Effects of hormone replacement therapy in rheumatoid arthritis: a double blind placebo-controlled study

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Abstract

Aims—To study the effects of ovarian hormone replacement therapy (HRT) on bone mineral density and disease activity in postmenopausal women with rheumatoid arthritis (RA).

Method—A placebo controlled double-blind study was carried out on 62 patients with RA, 22 on placebo and 40 on HRT (transdermal oestradiol patches twice weekly for 48 weeks plus northingestren tablets when clinically indicated). Bone mineral density of spine, hip and wrist was measured at 0 and 48 weeks and clinical and laboratory measures of general well-being and disease activity at 0, 12, 24 and 48 weeks.

Results—Thirteen of 22 (59%) of placebo and 31 of 40 (78%) of the HRT group completed 48 weeks in the study. At entry, bone mineral density (BMD) values in the lumbar spine and femoral neck were similar to those in age and sex matched controls in both treatment groups, whereas at the distal radius, BMD was significantly reduced to approximately 50% of control values (both p < 0.001 from controls). In the HRT group, spine BMD increased significantly by a median of +0.94% at 48 weeks (p = 0.024), but did not change significantly in the placebo group. BMD at the femoral neck and distal radius did not change in either group. In the HRT group, there was significant improvement in well being as assessed by the Nottingham Health Care Profile (p < 0.01) and in the articular index (p < 0.05). There were no significant changes in ESR or CRP in either group.

Conclusion—Transdermal HRT was well tolerated, increased well being, reduced articular index and increased lumbar spine bone density over a one year period in postmenopausal women with RA. Although no laboratory evidence was found of a disease modifying effect, the symptomatic benefits and improvements in bone density indicate that HRT may be a valuable adjunct to conventional anti-rheumatic therapy in RA.

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While the causes of systemic osteoporosis in RA are unclear, contributing factors include corticosteroid use, immobilisation, postmenopausal status, and the bone resorbing effects of pro-inflammatory cytokines. Whatever the underlying cause, postmenopausal women with RA represent a group at increased risk of osteoporotic fracture and this may contribute to the morbidity already experienced by these individuals.

The role of sex hormones in protecting against osteoporosis is well established and it has been suggested that hormonal contraceptives and ovarian hormone replacement therapy (HRT), may protect against the development and progression of RA.

In the light of this, postmenopausal women with RA constitute a group who might be expected to derive particular benefit from HRT. Although short term oestrogen therapy has been shown to be of benefit in suppressing some aspects of disease activity in RAint the long-term effects of HRT in this situation are poorly documented. The aim of this study was to evaluate the effects of HRT on regional bone mass, disease activity and general well being in postmenopausal women with RA.

Patients and methods

Consecutive postmenopausal and perimenopausal women attending outpatient clinics at the Centre for Rheumatic Disease, Glasgow, were invited to participate in the study and 62 were enrolled. All had definite or classic rheumatoid arthritis (American Rheumatism Association criteria), were in Steinbrocker functional class I and II, and had oestriadiol and gonadotrophin levels consistent with a postmenopausal state. For ethical reasons, those with significant menopausal symptoms were excluded. Patients were randomised on a double blind basis to receive either placebo (n = 22) or hormone replacement therapy (HRT) (n = 40). The larger number of patients in the HRT wing of the study arose because of an interruption in the availability of placebo medication resulting in a 2:1 ratio of randomisation in favour of the active treatment. HRT consisted of oestradiol patches twice weekly (Estraderm 50; Ciba-Geigy), supplemented in 33/40 (82%) of cases with oral northingestren 1 mg daily for 10 days on a cyclical basis. The placebo group received matching therapy. Patients were supervised by a gynaecologist (UB) who was aware of which treatment was being given; all other investigators...
and the patients were ‘blind’ to the identity of the therapy. Clinical measurements of disease activity, general well being and functional status included: Ritchie articular index, duration of morning stiffness, pain score (visual analogue scale; 0–10) and general well being score (visual analogue scale 0–10). General health status was assessed by the Nottingham Health Profile questionnaire. Standard antirheumatic therapy including non-steroidal anti-inflammatory drugs and second line antirheumatic therapy were continued and doses adjusted according to standard clinical practice during the study. Biochemical and haematological variables were measured using standard laboratory techniques. Bone mineral density (BMD) was measured at 0 and 48 weeks by dual photon absorptiometry at the lumbar spine (mean of values in lumbar vertebrae 2–4) and in the femoral neck, using a Lunar DP3 dual photon absorptiometer. The long-term precision of this instrument for the lumbar spine measurements is 2-0% and 3-0% for the femoral neck. BMD at the distal 1/3 of the radius was measured by single photon absorptiometry using a Norland 287 osteodensitometer (long-term precision 3%). BMD measurements were expressed in relation to locally-derived age and sex matched normals.

As some of the data were not normally distributed, non-parametric (Wilcoxon matched pairs signed rank test for paired samples and the Mann Whitney U test) were used in statistical analysis.

