

ORIGINAL ARTICLES

Hormone Replacement Therapy (HRT) or Etidronate for Osteoporosis in Postmenopausal Asthmatics on Glucocorticoids: a Randomised Factorial Trial

IA Campbell¹, JG Douglas², RM Francis³, RJ Prescott⁴, DM Reid⁴,
on behalf of the Research Committee of the British Thoracic Society.

¹Chest Department, Llandough Hospital, Penarth, UK

²Department of Respiratory Medicine, Aberdeen Royal Infirmary, UK

³Musculoskeletal Research Group, School of Clinical Medical Studies, University of Newcastle, UK

⁴Medical Statistics Unit, Public Health Sciences, University of Edinburgh, UK

⁵Department of Medicine and Therapeutics, University of Aberdeen, Medical School, Foresterhill, Aberdeen, UK

Correspondence to

Dr. Ian A. Campbell, OPD, Llandough Hospital, Penarth, Vale of Glamorgan, CF64 2XX.
Tel: 00 44 29 20715417 Fax: 00 44 29 20350056 Email: ian.campbell@cardiffandvale.wales.nhs.uk

Conflicts of Interest

None

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Abstract

Introduction

The study was designed to establish the effects of HRT on osteoporosis and fractures over five years in postmenopausal women with asthma receiving regular glucocorticoids and to compare with etidronate.

Methods

Postmenopausal patients receiving inhaled and/or oral glucocorticoids were randomly assigned to HRT, cyclical etidronate, HRT plus cyclical etidronate or no treatment for five years. The trial was multi-centre and aimed to recruit 750 patients. Outcomes were fractures and changes in bone mineral density (BMD).

Results

For reasons detailed in the discussion section of the text, only 50 patients were entered. Three did not fulfil the eligibility criteria and were excluded from the analysis. Among the remaining 47 patients, three (6%) experienced new, symptomatic fractures, one on etidronate and two in the no treatment group. New or worsening morphometric fractures of the thoracolumbar spine occurred in 50% of the 22 patients with spinal radiographs on entry and at five years (one HRT, three etidronate, two HRT plus etidronate and five on no treatment). BMD improved by approximately 1% per annum in those receiving HRT and/or etidronate; comparisons of HRT vs no HRT tended to favour HRT but were only statistically significant at proximal femur. The same trends emerged in the etidronate vs no etidronate comparison, but none reached the 5% level of statistical significance.

Discussion

For postmenopausal patients receiving glucocorticoids for asthma, HRT appears as effective as etidronate in preventing loss of BMD over five years and may have a similar effect on fracture prevention.

Key Words

Asthma, Glucocorticoids, HRT, Etidronate, Osteoporosis

Introduction

Prior to the Women's Health Initiative Study and the Million Women Study,^{1,2} hormone replacement therapy (HRT) was commonly used for the prevention and treatment of osteoporosis in post-menopausal women.^{3,4} Although HRT is now rarely used for the prevention and treatment of osteoporosis, it may have a place in women with severe climacteric symptoms and those unable to take other treatments.^{5,6} There have been few reports of prospective studies of HRT used for the prevention and treatment of osteoporosis in post-menopausal women receiving glucocorticoids, one of which was in patients with rheumatoid arthritis⁷ and the other in a small population of 15 patients with asthma who were followed up for only one year.⁸ There have been no reports of long-term studies of the effect of HRT on the occurrence of fractures in women with asthma receiving glucocorticoids.

In August 1992 the Research Committee of the British Thoracic Society (BTS) initiated a prospective study of HRT and/or etidronate (ET) in this group of patients, a trial which is now likely to remain unique in terms of the long-term data provided on the use of HRT in patients receiving glucocorticoids. The results of a sister study where patients were randomised to etidronate +/- calcium have been published, showing some benefit on BMD from etidronate over a five year period.⁹

Materials and Methods

The study population, drawn from 13 centres in the United Kingdom, consisted of post-menopausal outpatients with asthma (as diagnosed by the participating physician), aged <60 years, who had been taking oral and/or inhaled glucocorticoid treatment for at least one year, including those with pre-existing osteoporosis and with vertebral and non-vertebral fractures. Classification as post-menopausal was decided by the participating physician and local gynaecologist. Patients were stratified according to the use of glucocorticoids (oral; inhaled and no more than three months oral in past year; inhaled and no more than 30 days of oral glucocorticoid ever) and, within each stratum and centre, treatment was allocated (by telephone from a central office) in random order in permuted blocks of four within a factorial, open design so that patients received one of the four following regimens: (1) HRT plus ET; (2) HRT alone; (3) ET alone; (4) No treatment. HRT was prescribed according to the advice of local gynaecologists, as preparations containing a minimum oestrogen dose of 2mg oestradiol or 0.625mg conjugated oestrogen or 50mcg transdermal oestradiol. Etidronate was given orally in a dose of 400mg daily on an empty stomach (two hours before or after food) for two weeks every three months.

