.06 (0.14)$^{+}$ ($n = 26$)	−0.10 (0.16)$^{++}$ ($n = 26$)
Serum APL (IU/l)			
12 months	0.50 (8.80) ($n = 30$)	−12.9 (12.7)*** ($n = 31$)	−14.5 (11.3)*** ($n = 30$)
24 months	−0.36 (9.63) ($n = 25$)	−14.3 (14.4)$^{+++}$*** ($n = 27$)	−13.0 (14.0)$^{+++}$*** ($n = 27$)
36 months	0.79 (10.8) ($n = 19$)	−17.1 (15.4)$^{+++}$* ($n = 26$)	−12.8 (12.9)$^{+++}$** ($n = 25$)
Urinary Ca/Cr (mmol/mmol)			
12 months	−0.11 (0.21)$^{+}$ ($n = 29$)	−0.11 (0.15)$^{+++}$ ($n = 30$)	−0.16 (0.28)$^{++}$ ($n = 29$)
24 months	−0.09 (0.20)$^{+}$ ($n = 25$)	−0.20 (0.14)$^{+++}$** ($n = 27$)	−0.19 (0.22)$^{+++}$* ($n = 26$)
36 months	−0.07 (0.20) ($n = 19$)	−0.08 (0.17)$^{+}$ ($n = 26$)	−0.15 (0.24)$^{++}$ ($n = 26$)
Urinary OHPr/Cr (mmol/mmol)			
12 months	0.004 (0.008) ($n = 29$)	−0.005 (0.007)$^{+}$ ($n = 30$)	−0.004 (0.012) ($n = 29$)
24 months	−0.002 (0.005) ($n = 25$)	−0.004 (0.006)$^{++}$ ($n = 27$)	−0.007 (0.009)$^{+++}$*** ($n = 26$)
36 months	0.002 (0.005)$^{+}$ ($n = 19$)	−0.002 (0.006)** ($n = 26$)	−0.005 (0.009)$^{+}$* ($n = 26$)

Values are the mean (SD).
$^{+}p < 0.05$ vs. baseline; $^{++}p < 0.01$ vs. baseline; $^{+++}p < 0.001$ vs. baseline.
$^{*}p < 0.05$ vs. untreated controls; $^{**}p < 0.01$ vs. untreated controls; $^{***}p < 0.001$ vs. untreated controls.

Table 3. Changes in bone density

	Untreated	Transdermal	Oral
L2–4			
12 months	−0.008 (0.037) (n = 30)	0.033 (0.034)$^{+++***}$ (n = 31)	0.032 (0.034)$^{+++***}$ (n = 29)
24 months	−0.024 (0.028)$^{+++}$ (n = 25)	0.032 (0.041)$^{+++***}$ (n = 26)	0.035 (0.034)$^{+++***}$ (n = 27)
36 months	−0.039 (0.041)$^{+++}$ (n = 19)	0.046 (0.040)$^{+++***}$ (n = 26)	0.038 (0.063)$^{++***}$ (n = 26)
Femoral neck			
12 months	−0.019 (0.036)$^{++}$ (n = 28)	0.015 (0.044)** (n = 29)	0.003 (0.037)* (n = 28)
24 months	−0.038 (0.034)$^{+++}$ (n = 24)	0.021 (0.040)$^{+}$*** (n = 27)	0.001 (0.040)*** (n = 25)
36 months	−0.044 (0.033)$^{+++}$ (n = 18)	0.020 (0.048)$^{+}$*** (n = 26)	0.009 (0.056)*** (n = 24)
Ward's triangle			
12 months	−0.010 (0.037) (n = 28)	0.008 (0.061) (n = 29)	0.001 (0.004) (n = 28)
24 months	−0.035 (0.030)$^{+++}$ (n = 24)	0.006 (0.053)** (n = 27)	0.001 (0.047)* (n = 25)
36 months	−0.042 (0.039)$^{+++}$ (n = 18)	0.009 (0.060)*** (n = 26)	−0.009 (0.072)* (n = 24)
Trochanter			
12 months	−0.002 (0.025) (n = 28)	0.016 (0.006)$^{++}$ (n = 28)	0.023 (0.008)$^{++***}$ (n = 28)
24 months	−0.011 (0.006) (n = 24)	0.010 (0.006)* (n = 27)	0.011 (0.010)* (n = 25)
36 months	−0.013 (0.008) (n = 18)	0.022 (0.009)$^{+}$*** (n = 26)	0.029 (0.015)** (n = 23)

