

EFFECT OF HORMONE REPLACEMENT THERAPY ON BONE MASS IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH AND WITHOUT STEROIDS

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Objective. To assess the effect of hormone replacement therapy (HRT) on bone mass in rheumatoid arthritis (RA) patients treated with and those not treated with steroids.

Methods. Two hundred postmenopausal women with RA (ages 45–65 years) were randomly allocated to receive transdermal estradiol (hormone replacement therapy; HRT) (50 μ g daily) or calcium supplementation (400 mg daily) for 2 years. Forty-two of the patients (21%) were taking corticosteroids. Bone mineral density of the lumbar spine (BMDLS) and of the proximal femur (BMDF) was measured at study entry and at 12 months and 24 months.

Results. In the HRT group overall, mean BMDLS had changed by +2.22% (95% confidence interval [95% CI] +0.72, +3.72) and mean BMDF by -0.41% (95% CI -1.89, +1.07) after 24 months. In the calcium group, mean BMDLS changed by -1.19% (95% CI -2.29, -0.09) and mean BMDF by -0.56% (95% CI -2.60, +1.48). Differences between treatment groups were significant for the spine only ($P < 0.001$). In the 21 HRT-treated patients taking steroids, BMDLS increased by 3.75% (95% CI +0.72, +6.78) and BMDF by 1.62% (95% CI -1.27, +4.51).

Conclusion. This study shows that HRT increases spinal BMD and maintains femoral BMD in postmenopausal RA. HRT is also an effective agent in preserving bone mass in patients taking low-dose corticosteroids.

Diffuse osteoporosis is a recognized complication of rheumatoid arthritis (RA), although its severity is dependent on disease activity, disability, and treatment (1–5). RA carries a 2-fold risk of osteoporotic fracture at the spine (6) and hip (7). The deleterious effects of corticosteroids on bone metabolism in RA are well described (1,3,8), being associated with an increased risk of fracture (8–10), although there is still some controversy over their safety in lower doses (11,12). Despite these findings, there have been few intervention studies assessing therapies that prevent bone loss in RA, and there are no published data from randomized trials evaluating hormone replacement therapy (HRT) in steroid-induced bone loss in RA or any other disease. Estrogen replacement therapy can prevent bone loss in the perimenopausal period (13,14) as well as during late menopause (15,16) and is associated with a 50% reduction in the rate of osteoporotic fracture in normal female subjects (17,18). However, its efficacy in preventing the osteoporosis associated with systemic inflammatory disorders (of any etiology) is not well documented, although a recent controlled study of 40 patients with RA demonstrated significant increments in bone mass at the spine and femur after 1 year in 15 patients who completed HRT treatment (19).

We report the results of a 2-year prospective study comparing HRT with low-dose calcium supplementation in 200 postmenopausal women with RA, including 42 who were receiving corticosteroids. This cohort has previously been described (1) as having reduced femoral bone mineral density (BMD), a 7%, steroid-associated, reduction in BMD, and an increased risk of vertebral fracture (6). Calcium supplementation was used as the comparison therapy, representing "traditional" treatment, since at the time of study design in 1988, it was considered to be ethically and technically difficult to maintain patients on a

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2-year regimen of a hormonal placebo that results in regular bleeds.

PATIENTS AND METHODS

Patients. Three hundred forty-six female patients with RA aged 45–65 years were identified from clinic patient registers and invited to participate in a 2-year study of osteoporosis at 5 centers in northeast London. Two hundred twenty-seven patients were interviewed, of whom 200 were included, having satisfied the following criteria: >3 years since last menstrual period or follicle-stimulating hormone level >15 IU/liter, and no contraindications to HRT (i.e., history of endometrial or breast cancer, thromboembolic disease, or uncontrolled hypertension). Patients with concurrent disease known to affect bone metabolism were also excluded. One-hundred seventy-three patients (87%) were white, 14 (7%) were Asian Indian, and 13 (7%) were black. One hundred thirty-two patients (66%) were receiving slow-acting antirheumatic drugs and 42 (21%) were taking glucocorticoids (mean daily dosage 6.9 mg of prednisolone). Thirty-six patients (18%) had undergone hysterectomy and 6 (3%) had undergone bilateral total hip replacement.

