Influence of Hormone Replacement Therapy on Disease Progression and Bone Mineral Density in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Hormone replacement therapy (HRT) is known to exert a positive effect in preventing bone loss and a beneficial effect on the disease activity in rheumatoid arthritis (RA). We evaluated the effects of HRT on bone mineral density (BMD) and on the course of established RA.

Methods. Eighty-eight postmenopausal women with RA were randomly allocated to receive HRT, vitamin D3, and calcium supplementation or vitamin D3 and calcium supplementation alone for 2 years. The effects of additional HRT on laboratory and clinical measures of disease activity, quality of life, and BMD and on radiographic joint damage were investigated.

Results. Treatment with HRT suppressed signs of inflammation as shown by reduction in erythrocyte sedimentation rate (ESR) ($p = 0.025$) and an elevation in hemoglobin concentration ($p = 0.007$), a better clinical outcome assessed by response on the Disease Activity Score 28 (DAS28) ($p = 0.036$), increased BMD in the forearm, proximal femur and spine ($p < 0.01$), and retarded ($p = 0.026$) progression of joint destruction among patients with radiological progressive disease. No significant effect on quality of life was seen.

Conclusion. Two years of HRT in women with active RA had significant ameliorating effects on inflammation, DAS28 response, and BMD and was associated with slower progression of radiological joint destruction. The mechanisms by which HRT exerts its effects remain to be elucidated. We suggest HRT can be used in addition to conventional therapy in the management of postmenopausal patients with RA. (J Rheumatol 2003;30:1456–63)

Key Indexing Terms:
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Clinical data indicate that sex hormones influence the course of rheumatoid arthritis (RA). Indeed, during pregnancy, when several steroids such as estrogen, progesterone, and glucocorticosteroid increase in serum, the disease activity is ameliorated in 75% of women with RA, whereas after delivery flares occur in up to 90% of patients[1,2]. Also, use of oral contraceptives was shown to protect against the development of RA[3]. The highest incidence of developing RAcoincides with the menopause, indicating that a decrease in estrogen production may increase the risk of joint inflammation[4]. Further, type II collagen induced arthritis was exacerbated by castration in female mice, whereas subsequent estradiol treatment ameliorated the arthritis[5].

Early trials on sex hormones in the 1930s were hopeful[6,7], while subsequent reports in the 1960s with a progestogen with some estrogenic properties revealed unequivocal results[8,9]. In the 1980s and 1990s some studies evaluating the influence of HRT in RA indicated an antiinflammatory effect[10-12], while others did not[13]. HRT is composed primarily of estrogens, and also a progestogen for

the protection of the endometrium. Both steroids influence the endocrine and immune systems in a complex way. Since most previous trials have been conducted in a time period less than one year, there was a need to evaluate the effects of HRT in RA with longer followup.

RAis associated with bone loss, including both periarticular and generalized osteoporosis, leading to increased prevalence of osteoporotic fractures[14,15]. Several mechanisms are believed to contribute to the reduced bone mass, such as local and systemic inflammation, impaired physical mobility, postmenopausal status, and the use of corticosteroids[16-19]. HRT is known to prevent osteopenia and reduce the incidence of fractures in healthy women[20-22], and it has also been shown that HRT increases bone mineral density (BMD) in women with RA[12,23,24]. However, it is unknown if HRT influences the development of joint erosions.

The aim of this 2 year prospective, controlled study was to assess the effects of HRT regarding clinical and laboratory measurements of disease activity, quality of life, BMD, and radiological progression of joint destruction in postmenopausal patients with active RA.

MATERIALS AND METHODS

Patients. A total of 592 female patients with RAaged between 45 and 65 years were identified from rheumatology clinic registers in Göteborg and Borås, Sweden. They were invited by mail to participate in a 2 year clinical randomized, single blind, controlled study. The women were required to be postmenopausal, defined as no menstruation in the previous year and serum follicle-stimulating hormone (FSH) concentration > 50 IU/l (Diagnostic Products Corp., Los Angeles, CA, USA). Patients were to fulfill the American Rheumatism Association 1987 revised criteria for adult RA[25], and to have active disease that met at least 2 of the following criteria: (1) at least 6 painful joints; (2) at least 3 swollen joints; (3) ESR > 20 mm/h; and (4) C-reactive protein (CRP) > 10 mg/l. A maximum daily dose of 7.5 mg prednisolone was accepted, and patients were allowed to undergo intraarticular and intramuscular glucocorticosteroid injections during the study period. All patients gave informed consent and the Ethics Committee at the University of Göteborg approved the study.