Values are the mean (SD).
^{+}p <0.05 vs. baseline; ^{++}p <0.01 vs. baseline; ^{+++}p <0.001 vs. baseline.
$^{*}p$ <0.05 vs. untreated controls; $^{**}p$ <0.01 vs. untreated controls; $^{***}p$ <0.001 vs. untreated controls.

skin reaction to the patch. Ten patients (5 treated and 5 untreated) withdrew for miscellaneous reasons which included fear of breast cancer, moving away, poor compliance, commencing steroids for asthma and personal reasons.

The annual changes from baseline in the biochemical markers of bone turnover from baseline are shown in Table 2. There were no significant differences between the two treatment groups for any variable at any timepoint.

The in vivo precision of the bone density measurements during the entire study was 0.9% for the lumbar spine, 1.6% for the femoral neck, 2.7% for Ward's triangle and 2.3% for the trochanteric region. Table 3 shows the absolute changes in bone density at the various sites at yearly intervals. Mean bone density had declined by 4% in the spine and by 5% in the femoral neck in the untreated group after 3 years. The mean percentage changes are shown in Figs. 1 and 2. There was a significant increase in mean bone density with both treatments at 3 years with no significant differences between treatments. The individual percentage changes at 3 years are shown in Figs. 3 and 4. There was a

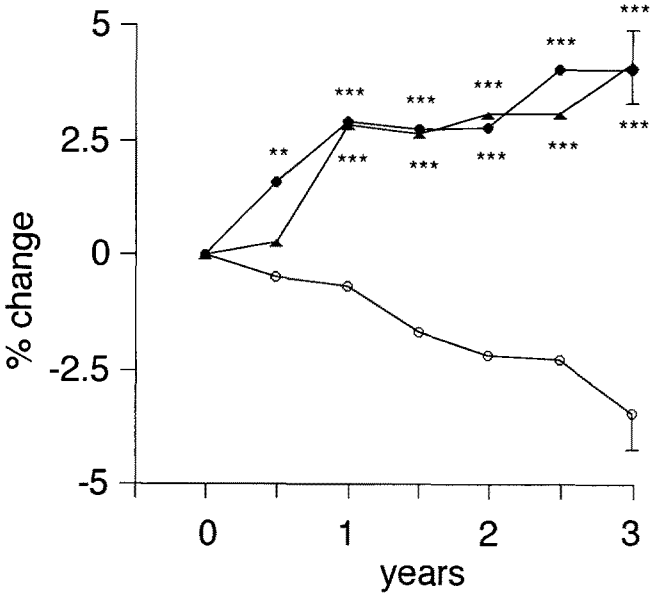

Fig. 1 Bone density changes (mean percentage initial value) in the lumbar spine L2–4. *Open circles*, untreated; *filled circles*, transdermal; *filled triangles*, oral. $^{***}p$ <0.001 vs. untreated.

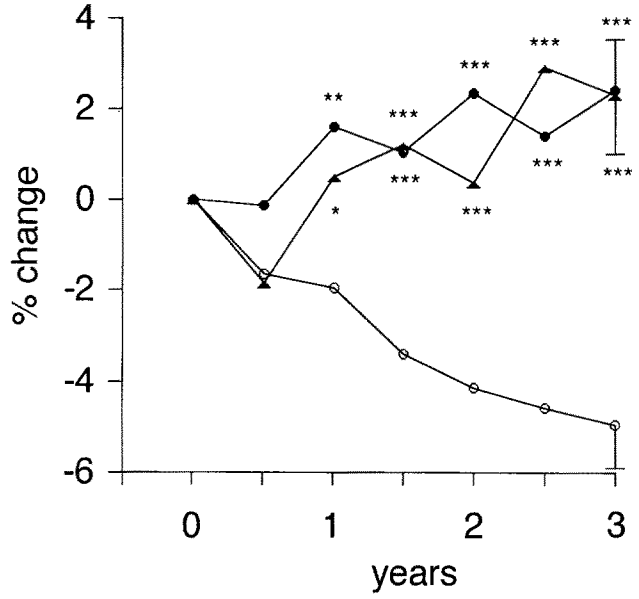

Fig. 2 Bone density changes (mean percentage initial value) in the femoral neck. *Open circles*, untreated; *filled circles*, transdermal; *filled triangles*, oral. ***p <0.001 vs. untreated.