An additional group of 18 patients (untreated comparison group) was followed up for 2 years without HRT or calcium supplements and monitored with annual dual x-ray absorptiometry (DXA) scans. Twelve patients in this group had declined to participate in the intervention study and 6 did not meet the inclusion criteria due to previous cardiovascular disease. Patients in this group were similar to the treatment groups in terms of age, years since menopause, weight, and disease activity, but tended to have higher disability scores.

Treatment. After giving informed consent, all steroid-treated and non-steroid-treated patients were allocated by block randomization, using standard randomization tables and coded envelopes, to receive either continuous transdermal estradiol, 50 µg daily with oral norethisterone, 1 mg, for 12 days per month (Estrapak 50 [Estraderm 50 in patients who had undergone hysterectomy]; Ciba Pharmaceuticals, Horsham, UK) or elemental calcium, 400 mg daily, in the form of calcium lactate-gluconate and calcium carbonate (Sandocal, Sandoz, Frimley, UK). Patients continued to receive routine antirheumatic medication at the discretion of the clinician, not the investigator.

Assessments. BMD at the lumbar spine (BMDLS) (L1–L4) and the total proximal femur (BMDF) was measured at study entry, and at 12 and 24 months, using DXA (Hologic QDR1000/W). The coefficient of variation of replicate in vivo measurements at our institution was 0.9% and 1.5% for BMDLS and BMDF, respectively. Vertebrae involved in degenerative disease or fracture, as assessed on plain radiography or DXA scan, were excluded from analysis. Scans were evaluated by technicians who were blinded to the patient's treatment group.

The Health Assessment Questionnaire (HAQ) (20) was used to score patient disability at study entry, and parameters of disease activity measured at entry included early morning stiffness, Ritchie articular index (21), pain (using a 10-cm visual analog scale), and erythrocyte sedi-

Table 1. Reasons for failure to complete trial*

	Treatment group	
	HRT (n = 37)	Calcium (n = 16)
Withdrawn	20	12
Cancer fear	5	
Bleeding	4	
Advised against	1	
Changed to HRT		1
Hyperparathyroid		1
Other	10	10
Side effects	12	0
Premenstrual syndrome	6	
Menorrhagia	3	
Hypertension	2	
RA worsening	1	
Died	3	3
Moved away	2	1

* HRT = hormone replacement therapy; RA = rheumatoid arthritis.

mentation rate. Questionnaires about smoking habits, alcohol consumption, and past and present calcium intake were also completed.

Statistical analysis. It was estimated that an n-value of 100 patients in each group would be sufficient to detect a 2% difference between treatments at the 5% significance level with 80% power. Comparisons of baseline data were performed using Student's 2-tailed *t*-test and chi-square. Analysis of covariance was used when there were potential confounding variables. Non-normal data were compared after logarithmic transformation. Longitudinal intergroup analyses of BMD data were performed on an intent-to-treat basis, using Student's 2-tailed *t*-test and analysis of covariance to correct for baseline differences.

RESULTS

Of the 200 patients recruited, 100 were assigned to each treatment arm. One hundred forty-seven patients completed the 2-year study (84 in the calcium treatment group and 63 in the HRT group). Table 1 gives the reasons patients failed to complete the study. Three HRT patients died (myocardial infarction, hepatoma, and rheumatoid vasculitis, respectively) and 2 patients became hypertensive (which persisted after cessation of treatment and was unlikely to be related to HRT). Six patients experienced patch-induced urticaria and had their treatment changed to oral conjugated estrogens (Prempak-C, 0.625 mg/day). Three patients receiving calcium died (pneumonia, myeloma, and rheumatoid vasculitis, respectively) and 1 developed hyperparathyroidism. There were no significant differences between patients who completed and patients who withdrew from the study, except that the

Table 2. Baseline characteristics of the rheumatoid arthritis patients not receiving corticosteroids, by treatment group*