Treatment. Patients were allocated by simple randomization by an independent research nurse to one of 2 treatment groups, the HRT group or the control group. All patients were treated with a daily dose of 500 mg calcium and 400 IU vitamin D3. The HRT group was treated either sequentially with 2 mg micronized estradiol (E_2) for 12 days followed by 10 days of 2 mg E_2 plus 1 mg noretisterone acetate followed by 6 days of 1 mg E_2 or one tablet per day containing 2 mg E_2 plus 1 mg noretisterone acetate as continuous combined treatment. Women who were more than 2 years postmenopausal were given the continuous regimen. Those with a previous hysterectomy were given 2 mg E_2 daily. The investigators at the rheumatology departments were blinded to the identity of the therapy. Regular medication for RA could be altered by the clinician (not by the investigator).

Assessment of outcome variables. The same rheumatologist assessed disease activity at all time points, calculated by the Disease Activity Score 28 (DAS28)[26] using the following formula:

$$DAS28 = 0.56\sqrt{\quad} + 0.28\sqrt{\quad} + 0.70\ln ESR + 0.014\ GH$$

where tender joint count (TJC), swollen joint count (SJC), and patient's assessment of general health (GH) using a 100 mm visual analog scale (VAS). Good response was defined as > 1.2 improvement in the DAS28 from baseline, and a DAS28 ≤ 3.2 attained during the followup. Nonresponders were defined as patients with an improvement ≤ 0.6 or patients with improvement > 0.6 but ≤ 1.2 and a DAS28 > 5.1 attained during followup. The remaining patients were classified as moderate responders. Patients with DAS28 > 3.3 at start were included in the analysis of response.

A standardized questionnaire including physical activities, the Health Assessment Questionnaire (HAQ) estimating the disability[27,28], and a Swedish version of the Quality of Life Scale (QOLS)[29] were used at study entry and after 12 and 24 months. The physical activity was estimated by the number of gymnastic exercises every week and by a physical activity scale graded 1–4. Grade 1 was defined as sedentary, grade 2 as walking and sedentary labor, grade 3 as mainly walking and no lifting, and grade 4 as walking and lifting.

Venous blood samples were obtained at study entry and after 12 and 24 months in the morning after an overnight fast and were stored at –70°C until the time of analysis. ESR, CRP, orosomucoid, hemoglobin (Hb), and serum Fe and total iron binding capacity (TIBC) were measured using standard laboratory techniques.

BMD at left forearm, left hip, and lumbar spine was measured at study entry and at 12 and 24 months by dual energy x-ray absorptiometry (DEXA) with a Hologic QDR-4500Adevice. The precision of this instrument for the lumbar spine and in the total hip was 0.4%. It was not possible to measure all skeletal sites in every patient because of the presence of prostheses and osteosynthetic materials.

Radiographs of hands, wrists, and forefeet were obtained at baseline and after 12 and 24 months. Radiographs were masked for identity and sequence, and evaluated by Dr. A. Larsen[30], who was blinded to patients' treatment. Briefly, 40 joints were scored in each patient from 0 (normal) to 5 (maximal destruction). Scores for each patient were summarized and then divided by the number of examined joints to give the mean Larsen score for each patient ranging from 0 to 5.

Gynecologists examined all patients at study entry and after 12 and 24 months. S-estradiol was measured (around 12 h after tablet intake) at baseline and yearly thereafter using a radioimmunoassay (Clinical Assays™, DiaSorin, Vercelli, Italy). Patients were also contacted by telephone by a research nurse after 3, 9, and 18 months for checking the compliance with HRT.

Statistical analysis. Before the start of the trial a power calculation concerning the number of patients needed to detect a significant difference of BMD between study groups at the significance level 0.05, 2-tailed test with 90% power, was conducted. The number of patients included in the trial was sufficient. For other study variables, no power calculation could be done since there were no previous data enabling such analysis. All variables were analyzed using Fisher's permutation test[31], which includes Fisher's exact test as a special case, or Mann-Whitney U test for comparisons between groups. Fisher's test for paired comparisons or Wilcoxon rank sum test was used within the treatment groups. All tests were 2-tailed and $p < 0.05$ was considered statistically significant.