significant difference between bone density changes in the untreated group compared with the treated groups in the lumbar spiune (p <0.001), femoral neck (p <0.001), Ward's triangle (p <0.01) and trochanteric region (p <0.02).

In the 37 non-hysterectomized women who completed treatment the percentage change in bone density at the femoral neck positively correlated with time since menopause (Spearman r = 0.35, p <0.05).

Femoral Neck Bone Losers

At 3 years 6 (12%) women had lost bone significantly from the femoral neck (Fig. 4) and 1 (2%) of these also had lost bone significantly from the lumbar spine (Fig. 3). Mean bone loss (± SEM) calculated by linear regression analysis was 5.0% ± 1.0. Seven (14%) women had lost bone significantly from Ward's triangle and 3 (6%) from the trochanteric region.

Table 4 compares the demographic variables for these femoral neck bone losers with the 10 women, 5 each from the two treatment groups, who had the greatest response to treatment ('best' responders) and with a third group comprising the remaining treated women who completed the study ('average' responders). The best responders were further past the menopause than the bone losers (p <0.01) and the average responders (p <0.005). All the bone losers complied with treatment as judged by returned medication and diary cards and had appropriate bleeding patterns (non-hysterectomized only). Table 5 compares the baseline bone density measurements at each site, the biochemical markers of bone turnover and the oestradiol levels in the three groups. The best responders had the lowest pretreatment bone density at each site and there was a greater fall in serum calcium in the best responders as compared with the bone losers at 12 and 24 months (p <0.05). The best responders had a higher oestradiol level than the average responders throughout the study but this was only significant at 2 years (p <0.05).

Mean LDL cholesterol values of the bone losers were compared with the average and best responders combined according to treatment group. In the transdermal group, the pretreatment LDL was significantly higher than in the remainder (178 mg/dl (n = 4) vs. 137 mg/dl

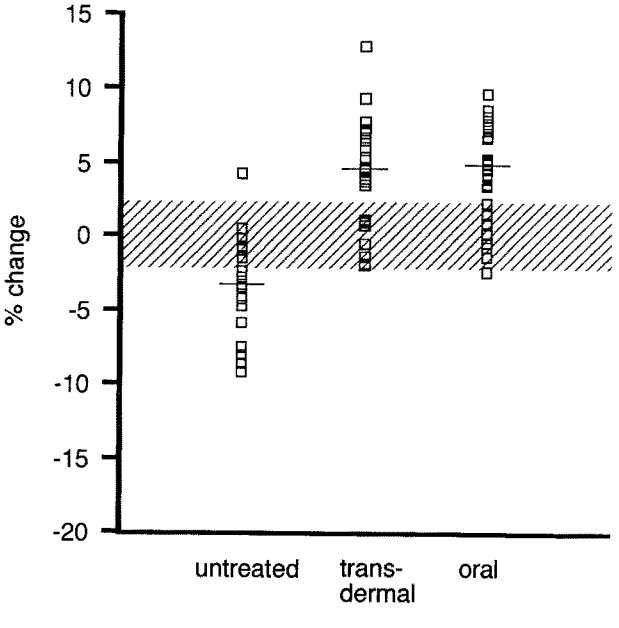

Fig. 3 The individual percentage changes in lumbar spine bone density at 3 years in the three groups. The *shaded area* represents twice the coefficient of variation of the measurement.