Results

PRE-TREATMENT CHARACTERISTICS

Both groups were well matched at the outset of the study for the following variables (expressed as medians and range); age: placebo = 55 (41–69) v HRT = 53 (41–64) years; age at menopause: placebo = 48 (39–55) v HRT = 48 (30–53) years; duration of RA: placebo = 17 (2–40) v HRT = 11 (2–45) years. Of the placebo group, 63% were taking disease modifying drugs (salazopyrine 4 (28%); gold 5 (35%); penicillamine 3 (21%); methotrexate 2 (14%), compared with 65% of the HRT group (salazopyrine 10 (30%); penicillamine 5 (16%); gold 10 (33%); hydroxychloroquine 3 (10%) azathioprine 2 (6%)). One patient treated with HRT was on low dose prednisolone. BMD values in the spine and femoral neck did not differ significantly from those in locally-derived age and sex matched controls; Lumbar spine BMD (placebo) = 92% (71–118) v (HRT) = 98% (70–120); femoral neck BMD (placebo) = 96% (77–121) v 93% (59–126).

BMD of the distal radius was, however, substantially reduced in both groups compared with controls; placebo 49% (36–73) v 55% (25–71); both p < 0.001 from controls.

COMPLIANCE AND TOLERABILITY

HRT therapy was well tolerated; 31 of the original 40 (78%) patients randomised to HRT were still receiving treatment by one year in comparison with 13 of the 22 (59%) of patients in the placebo group. Reasons for withdrawal were varied and included; menstrual bleeding (1 placebo, 2 HRT); depression (1 placebo); unable to attend for follow up (2 HRT); abnormal lipids (1 placebo); poor compliance (1 HRT); death due to intercurrent illness (1 placebo, 1 HRT); skin reaction to patches (1 HRT); poor symptomatic response (4 placebo). Data from patients who withdrew were not included in further analysis.

SYMPTOMS AND DISEASE ACTIVITY

Changes in clinical and laboratory indices of disease activity and in the Nottingham Health Profile assessment are summarised in the table. In the HRT group there was a statistically significant improvement in subjective overall well being as assessed by a visual analogue scale at week 12 and 48 (both p < 0.05 from baseline) and in the Ritchie articular index by week 48 of the study (p < 0.05 from baseline). There were no changes in laboratory indices of

| Effect of HRT and placebo on clinical and laboratory indices of disease activity and on general well being |
|---|---|---|---|---|---|---|---|---|---|
| Time (weeks) | Placebo | HRT |
| 0 | 12 | 24 | 48 | 0 | 12 | 24 | 48 |
| **Clinical indices of disease activity** | | | | | | | | | |
| Articular index | 28 | 15 | 15 | 14 | 24 | 20 | 16 | 15* |
| Pain score (cm)§ | 6-0 | 6-3 | 5-1 | 7-0 | 5-0 | 5-3 | 6-0 | 5-0 |
| Wellbeing score (cm)§ | 5-0 | 5-3 | 5-0 | 5-1 | 5-0 | 6-5* | 6-1 | 7-5* |
| Morning stiffness (minutes) | 30 | 45 | 30 | 30 | 60 | 60 | 60 | 60 |
| **Laboratory indices of disease activity** | | | | | | | | | |
| Haemoglobin (g/l) | 120 | 119 | 124 | 122 | 122 | 124 | 121 | 122 |
| ESR (mm/hr) | 28 | 23 | 32 | 32 | 34 | 38 | 35 | 31 |
| C-reactive protein (mg/l) | 12 | 10 | 10 | 12 | 19 | 16-5 | 17-8 | 17-5 |
| **Nottingham profile part I¶** | | | | | | | | | |
| Energy level | 60-8 | 62 | 60-8 | 63-2 | 60-8 | 24* | 24* | 25* |
| Pain perception | 57-8 | 54-4 | 49-4 | 49-2 | 46-5 | 36-5 | 48-9 | 46-5 |
| Emotional level | 26-2 | 13-4 | 9-8 | 19-2 | 24-8 | 0* | 0* | 7-2* |
| Sleep | 35 | 53-5 | 35 | 50-4 | 34 | 12-6 | 29-7 | 12-6* |
| Physical mobility | 41-8 | 49-2 | 42-8 | 44 | 47-9 | 41-9 | 41-9 | 48 |
| **Nottingham profile part II¶** | | | | | | | | | |
| Activities of daily living | 3 | 3-5 | 4 | 3 | 4 | 3 | 3-5 | 2-5* |

Values are medians.

* p < 0.05 significant difference from baseline.

† p < 0.05 significant difference between groups.

‡ Improvement reflected by a reduction in score.

§ Improvement reflected by an increase in score.

Normal reference range for: CRP < 10 mg/l; ESR < 30 mm; haemoglobin 115–145 g/l.
Hormonal Data
Median serum oestriadiol levels were low pre-treatment and did not differ between the groups (HRT 60 pmol/l; placebo 50 pmol/l). In the HRT group, oestriadiol increased significantly to a median of 120 pmol at week 12, 100 pmol at week 24 and 110 pmol/l at week 48 (all p < 0.01 from baseline). Oestriadiol levels did not change in the placebo group. Median LH and FSH levels were elevated to a similar degree in both groups before treatment: LH 44 u/l (HRT); 45 u/l (placebo); FSH 40 u/l (HRT); 40 u/l (placebo). LH fell significantly in the HRT group to 25 and 26 u/l at week 12 (both p < 0.001) and 36 u/l at week 48 (p < 0.05). There was no significant change in LH in the placebo group or in FSH in either group.