RESULTS

Patient population. The reply frequency was 81% (478/592) for the invitation letter. Seventy-two of the women were not postmenopausal and 19 did not fulfill the diagnostic criteria for RA. Some patients were not able to participate (299/387) for the following reasons: 159 patients had been treated with HRT during the last 2 years; 26 had a history of deep venous thrombosis or embolism, 23 of cancer in breast, uterus or ovaries; 18 had started disease modifying antirheumatic drugs (DMARD) or glucocorticosteroid therapy within the previous 3 months or had language problems or had moved to other parts of Sweden; 6 were treated with bisphosphonates; and 67 did not want to participate. Eighty-eight (23%)

of the probands entered the study (Figure 1). Forty-one patients were randomized to the HRT group and 47 to the control group. Eight of the 88 patients (9%) left the study before completing the 2 years (Figure 1). Patients who dropped out were included in calculations until withdrawal.

There were no significant differences in baseline characteristics between the study groups (Table 1). At study entry, 71 (81%) patients were taking DMARD, 30 (34%) methotrexate (MTX), 10 (11.5%) sulfasalazine, 9 (10%) hydroxychloroquine/chloroquine phosphate, 8 (9%) gold sodium aurothiomalate, 4 (5%) podophyllotoxine derivates, 3 (3.5%) auranofin, 3 (3.5%) cyclosporin A, 2 (2.5%) azathioprine, one (1%) cyclophosphamide, and one (1%) combination of MTX and auranofin. Nineteen (22%) of the

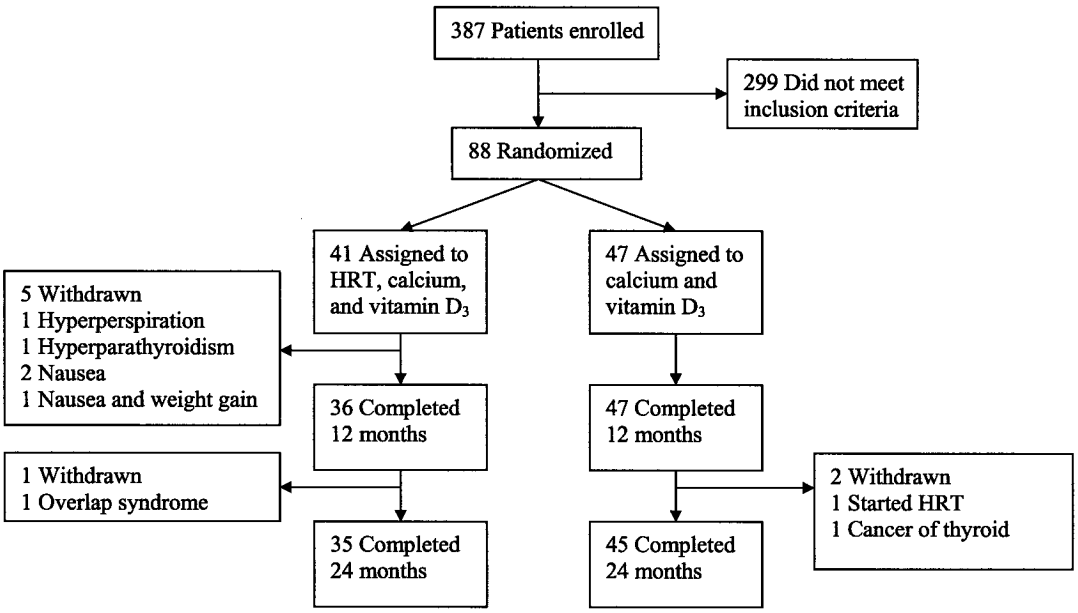

Figure 1. Procedure of the trial and reasons for discontinuation during the first and second year.

Table 1. Baseline characteristics of patients in the hormone replacement therapy (HRT) and control groups*. Values are mean ± SD when not given otherwise.