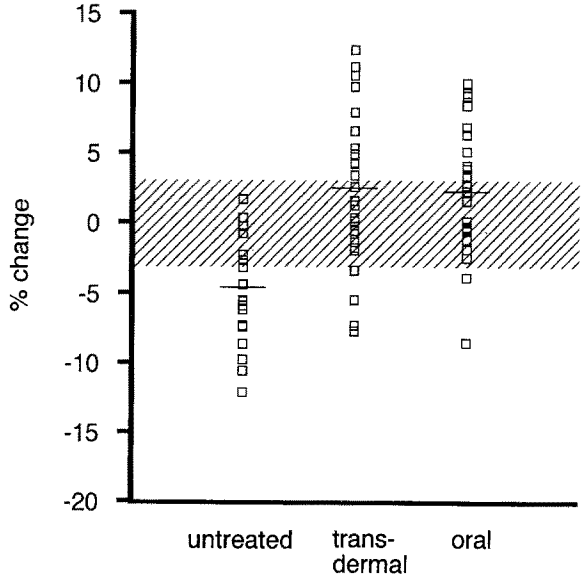

Fig. 4 The individual percentage changes in femoral neck bone density at 3 years in the three groups. The *shaded area* represents twice the coefficient of variation of the measurement.

Table 4. Comparison of femoral neck bone losers with best and average responders: demographics

	Bone losers	Average responders	Best responders
Number (transdermal + oral)	6 (4+2)	34 (17+17)	10 (5+5)
Age (yr)	52.1 (3.19)	51.5 (3.73)	53.8 (3.08)
Weight (kg)	62.3 (4.34)	62.5 (7.29)	61.9 (6.95)
Months since menopause (median and range)	11 (7–36)	18 (6–84)	42 (24–60)*
Parity (*n*)	3	2*	2
Previous oral contraceptives (%)	50	65	60
Hysterectomy (%)	17	18	40
Smoker (%)	17	18	10
Alcohol (g/week) (median and range)	3.5 (0–6)	2.5 (0–28)	2 (0–14)
Family history of osteoporosis (%)	66	41	40
Daily exercise (kJ (kcal)/day)	2447 (347)	2379 (296)	2510 (630)

Values are the mean (SD) unless otherwise stated.
*p <0.05 vs. bone losers.

Table 5. Comparision of femoral neck bone losers with best and average responders: baseline bone density, biochemistry and oestradiol

	Bone losers (n = 6)	Average responders (n = 34)	Best responders (n = 10)
Bone density (g/cm²)			
L2–4	1.233 (0.189)	1.155 (0.142)	1.325 (0.174)
Femoral neck	0.975 (0.118)*	0.912 (0.132)**	0.806 (0.093)
Ward's triangle	0.844 (0.130)	0.808 (0.143)*	0.696 (0.142)
Trochanter	0.810 (0.130)	0.789 (0.110)	0.732 (0.113)
Oestradiol (pg/ml)[a]			
12 months	64 (49–72)	46 (37–56)	51 (39–67)
24 months	49 (35–69)	42 (34–56)*	54 (48–57)
36 months	48 (44–50)	46 (31–67)	65 (41–69)
Calcium (mmol/l)			
12 months	0.01 (0.07)*	−0.05 (0.10)	−0.11 (0.08)
24 months	0.04 (0.11)*	−0.03 (0.10)	−0.09 (0.03)
36 months	0.02 (0.03)	−0.01 (0.11)	−0.01 (0.14)
OHPr/Cr (mmol/mmol)			
12 months	−0.012 (0.009)	−0.001 (0.009)	−0.004 (0.013)
24 months	−0.01 (0.009)	−0.003 (0.005)	−0.007 (0.013)
36 months	−0.011 (0.012)	−0.002 (0.005)	−0.004 (0.012)

Values are the mean (SD) unless otherwise stated.
[a]Median and 95% confidence interval.
*p <0.05 vs. best responders; **p <0.01 vs. best responders.

(n = 21), p <0.005), but there was a similar response to treatment: a 9.3% fall in the bone losers over the first 12 months and a 9.2% fall in the remainder over the corresponding period. In the oral group thre was no significant difference between the bone losers and the remainder for mean pretreatment LDL (162 mg/dl (n = 2) vs. 139 mg/dl (n = 21)) and again there was a similar response to treatment in the first 12 months: a 20% fall and an 18% fall, respectively.