	Treatment group	
	HRT (n = 79)	Calcium (n = 79)
Age (years)	55.8 ± 5.5	56.1 ± 4.3
Menopausal years	7.5 ± 6.2	8.1 ± 5.8
Hysterectomy (%)	26	12†
Weight (kg)	63.8 ± 10.2	66.9 ± 12.5
Disease duration (years)	11.2 ± 9.1	11.5 ± 8.9
HAQ score (0-3 scale)	1.4 ± 0.9	1.4 ± 0.9
RAI (0-84 scale)	10.3 ± 7.9	11.5 ± 8.9
Pain VAS (0-10 cm)	3.9 ± 2.4	4.3 ± 2.7
ESR (mm/hour)	31.2 ± 21.2	34.0 ± 24.3
Morning stiffness (minutes)	31.1 ± 35.8	49.5 ± 52.3‡
Calcium intake (mg/day)	705 ± 466	635 ± 212
BMDLS (gm/cm ²)	0.91 ± 0.15	0.93 ± 0.16
BMDF (gm/cm ²)	0.81 ± 0.15	0.80 ± 0.15

* Except for % with hysterectomy, values are the mean ± SD. HRT = hormone replacement therapy; HAQ = Health Assessment Questionnaire; RAI = Ritchie articular index; VAS = visual analog scale; ESR = erythrocyte sedimentation rate; BMDLS = bone mineral density, lumbar spine; BMDF = BMD, femur.

† $P = 0.02$ versus HRT group.

‡ $P < 0.01$ versus HRT group.

latter group had better reported function (mean HAQ score 1.1, versus 1.5; $P = 0.03$).

Patients were divided into those not taking steroids (n = 158) and those concurrently taking steroids (n = 42). Table 2 presents characteristics of the non-steroid-treated patients entering the study, according to HRT or calcium treatment. Previous hysterectomy was more common in the HRT group

($P = 0.02$) and mean duration of morning stiffness was higher in the calcium group ($P < 0.01$), but all other parameters of disease activity were similar. Baseline mean BMDLS was nonsignificantly lower in the HRT group, and the difference in the mean values was reduced after correction for body mass. Black patients had higher initial mean BMD than did white patients, but subsequent responses to treatment were similar.

Bone density data were available on 193 patients at study entry (95 HRT-treated, 98 calcium-treated), 164 patients after 12 months (81 HRT-treated, 83 calcium-treated), and 162 patients after 24 months (82 HRT-treated, 80 calcium-treated). Table 3 provides unadjusted mean values for all available scans in each group. Figure 1 shows the percentage changes in BMDLS and BMDF for non-steroid-treated patients who had baseline scans, following an intent-to-treat analysis. The difference in the mean change in spinal bone density between HRT-treated and calcium-treated patients was significantly different after 12 months ($P = 0.01$) and 24 months ($P < 0.001$). In the HRT group, mean BMDLS increased by 1.64% (95% confidence interval [95% CI] +0.37, +2.91) after 12 months and by 2.22% (95% CI +0.72, +3.72) after 24 months. In the calcium-treated group, mean BMDLS changed by -0.23% (95% CI -1.01, +0.55) after 12 months and by -1.19% (95% CI -2.29, -0.09) after 24 months. There were no significant differences between treatment groups in femoral BMD at either time point (Figure 1). Mean BMDF changed by -0.41% (95% CI

Table 3. Sequential measurements of BMD at the spine and femur in the rheumatoid arthritis patients, by treatment group*

Group	Study entry	12 months	24 months
Non-steroid-treated			
HRT group			
BMDLS	0.89 ± 0.16 (75)	0.91 ± 0.15 (63)	0.91 ± 0.15 (63)
BMDF	0.79 ± 0.18 (73)	0.80 ± 0.19 (62)	0.80 ± 0.19 (55)
Calcium group			
BMDLS	0.92 ± 0.16 (77)	0.94 ± 0.17 (67)	0.92 ± 0.17 (64)
BMDF	0.80 ± 0.15 (73)	0.80 ± 0.15 (64)	0.79 ± 0.14 (61)
Steroid-treated			
HRT group			
BMDLS	0.81 ± 0.15 (20)	0.85 ± 0.17 (18)	0.85 ± 0.14 (19)
BMDF	0.71 ± 0.12 (21)	0.73 ± 0.11 (17)	0.73 ± 0.11 (18)
Calcium group			
BMDLS	0.90 ± 0.15 (21)	0.91 ± 0.17 (16)	0.92 ± 0.21 (16)
BMDF	0.79 ± 0.14 (20)	0.77 ± 0.15 (15)	0.79 ± 0.16 (16)
Untreated comparison group			
BMDLS	0.88 ± 0.17 (18)	0.87 ± 0.18 (18)	0.86 ± 0.16 (18)
BMDF	0.82 ± 0.13 (18)	0.81 ± 0.13 (18)	0.79 ± 0.15 (18)

* Values are the unadjusted mean ± SD (n). HRT = hormone replacement therapy; BMDLS = bone mineral density, lumbar spine; BMDF = BMD, femur.