	HRT, n = 41	Controls, n = 47
Age, yrs	57.0 ± 5.5	58.1 ± 4.7
Weight, kg	66.9 ± 11.1	66.1 ± 13.9
Height, cm	163.3 ± 5.5	162.6 ± 6.9
Disease duration, yrs	16.4 ± 11.9	15.5 ± 11.7
Years after menopause	8.4 ± 6.0	8.3 ± 5.3
Disease modifying antirheumatic drugs, %	83	79
Corticosteroid treatment, %	24	19
Nonsteroidal antiinflammatory drugs, %	78	77
Larsen score (0–5)	1.28 ± 1.10	1.43 ± 1.04
Positive serum test for rheumatoid factor, %	83	85
Erythrocyte sedimentation rate, mm	30.8 ± 19.1	26.5 ± 15.1
C-reactive protein, mg/l	18.0 ± 17.5	15.5 ± 15.8
Orosomucoid, g/l	1.2 ± 0.4	1.2 ± 0.3
Hemoglobin, g/l	128.2 ± 10.1	129.0 ± 13.3
Serum iron, µmol/l	14.6 ± 5.8	13.7 ± 6.4
Total iron binding capacity, µmol/l	65.0 ± 8.0	62.6 ± 8.2
BMD		
Forearm, g/cm^2	0.48 ± 0.10	0.46 ± 0.11
Total hip, g/cm^2	0.77 ± 0.15	0.78 ± 0.17
Lumbar spine (g/cm^2)	0.83 ± 0.14	0.88 ± 0.13
Health Assessment Questionnaire (0–3)	0.99 ± 0.69	1.0 ± 0.67
Quality of Life Scale (16–112)	88.2 ± 11.6	89.0 ± 11.7
Disease Activity Score 28	5.2 ± 1.0	5.3 ± 1.0
Exercise per week	0.5 ± 0.7	0.7 ± 1.4
Daily physical activity (1–4)	1.9 ± 0.7	2.0 ± 0.6

patients were treated with corticosteroids at a mean dose of 4.6 mg prednisolone, and 68 (77%) were treated with nonsteroidal antiinflammatory drugs (NSAID). There were no significant differences with respect to the proportion of patients treated with DMARD, MTX, NSAID, or corticosteroids between the HRT and control groups at study entry or at 12 and 24 months. No significant dissimilarities were observed regarding changes of DMARD or amounts of corticosteroids injected intraarticularly and intramuscularly between the groups.

Fourteen patients obtained sequential HRT and 23 the continuous combined regimen. Four women had undergone hysterectomy and were treated with E_2 alone. S-estradiol remained constantly low in the controls, while increasing significantly in the HRT group and reaching expected values (Table 2).

Clinical disease activity, anthropometric data, and physical activity. According to the DAS28 response, the patients were divided into good responders (4 HRT and 4 controls), moderate responders (18 HRT, 13 controls), and nonresponders (12 HRT, 25 controls). In the HRT group, 65% (22/34) were responders compared to 40% (17/42) in the control group ($p = 0.036$). In addition, the DAS28 decreased significantly more in the HRT group compared to controls ($p = 0.027$) (Table 3).

Table 2. Serum concentrations of estradiol (pmol/l) at baseline and at 12 and 24 months in the hormone replacement therapy (HRT) and control groups. Normal value for postmenopausal women is < 92 pmol/l. Values are means ± SD.

	HRT	Controls
Baseline	47.7 ± 47.9	37.2 ± 25.5
12 months	177.6 ± 139.4*†	38.3 ± 33.2
24 months	176.1 ± 124.0*†	37.8 ± 39.2

* $p < 0.001$ for comparison with controls from baseline. † $p < 0.001$ for comparison with baseline.

The HRT patients gained weight ($p = 0.008$) when tested within the HRT group, but there was no significant difference in weight between the HRT and control groups (Table 3). HAQ, QOLS, height, and the measures of physical activity did not change significantly during the trial.

Laboratory measurement of inflammation. HRT resulted in decreases of inflammatory measures (Table 3). ESR and orosomucoid decreased significantly and Hb increased significantly. Serum Fe, TIBC, and saturation of transferrin also increased significantly.

Bone mineral density. As shown in Table 4, BMD increased significantly in the lumbar spine, total hip, and forearm in the HRT group. The percentage increase in BMD in the HRT group was 3.6% in the forearm, 4.0% in the total hip, and 7.1% in the lumbar spine, compared to decreases of 2.4%, 0.6%, and 0.8%, respectively, in the controls (Figure 2). Thirteen patients were treated with corticosteroids during the entire study period, 5 in the HRT group and 8 in the control group, with a mean dosage of 4.3 and 5.2 mg, respectively. BMD increased significantly in the lumbar spine and hip among the steroid treated women in the HRT group (Table 4).