Consistent with accepted practice in 1992, verbal informed consent was obtained from patients without the use of a written information sheet. Ethical approval was obtained from the appropriate local research ethics committee. All work was conducted in accordance with the Helsinki declaration of 1975 as revised in 1983.

Patient Data, End-Points and Quality Control Measures

On entry to the study the age, sex, weight, height, number of years of treatment with inhaled glucocorticoid and with continuous oral glucocorticoid, mean daily dose of the inhaled and/or oral glucocorticoid over the previous year, assessment of physical activity on a three point scale (limited, normal, or regular brisk exercise), and history of osteoporosis related fracture (defined as such by the clinician) were recorded.

Lateral radiographs of the dorsal and lumbar spine were obtained. In those centres with the facilities, bone densitometry was measured at the lumbar spine and the proximal femur using dual energy x-ray absorptiometry (DXA); 15 centres used Lunar DPX machines and six used Hologic QDR machines (1000, 1000W or 2000).

Because of systematic differences in absolute BMD measurements from different machines, the baseline comparisons of BMD data were standardised using published equations.¹⁰ Quality control was performed according to local practice and no cross calibration phantoms were used. Changes in BMD from baseline were calculated after logarithmic transformation and presented as percentage change.

Information on glucocorticoid dosage, physical activity, new symptomatic fractures, and BMD was requested annually over five years using a review form sent from the co-ordinator to the physician for completion and return. The occurrence of new symptomatic fractures was based on patients' answers in response to direct questioning by the physicians. Although centres were asked to measure height in a standardised manner, this was not always done satisfactorily and the results were not suitable for analysis.

Lateral radiographs of the dorsal and lumbar spine were repeated at five years unless clinically indicated at other times.

These radiographs were inspected for fractures and morphometric measurements were performed on the radiographs at entry and at five years by a single observer without knowledge of the treatments received by the patients. An incident vertebral fracture was defined by quantitative morphometry as a loss of vertebral height of 20% or more at the anterior, mid, or posterior regions on each vertebral body from T4 to L4, whether or not the vertebra was intact at baseline. All fractures so defined were validated using semi-quantitative visual identification as recommended by Genant et al.¹¹

It was calculated that 750 patients in the trial should yield 80% power to detect statistically significant differences at the 5% level between HRT and no HRT or between etidronate and no etidronate when symptomatic fracture rates were assumed to be 3% vs 8% in treatment and placebo groups respectively.

Analysis was by intention to treat after exclusion of ineligible patients. Contingency tables were analysed by Fisher's Exact Test. For the analysis of BMD data, a repeated measures analysis of covariance was conducted, using a Toeplitz covariance structure

Results

Despite extending the period of intake by just over a year, recruitment to the study was low, with just 50 patients entered into the trial between August 1992 and October 1995 by 17 physicians from 13 centres. Three patients were ineligible for entry as they were pre-menopausal (2) or post-hysterectomy (1), leaving 47 patients for analysis. Fourteen patients were taking continuous oral glucocorticoid, 18 continuous inhaled glucocorticoid plus no more than three months of oral glucocorticoid in the preceding year and 15 had received continuous inhaled glucocorticoid and no more than 30 days of oral glucocorticoid ever. The treatment groups (11 HRT, 10 ET, 13 HRT/ET, 13 no treatment) were comparable in terms of these and other baseline characteristics measured at entry. One patient randomised to ET was treated with HRT (it proved impossible to ascertain whether this was an error by the physician or the general practitioner). This patient did not have BMD measurements and was lost to follow-up after two years, during which period no symptomatic fractures were reported. For purposes of the analysis the patient was retained in the ET group. Two died during the five years of follow-up (an HRT/ET patient from septicaemia and an ET patient from aortic valve disease). One patient was unable to tolerate ET (gastro-intestinal upset) and three patients the combination of HRT and ET (one due to excessive vaginal bleeding, one due to hypertension and one due to gastro-intestinal upset and headache). In the absence of any indication of an interaction between HRT and ET, the factorial design was utilised to compare HRT vs no HRT, and ET vs no ET.

Fractures

Of the 47 patients, three (6%) experienced new, symptomatic vertebral or non-vertebral fractures over five years: one ET (wrist and symptomatic vertebral fractures) and two on no treatment (both symptomatic rib fractures). Comparisons of HRT versus No HRT and of ET versus No ET are shown in Table I.

Twenty-two patients (five ET, eight no treatment, three HRT and six HRT/ET) had radiographs of the thoraco-lumbar spine on entry and at five years after entry. New or worsening semi-quantitative vertebral fractures were observed in 11 (50%) of these (three ET, five no treatment, one HRT and two HRT/ET).