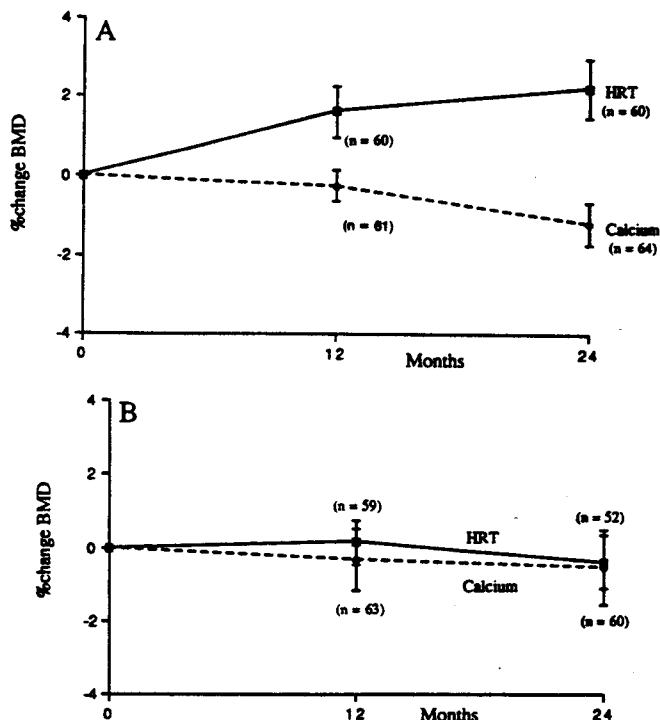


Figure 1. Changes at 12 months and at 24 months in spinal bone mineral density (BMD) (A) and femoral BMD (B) in non-steroid-treated rheumatoid arthritis patients receiving hormone replacement therapy (HRT) or calcium. For change in spinal BMD, the difference between the HRT group and the calcium group was significant at 12 months ($P = 0.01$) and at 24 months ($P < 0.001$); for change in femoral BMD, the difference between treatment groups was not significant at either time point. Values are the unadjusted mean \pm SD.

-1.89, +1.07) and by -0.56% (95% CI -2.60, +1.48) after 24 months in the HRT and calcium groups, respectively. The results remained similar when analyses were based only on patients who completed the study, and following adjustment for baseline weight and BMD. There were no differences in response to HRT by hysterectomy status (as an indicator of unopposed estrogen therapy).

Forty-two patients (21 in each treatment arm) were receiving concurrent corticosteroid therapy (Table 4). The mean daily dose and cumulative dose of prednisolone were similar in the 2 groups. Baseline BMDLS and BMDF were again lower in the HRT group, explained by a lower mean weight in these patients (61.3 kg versus 68.9 kg; $P < 0.05$). In the HRT group, the response to HRT in terms of spine BMD correlated with initial BMD ($r = -0.35$, $P < 0.05$), although there was no relationship between baseline BMDF and changes at the femur. Figure 2 shows changes in BMDLS and BMDF in patients receiving

steroids, adjusted for baseline BMD and weight. There was a significant difference between treatment groups in spinal bone density after 24 months ($P < 0.05$), but not in femoral bone density. In the HRT group, mean BMDLS increased by 3.75% (95% CI +0.72, +6.78) and mean BMDF by 1.62% (95% CI -1.27, +4.51) after 24 months. Among the 4 patients who had undergone hysterectomy and were receiving estradiol only, the mean BMDLS fell significantly compared with that of patients with intact uteri who were taking combined HRT ($P < 0.01$). In patients taking calcium, mean BMDLS changed by -0.85% (95% CI -4.89, +3.19) and mean BMDF by +1.12% (95% CI -3.36, +5.60) after 24 months.