Radiological disease progression. The mean Larsen score at study entry and the progression scores from study entry to 12 and 24 months are given in Table 5. Patients were divided into 4 groups according to the level of radiological progression (Figure 3). During the 2 years of followup, 45% and 42% of patients did not progress radiologically in the HRT and control groups, respectively. Among the patients with increasing joint destruction the HRT patients progressed less compared to the controls ($p = 0.026$). The mean progression Larsen score in the whole HRT group was 0.061 contrasted with 0.10 in the controls after 24 months ($p > 0.05$). A few radiographs were lacking due to poor quality or were not obtained.

Table 3. Effect of hormone replacement therapy (HRT) on Disease Activity Score 28, weight, and laboratory measures of inflammation. Changes after 12 and 24 months of treatment are shown. Values are means ± SEM.

	HRT		Controls	
	12 Months	24 Months	12 Months	24 Months
Disease Activity Score 28	–0.77 ± 0.15[e]	–1.24 ± 0.13[a,e]	–0.52 ± 0.16[e]	–0.76 ± 0.15[e]
Weight, kg	0.5 ± 0.4	1.4 ± 0.5[e]	0.0 ± 0.5	0.3 ± 0.6
Erythrocyte sedimentation rate, mm	–3.5 ± 2.7	–8.3 ± 3.1[a,e]	+1.0 ± 2.8	–0.58 ± 2.6
C-reactive protein, mg/l	+2.5 ± 4.3	–3.1 ± 2.9	+0.80 ± 2.4	–0.089 ± 2.5
Hemoglobin, g/l	+1.1 ± 1.3[c]	+2.9 ± 1.3[c,d]	–2.9 ± 1.5[d]	–2.4 ± 1.5
Serum iron, µmol/l	+1.1 ± 1.3	+3.2 ± 1.3[b,d]	+0.72 ± 1.0	+0.044 ± 0.9
Total iron binding capacity, µmol/l	+1.6 ± 1.4	+3.0 ± 1.5[d]	–0.53 ± 0.8	+0.80 ± 1.0
Saturation of transferrin, %	+1.0 ± 1.9	+3.9 ± 1.9[b]	+1.5 ± 1.6	–0.20 ± 1.6
Orosomucoid, g/l	–0.11 ± 0.06[a,d]	–0.26 ± 0.06[c,e]	+0.0081 ± 0.04	–0.024 ± 0.04

[a] $p < 0.05$ for comparison with controls from baseline. [b] $p < 0.05$ for comparison with controls from 12 months. [c] $p < 0.01$ for comparison with controls from baseline. [d] $p < 0.05$ for comparison with baseline. [e] $p < 0.01$ for comparison with baseline.

Table 4. Effects of HRT on bone mineral density (BMD) at baseline and after 12 and 24 months of treatment. Values are means ± SD. Numbers of patients with available data are shown in parentheses.

	HRT			Controls		
	Baseline	12 Months	24 Months	Baseline	12 Months	24 Months
BMD, forearm, g/cm^2						
All patients	0.48 ± 0.10 (37)	0.47 ± 0.09 (33)	0.48 ± 0.09 (30)[b,c,g]	0.46 ± 0.11 (44)	0.46 ± 0.10 (45)[h]	0.45 ± 0.10 (40)[h]
Corticosteroid treated	0.40 ± 0.11 (4)	0.40 ± 0.10 (4)	0.41 ± 0.09 (4)	0.50 ± 0.12 (7)	0.49 ± 0.11 (7)	0.48 ± 0.12 (6)
BMD, total hip, g/cm^2						
All patients	0.77 ± 0.15 (41)	0.78 ± 0.14 (36)[d,j]	0.79 ± 0.14 (35)[a,d,g,j]	0.78 ± 0.17 (46)	0.78 ± 0.17 (46)	0.76 ± 0.16 (42)
Corticosteroid treated	0.68 ± 0.15 (5)	0.70 ± 0.16 (5)	0.71 ± 0.16 (5)[f]	0.81 ± 0.14 (8)	0.81 ± 0.14 (8)	0.79 ± 0.15 (7)
BMD, lumbar spine, g/cm^2						
All patients	0.83 ± 0.14 (41)	0.87 ± 0.13 (36)[d,j]	0.88 ± 0.15 (35)[b,d,g,j]	0.88 ± 0.13 (46)	0.87 ± 0.13 (46)	0.86 ± 0.12 (42)
Corticosteroid treated	0.74 ± 0.14 (5)	0.79 ± 0.12 (5)[e]	0.80 ± 0.11 (5)[e]	0.88 ± 0.16 (8)	0.87 ± 0.13 (8)	0.84 ± 0.13 (7)