Comparisons of HRT versus No HRT and of ET versus No ET in terms of these fractures are presented in Table II.

The three patients with symptomatic vertebral and/or non-vertebral fractures were all within the group of 11 patients with new or worsened semi-quantitative vertebral fractures. Thus, overall, at least 23% of the patients experienced one or other of both types of fracture over the five years of the study.

Table I: Patients with Symptomatic New Vertebral and Non-Vertebral Fractures over 5 Years

Treatment	HRT	No HRT	ET	No ET
No. Patients	23	24	24	23
No. with new fractures	0	3(13%)	1(4%)	2(8%)
	$p = 0.25$		$p = 0.97$	

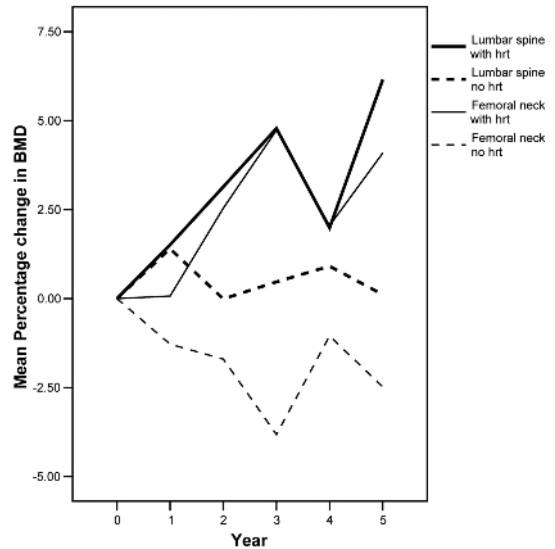
Table II: Patients with Thoraco-Lumbar Spinal Radiographs at Entry and at Five Years: Number of Semi-Quantitati Vertebral Fractures Observed.

Treatment No ET	HRT	No HRT	ET
No. Patients 11	9	13	11
No. Patients with new or worsened fractures 6(55%)	3(33%)	8(62%)	5(45%)
	$p = 0.39$		$p = 1.0$

Bone Mineral Density

Twenty-six patients had at least one set of BMD measurements of lumbar spine and femoral neck by Dual Energy X-ray Absorptiometry at baseline and during follow-up. The numbers of patients having BMD measurements each year over the five years follow-up are shown in Table III, as are the changes in BMD. In the comparison of HRT versus No HRT, there were almost uniform positive trends with HRT, both in the lumbar spine (L2-L4) and at the proximal femur (Figure 1), with BMD improving by approximately 1% per annum.

Figure 1: Mean Percentage Changes in BMD at Lumbar Spine and at Femoral Neck for HRT vs No HRT



At the proximal femur, the changes were significant at the 5% level (HRT by time interaction: $p = 0.03$; HRT main effects: $p = 0.05$). Similar trends were found in the comparison of ET versus No ET (Figure 2), although none was statistically significant.

Figure 2: Mean Percentage Changes in BMD at Lumbar Spine and at Femoral Neck for Etidronate vs No Etidronate

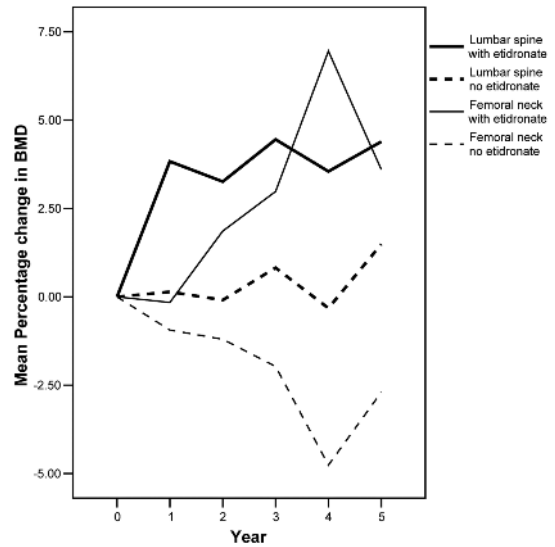


Table III: Changes in Bone Mineral Densities from Pre-Treatment, Expressed as a Percentage of Pre-Treatment Level*