In the comparison group of 18 untreated patients, mean BMDLS changed by -0.90% (95% CI -1.98, +0.18) and -1.46% (95% CI -3.16, +0.26) and mean BMDF by -0.85% (95% CI -2.27, +0.57) and -1.05% (95% CI -3.97, +0.21) after 12 and 24 months, respectively. Femoral bone loss did not differ significantly between the untreated comparison group and the non-steroid-treated patients receiving either HRT or calcium.

Age was an important predictor of response to therapy, as seen by changes in spine BMD among patients receiving HRT and in hip BMD among those receiving calcium. Analysis of patients in the upper age tertile in the HRT group (60-65 years) showed that

Table 4. Baseline characteristics of the rheumatoid arthritis patients receiving corticosteroids, by treatment group*

	Treatment group	
	HRT (n = 21)	Calcium (n = 21)
Age (years)	58.7 \pm 4.2	56.2 \pm 5.7
Menopausal years	9.5 \pm 5.8	8.1 \pm 6.5
Hysterectomy (%)	19	10
Weight (kg)	61.3 \pm 9.7	68.9 \pm 13.9†
Disease duration (years)	12.0 \pm 13.0	14.4 \pm 11.3
HAQ score (0-3 scale)	1.6 \pm 0.9	1.8 \pm 1.5
RAI (0-84 scale)	13.1 \pm 10.0	10.7 \pm 10.1
Pain VAS (0-10 cm)	5.3 \pm 2.5	4.1 \pm 2.6
ESR (mm/hour)	43.9 \pm 29.1	36.8 \pm 22.7
Morning stiffness (minutes)	54.5 \pm 48.0	38.3 \pm 33.7
Calcium intake (mg/day)	652 \pm 261	790 \pm 269
Prednisolone dose (mg/day)	7.5 \pm 2.7	6.2 \pm 3.1
Cumulative prednisolone dose (mg months)	479.3 \pm 820.7	522.5 \pm 580.9
BMDLS (gm/cm ²)	0.81 \pm 0.15	0.90 \pm 0.16‡
BMDF (gm/cm ²)	0.71 \pm 0.12	0.79 \pm 0.14†

* Except for % with hysterectomy, values are the mean \pm SD. See Table 1 for definitions.

† $P < 0.05$ versus HRT group.

‡ $P = 0.07$ versus HRT group.

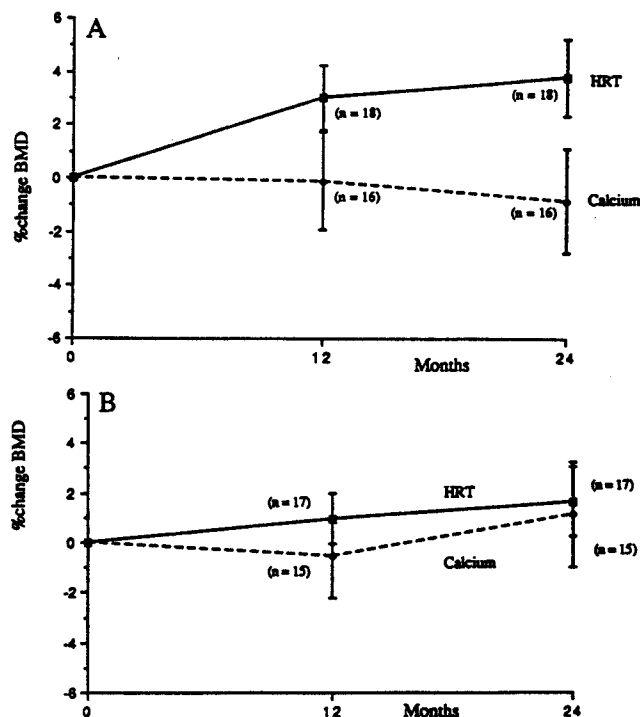


Figure 2. Changes at 12 months and at 24 months in spinal bone mineral density (BMD) (A) and femoral BMD (B) in steroid-treated rheumatoid arthritis patients receiving hormone replacement therapy (HRT) or calcium. For change in spinal BMD, the difference between the HRT group and the calcium group was significant at 24 months ($P < 0.05$) but not at 12 months; for change in femoral BMD, the difference between treatment groups was not significant at either time point. Values are the mean \pm SD, corrected for initial BMD and weight.

mean BMDLS rose by 5.71% (95% CI +3.84, +7.56), and among those in the upper age tertile in the calcium group (59–65 years), mean BMD rose by 2.80% (95% CI -0.04, +2.84). There was no effect of the patient's estimated dietary calcium intake on subsequent changes in BMD in either treatment group.