[a] $p < 0.05$ for comparison with controls from 12 months. [b] $p < 0.01$ for comparison with controls from 12 months. [c] $p < 0.01$ for comparison with controls from baseline. [d] $p < 0.001$ for comparison with controls from baseline. [e] $p < 0.05$ for comparison with baseline. [f] $p < 0.05$ for comparison with 12 months. [g] $p < 0.01$ for comparison with 12 months. [h] $p < 0.01$ for comparison with baseline. [j] $p < 0.001$ for comparison with baseline.

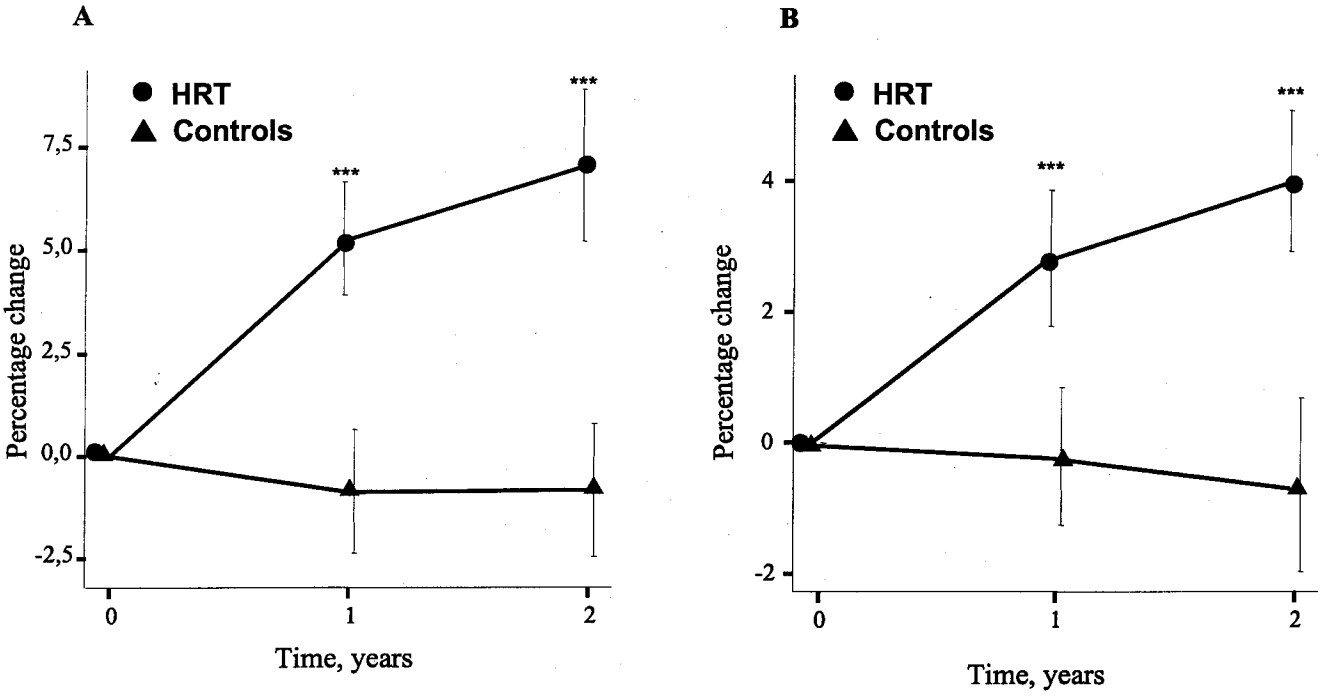

Figure 2. Percentage change of BMD in (A) lumbar spine and (B) total hip. Lines show means and error bars show 95% confidence interval of mean. ***p < 0.001 between HRT and control groups.