Bone Density Data
These are shown in fig A–C. In the HRT group, lumbar spine BMD values increased significantly by a median of +0.94% (p < 0.03), whereas there was no significant change in the placebo group (+0.50%, p > NS). Unfortunately, a combination of technical difficulties in positioning patients for hip scans, combined with a malfunction of our wrist densitometer during the study meant that there were relatively few paired BMD measurements available for the femoral neck and wrist particularly in the placebo group. Although there was a trend in favour of HRT there was no significant change in either femoral neck BMD or wrist BMD values between 0 and 48 weeks; femoral neck; +0.69% (HRT) v -0.65 (placebo); wrist; +2.72% (HRT) v +1.60% (placebo).

Discussion
Hormone replacement therapy offers several potential benefits for postmenopausal women with rheumatoid arthritis. Apart from the well documented protective effect of HRT on postmenopausal bone loss and osteoporotic fracture, there is evidence to suggest that sex hormones may protect against the development of RA, or modulate disease activity. The therapeutic effects of sex hormones in RA have been little studied although a recent short term crossover trial of unopposed oestrogen suggested that this hormone may suppress some aspects of disease activity. In this study, we investigated the longer term effects of conventional HRT on disease activity and bone density in RA. We found that over a one year period, transdermal HRT resulted in a significant increase in median bone density of...
the lumbar spine of approximately 1% with a slight decrease (-0.5%) in placebo-treated patients. These data are qualitatively similar to those recently reported by Stevenson et al.\(^1\) who found a 2.5% increase in mean spinal BMD after 18 months of treatment with the same dose of transdermal oestrogen in normal postmenopausal women.

The loss of bone in placebo treated patients was greater in their study, however, (~2%) possibly due to the fact that their patients were studied within two to three years of the menopause compared with five to seven years in this study. Like Stevenson et al.\(^1\) and Sambrook et al.,\(^2\) who also studied the effects of sex hormones on bone density in RA, we found the protective effect of HRT on femoral neck density much less marked than in the lumbar spine. A recent study by van der Brink et al.,\(^3\) however, showed improvements in BMD at both sites. There are several potential explanations for these differences. Perhaps the most likely is that the femoral neck measurements largely reflect changes in cortical bone which remodels at a much slower rate than the trabecular bone of the vertebral bodies and hence may require longer periods of treatment to show changes, particularly in the light of the poorer precision of BMD measurements at the femoral neck. It has also been suggested that higher doses of oestrogen may be needed to prevent femoral bone loss in some cases.\(^4\)

The plasma oestradiol concentrations achieved in the present study (100–120 pmol/l) have previously been shown—to the basis of biochemical measurements—to be effective in suppressing bone turnover in normal postmenopausal women.\(^5\) Some patients treated with HRT continued to lose bone despite this, however, (figure A–C) indicating that therapy may need to be tailored on an individual level on the basis of bone density measurements. Although the risk of osteoporotic fractures affecting both the hip and spine is increased by a factor of between 1.5–2.0 times in RA patients\(^1\) data has been presented to suggest that the pattern of bone loss in early RA is periarticular, rather than systemic in distribution.\(^6\) Our observations are consistent with this, as we found a marked reduction in bone density of the distal radius in RA patients, with BMD values in the spine and hip which were similar to those in an age and sex matched control population. While these data argue against a specific systemic osteoporosis in RA per se, it is possible that multiple factors such as steroid use, relative immobility, smoking and postmenopausal status may combine to increase the risk of bone loss and fracture in RA.\(^1\)\(^2\)

The second aim of our study was to assess the tolerability of HRT in RA and study its effects on general well being and disease activity. An important finding was the excellent tolerability of HRT; only one patient on HRT withdrew from the study due to difficulties with resumption of menstrual bleeding and overall, 76% of the HRT group were still on therapy at two years compared with 59% in the placebo group. The high rate of compliance may have related to the symptomatic benefits which occurred in the HRT group. Particularly striking were the improvements in energy level, emotional level, and sleep patterns as assessed by the Nottingham Health Profile and the general well being score and articular index. We were, however, unable to demonstrate any specific anti-rheumatic effect as reflected by changes in ESR or C-reactive protein levels. Most of the patients studied were also taking disease modifying drugs, however, and as a result, had relatively low levels of ESR and CRP; it would be interesting to repeat the study in a group of patients with more evidence of inflammatory activity. The higher CRP level in the HRT group at week 24 is of no statistical significance and was probably related to random variation about the mean of the generally higher CRP levels observed in the HRT group.

In summary, we have found that HRT therapy in postmenopausal women with RA increased bone density in the lumbar spine, resulted in a significant improvement in general well being, but—in this group of patients at least—did not alter laboratory indices of disease activity. These symptomatic benefits, coupled with the protective effect on spinal bone density, however, indicate that HRT may be a useful adjunct to conventional therapy in the management of RA.

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