Discussion

Our results are the first controlled prospective data beyond 2 years on the effects of either oral or transdermal HRT on the femoral neck. They have demonstrated an initial increase in bone density which was maintained at 36 months. During the first 12 months of HRT there was a greater percentage fall in urinary hydroxyproline/creatinine excretion than in serum alkaline phosphatase, indicating a greater reduction in bone resorption than formation thereby leading to a net gain of bone. By 36 months the biochemical indices showed a tendency to return towards their pretreatment values, perhaps indicating a resetting of the homeostatic balance between formation and resorption.

Postmenopausal oestrogen therapy reduces the risk of osteoporotic fractures at the femoral neck [7,8]. Fracture risk is determined by a number of factors including bone density, bone quality and the frequency and type of fall [14]. These results confirm our preliminary findings [5] that oral and transdermal HRT are

equally effective in the prevention of postmenopausal bone loss. Both therapies conserved bone in the femoral neck and suggest that this is an important mechanism whereby oestrogens reduce hip fracture risk. Transdermal combined HRT also effectively relieves menopausal symptoms, provides good cycle control with endometrial suppression [10] and produces favourable alterations in the lipid profile [11].

Skeletal responses to HRT may vary at different sites, with a greater response noted in the lumbar spine than in either the distal radius [4] or the femoral neck [5,6], perhaps due to varying rates of bone remodelling [6]. This was also observed in our present study. A variation in the rate of trabecular bone remodelling may also explain why fewer women receiving treatment lost bone at the lumbar spine than at the femoral neck, Ward's triangle and the trochanteric region.

Twelve per cent of women on treatment lost a significant amount of bone at the femoral neck despite taking a dosage that conserved bone mass in the group as a whole. In other studies where individual data have been reported, between 5% and 30% of women lost bone from the forearm or spine although bone conservation was achieved in the whole group [3,4]. However, previous studies have not specifically assessed patient compliance. Clearly there appears to be a wide variation in individual response to a given dose of HRT, but the reasons for this are not clear. In this study, women taking either treatment were similarly affected. Examination of the returned medication packs and completed diary cards showed that lack of compliance was not the explanation. In addition, the bone losers responded appropriately to treatment in terms of an increase in plasma oestradiol (which confirmed compliance) and a lowering in LDL cholesterol (indicative of a biological response). Changes in bone biochemistry were indicative of a treatment response in both bone losers and non-losers, although a difference in the balance between bone formation and resorption cannot be excluded between these two groups.

Two differences between the bone losers and the best/average responders were present. Firstly, the best responders had a lower pretreatment bone density at all sites and were further past the menopause than both the bone losers and the average responders. Lindsay and Tohme [6] also reported a similar finding amongst women with established osteoporosis. Furthermore, we have recently reported similar relationships between response to postmenopausal oestrogen therapy and time since menopause when related to changes in vessel tone in both the uterine [15] and the internal carotid [16] arteries. Thus, it appears that the longer the time of oestrogen deprivation (i.e. the time since menopause) the greater the capacity of oestrogen-sensitive tissues to respond to the reintroduction of oestrogen.

Secondly, the subgroup of bone losers may represent women with a lower biological response to oestrogen. This might explain why the bone losers had a significantly higher pretreatment LDL than the average and best responders (transdermal group only). It remains to be determined whether the bone losers will respond to higher dosage of oestrogen. A dose of 0.625 mg/day is the minimum bone-sparing dose of conjugated equine oestrogens in the metacarpals [17] and spine [3], but higher doses appear to have no additional effect [17]. Others have reported a progressive dose-related response with oral micronized oestradiol in the forearm [18] and in the spine [19]. No dose ranging studies have yet been performed at the femoral neck with transdermal therapy.

In conclusion, we have demonstrated that untreated postmenopausal women progressively lose bone from the proximal femur and lumbar spine. This loss is prevented by the use of HRT and the benefits of treatment are continued long term. Transdermal HRT is equally as effective as oral therapy in this respect. These observations re-emaphasize the importance of the early introduction of preventive therapy around the time of or soon after the menopause. Importantly, a small percentage of women do not achieve effective bone conservation despite taking standard doses of HRT. Thus, some form of monitoring of the treatment response, ideally with a follow-up bone density measurement, may be advisable. Whether higher doses of oestrogen will reduce bone loss in such women remains to be determined.

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