DISCUSSION

The main objective of the study was to analyze if the addition of HRT during 2 years in postmenopausal women with long-lasting and active RA had significant effects on BMD and on disease progression.

This report is the first to show a reduction of both clinical and laboratory activity of RA resulting from HRT in postmenopausal patients with RA, as indicated by better DAS28 response and reduction of markers of inflammation. The ESR and orosomucoid decreased in the HRT group in parallel with an increase in Hb and saturation of transferrin, most likely being secondary to reduction of inflammation. Previous trials have indicated some beneficial clinical effects of HRT in RA[10-12]. In a large HRT study, a subgroup of "compliers" who achieved high serum E_2 levels exhibited reductions in pain and articular index after 6 months[11]. In another 48 week trial, a significant improvement in well being assessed by the Nottingham Health Care Profile (NHP)[32] and a fall of articular index were observed[12]. However, van den Brink, *et al* found no effect of HRT on disease activity in a one year study of 40 women with RA[13].

Estrogen deficiency is known to increase bone remod-

Table 5. Mean Larsen score at baseline and progression score after 12 and 24 months in the HRT and control groups, for all patients and for patients who progressed radiologically during the study. Forty joints in the hands and feet were scored (in the hands, proximal interphalangeal joints of digits 1–5, metacarpophalangeal joints of digits 1–5, wrist areas 1–4, in the feet the interphalangeal joint of digit 1 and metatarsophalangeal joints of digits 1–5). Values are means ± SD. Numbers of patients with available data are shown in parentheses.

	HRT	Controls
Baseline		
All patients	1.28 ± 1.10 (40)	1.43 ± 1.04 (43)
Patients with radiological progression	1.12 ± 0.77 (18)	1.40 ± 0.84 (22)
Change from baseline to 12 months		
All patients	0.033 ± 0.070 (35)†	0.038 ± 0.058 (42)†
Patients with radiological progression	0.058 ± 0.084 (17)†	0.066 ± 0.061 (21)†
Change from baseline to 24 months		
All patients	0.061 ± 0.10 (33)†	0.10 ± 0.13 (38)†
Patients with radiological progression	0.11 ± 0.12 (18)*†	0.17 ± 0.14 (22)†

* $p = 0.026$ for the comparison with controls from baseline. † $p < 0.01$ for the comparison with baseline.

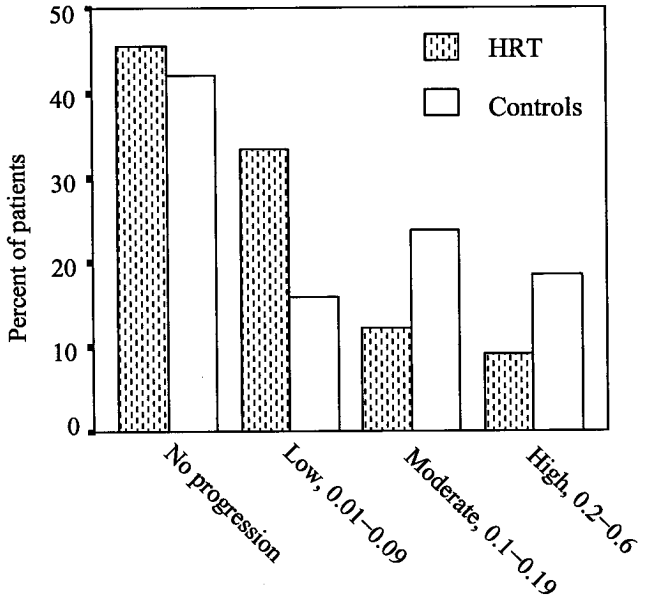

Figure 3. Progression of radiological joint destruction following 2 years of HRT. Patients are divided into 4 progression groups according to the mean increase of Larsen score after 2 years: no progression (Larsen 0), 15 HRT patients and 16 controls; low progression (0.01–0.09), 11 HRT patients and 6 controls; moderate progression (0.1–0.19), 4 HRT patients and 9 controls; and high progression (0.2–0.84), 3 HRT patients and 7 controls.