	Year 1			Year 2			Year 3			Year 4			Year 5		
	N	Geometric Mean	Geometric SD	N	Geometric Mean	Geometric SD	N	Geometric Mean	Geometric SD	N	Geometric Mean	Geometric SD	N	Geometric Mean	Geometric SD
Lumbar Spine															
HRT	13	101.5	5.4	9	103.1	5.4	9	104.8	7.1	9	102.0	10.8	9	106.2	9.0
No HRT	12	101.4	7.3	12	100.0	6.8	8	100.5	8.2	8	100.9	10.3	11	100.1	10.7
Etidronate	9	103.8	5.4	9	103.3	5.6	9	104.5	6.1	8	103.6	9.9	9	104.4	8.9
No Etidronate	16	100.1	6.4	12	99.9	6.7	8	100.8	9.3	9	99.7	10.7	11	101.5	11.5
Femoral Neck															
HRT	11	100.1	3.5	9	102.5	5.5	9	104.7	6.2	9	102.1	8.8	8	104.1	8.3
No HRT	12	98.7	6.6	12	98.3	6.2	8	96.2	9.1	8	99.0	9.5	11	97.5	9.5
Etidronate	9	99.8	6.9	9	101.9	7.3	9	103.0	8.0	8	107.0	5.4	9	103.6	8.1
No Etidronate	14	99.1	4.2	12	98.8	5.2	8	98.0	9.3	9	95.2	7.6	10	97.3	9.8

Discussion

This was the first study of HRT in patients with asthma receiving glucocorticoids that was designed with sufficient power to detect differences in fractures rates. In practice, recruitment proved difficult, resulting in loss of power to detect such differences. When considered in the light of publications questioning the safety of HRT^{1,2} the value of this trial appeared to be slight and initially its publication was not pursued. A subsequent change in the climate relating to HRT prescription^{5,6,12} and the fact that the trial remains the largest of its type in patient-years has led us to this late publication. No previous prospective study has included as many as 47 patients with asthma followed-up to five years. The results suggest that HRT is as effective as ET in increasing BMD and that its effect on preventing fractures also compares well with that of ET.

The sample size was lower than desirable to show treatment differences in BMD results, although the differences between HRT and no HRT were significant at the proximal femur. Possible reasons for the low recruitment were (a) the fact that in the 1990s many post-menopausal women attending chest clinics were already on HRT, (b) unfamiliarity of chest physicians with prescribing HRT, (c) the need to liaise with gynaecologists before the patient could enter the study, (d) the creation of trust hospitals and of fund-holding in primary care which generated problems over finance for HRT and ET and (e) some clinicians were deterred from participation because of the efforts needed to obtain the individual permission of every Local Ethics Research Committee in the era before the creation of Multi-centre Research Ethics Committees.¹³

The trial was open-label design but the end-points of vertebral fractures and BMD were measured blind to the treatment received. The diagnosis of asthma as made by the participating physician was accepted as sufficient to make a patient eligible for the study. It is likely that some patients had extrinsic, early onset asthma, some had late-onset intrinsic asthma and a proportion of both categories may have had concomitant chronic bronchitis and emphysema. However, all patients had received tablet and/or inhaled glucocorticoids regularly for at least one year prior to entry to the trial and for the five years of the follow-up.

Overall, at least, 23% of the patients developed symptomatic, new vertebral and non-vertebral fractures and/or asymptomatic, new or worsening thoraco-lumbar spinal fractures. In the previous study by the BTS of ET and/or calcium in asthmatic males and asthmatic post-menopausal females receiving glucocorticoids, symptomatic and/or asymptomatic fractures occurred in 17% over five years.⁹

Symptomatic vertebral and non-vertebral fractures occurred in 6%: when comparison of those on HRT with those not on HRT was made, no fractures were noted in those on HRT, whereas three developed in the patients not on HRT ($p = 0.25$). The overall fracture rate of 6% over five years is much like the 8% noted in the previous BTS study.⁹

Among 22 patients with radiographs of the thoraco-lumbar spine both at entry and at five years after entry to the trial, new or worsening fractures of the thoraco-lumbar spine were observed in 50%, there being a hint (not statistically significant) that HRT might possibly be associated with a reduction in this rate.

HRT and ET each tended to improve BMD at lumbar spine and femoral neck to a similar extent over the five years, although some HRT results were statistically significant and the ET results

were not. In the previous study, ET appeared to prevent a decline in BMD at the femoral neck rather than to increase it,⁹ although its effect on the lumbar spine was positive to the same sort of degree as in the current trial. The question of whether BMD measurements predict those about to fracture cannot be answered with our limited data.

Both types of anti-osteoporosis therapies studied in this trial appeared to increase BMD to a similar extent over five years and there was a suggestion that HRT might be at least as effective as ET in preventing fractures. In post-menopausal females with asthma who are unable to tolerate bisphosphonates, HRT is a reasonable alternative in the treatment and prevention of glucocorticoid-induced osteoporosis.

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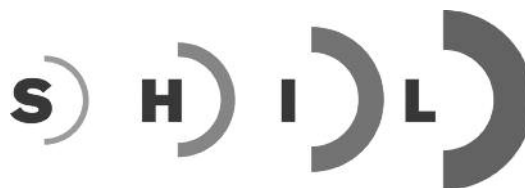
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