eling, and the sustained increase in bone turnover induces faster bone loss and consequently increased risk of osteoporosis. HRT is known to restore this imbalance[33,34]. RA is associated with focal bone loss and periarticular and generalized osteoporosis[16], and HRT has been shown to increase BMD in the femoral neck[23] and in the lumbar spine[12], and also in corticosteroid treated patients[24]. In our study, the effect of HRT on BMD was larger compared to previous reports, due probably to supplementation with calcium and vitamin D3, to the type of HRT, and to good compliance. The dropout rate was 15% in the HRT group and only 4% in the controls over 2 years. In comparison with other HRT trials in the 1990s, the withdrawal frequency was low[12,23,24]. BMD also increased significantly in the HRT treated women taking oral corticosteroid. We conclude that HRT has important effects on BMD, which is valuable since RA patients have increased risk of osteoporotic fractures[14] known to be associated with low bone mineral content[35]. However, to investigate the influence of HRT on fractures in RA a larger prospective controlled study is required.

We also studied the progression of radiological joint destruction in the patients. In both the HRT and control groups roughly 40% of the patients did not progress radiologically at all. However, among patients with progressive joint damage, the mean Larsen score increased significantly more in the control group compared to the HRT group ($p = 0.026$). This suggests a protective effect of HRT on joint destruction in postmenopausal women with RA. Since significant benefit of HRT on the radiological outcome was observed only in the subgroup of patients with radiological progressive disease, there is a need for future larger randomized studies to verify the proposed joint protective effect of HRT. Statistical analysis in this study estimated that 150 patients in all would be needed to achieve a power of 80% when comparing HRT versus controls to confirm the outcome. As the mean disease duration of patients in this study was high, we suggest a trial including patients with earlier disease to verify our results. An alternative approach to validate our findings would be to perform a large case-control study of the effect of HRT on joint destruction in postmenopausal women with RA.

Conflicting results regarding weight gain in women undergoing HRT have been reported, of which the majority have not displayed increased body weight[36]. The weight gain in our HRT patients might have been valuable in some respects, as the body fat depot is an important reservoir for

vitamin D and sex steroids, contributing to an increase in BMD, and may also provide protection from hip fractures.

The QOLS quality of life score did not change significantly during the trial. Conversely, other instruments like the NHP have shown improved well being from HRT in postmenopausal women[37] as well as in RA patients[12], probably reflecting the diverse characteristics of the instruments.

This study proceeded for 24 months, in contrast with the previous trials with duration of up to 12 months, and it seems likely that HRT requires a longer period to fully display its antiinflammatory qualities. The more favorable outcome in our study could also be associated with the type of HRT chosen. None of the preceding studies were intended to compare a combined regimen (E_2 and progesterone) to E_2 alone. Although in the study by Hall, *et al* about one-fourth of the women had undergone hysterectomy and received E_2 alone and no different disease activity response was observed[11]. In our study it was not possible to determine to what degree the different hormones contributed to the overall results. Only 4 patients were treated with E_2 alone and it was not considered appropriate to do further subgroup analyses.

The participation rate of potentially eligible patients was rather low mainly due to the large proportion of patients already taking HRT. However, we have no reason to believe that the patients not included in the study should respond differently to HRT, and therefore we consider that the results could be transferable to the broader population of postmenopausal patients with RA.

Sex hormones exert multiple immune-modulating effects, by mechanisms that remain to be elucidated. Macrophage-like cells exhibiting functional androgen and estrogen receptors[38] are highly activated in the RA synovium, and produce multiple cytokines such as interleukin 1 (IL-1), tumor necrosis factor-α (TNF-α), and IL-6. Estrogens seem to alter the balance between T-helper (Th)1 cells (cellular immunity) and Th2 cells (humoral immunity) in a direction possibly favorable in the case of RA. The presence of proinflammatory cytokines is also influenced by progesterone; for example, Miller, *et al* showed that the production by TNF-α of activated macrophages was inhibited by progesterone[39]. In addition, bone cells are influenced. 17ß-estradiol was found to increase the production of osteoprotegerin (OPG), which neutralizes the receptor activator of nuclear factor-κB ligand (RANKL), a cytokine that stimulates osteoclastogenesis[40,41]. We continue to investigate the effect of HRT on proinflammatory cytokines and biochemical markers of bone and cartilage metabolism in RA.

We showed that HRT containing estradiol and noretisterone acetate has a beneficial effect on disease activity, inflammation, BMD, and radiological progression in women with long-lasting RA. HRT was well tolerated with no serious side effects. HRT could be a valuable supplement to conventional therapy in the management of postmenopausal patients with RA.

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