DISCUSSION

The prevalence of osteoporotic fractures is increased among RA patients, irrespective of corticosteroid usage, and in the present cohort of patients the relative risk of vertebral fracture was >2 (6). Increased risk of fracture may be explained in part by increased susceptibility to falls, but diminished bone strength is also clearly important. Bone mass correlates with fracture risk (22,23), and although a number of studies have confirmed reduced bone mass in RA (2,3,5,9) there have been few intervention studies of

RA-associated bone loss. The present study has shown that, with HRT, mean BMDLS improves by $>2\%$ after 2 years, without significant change in BMDF. The effect of HRT on spinal bone mass in normal postmenopausal women is well established (13,14,24), and we confirm a similar effect in RA, with similar doses of estrogen. Two small studies of HRT in RA support our results. In a double-blind, controlled study, van den Brink and colleagues showed significant improvements in BMD at the spine and femur after 1 year in 15 female RA patients (mean age 61 years) treated with estradiol valerate (2 mg/day) (19). In an uncontrolled, observational study, Sambrook et al demonstrated mean annual changes in BMD of +2.0% and -1.2% at the spine and femur, respectively, in 11 patients taking differing preparations of HRT (25).

The difference in results for femoral BMD between our study and that of van den Brink et al may be explained in part by the greater age (and therefore responsiveness to treatment) of their patients. Previous evidence suggests a less favorable effect of HRT on bone mass at the femur compared with the spine (24), as seen in our study, but the difference in femoral bone loss between the HRT group and untreated comparison group (0.41% versus 1.88%), although not significant, suggests a beneficial effect of HRT at this site. In our cohort, older patients exhibited a highly favorable response to HRT, confirming its important role in the treatment of osteopenia in patients over age 60 (15,26). Long-term rates of drug tolerability in this group were no worse than in patients under 60 years old.

Osteoporotic fracture associated with long-term steroid use is a commonly encountered clinical problem (27), and in this cohort, steroid use was a highly important determinant of reduced bone mass (1). Although HRT has frequently been recommended for postmenopausal patients receiving steroids (28–30), to our knowledge, this is the first randomized study assessing HRT in steroid-related osteopenia. Two previous studies were small and nonrandomized: Lukert et al found a significant increase in spinal bone mass after 1 year in 8 postmenopausal female asthma patients who had undergone long-term steroid therapy and were given cyclical conjugated estrogens (31), and Sambrook's group of RA patients included 5 who took steroids (25).

This "high-risk" group of RA patients, i.e., steroid users, may particularly benefit from HRT. The mode of action of HRT in this setting requires clarification. Only 4 of our steroid-treated patients had had a hysterectomy and were taking estrogen alone, but, interestingly, this group lost significantly more bone

than did the remaining patients taking combined HRT. The recognized competition for osteoblast glucocorticoid receptors (32) and the positive results of a trial of progestagen in steroid-induced osteopenia (33) suggest that progestagen may be the more important component in HRT when it is used to treat patients who have received long-term steroid treatment.

Thirty-seven percent of the patients assigned to the HRT group failed to complete the study, compared with 16% of the group assigned to receive calcium. The number of patients fully complying with the HRT protocol may have been even fewer, since estradiol levels were lower than expected in some patients (34). The withdrawal rate for HRT in this study is similar to that in previous reports (35) and emphasizes the difficulty for clinicians in establishing satisfactory patient acceptance. There was no overall effect of HRT on RA disease activity in our patients, although a subgroup who achieved higher serum levels of estradiol exhibited a favorable disease activity response (reported in more detail elsewhere [34]). That there was no exacerbatory effect on disease activity is reassuring for clinicians prescribing HRT for the prevention of osteoporosis in RA. Other available therapeutic options, such as disodium etidronate and calcitonin, have proven efficacy in normal postmenopausal women (36,37), although only the latter has been studied in RA (38).

In this study, HRT was compared with low-dose calcium supplementation. The literature is unclear regarding the efficacy of calcium, though there are reports that it may be of value following completion of the accelerated perimenopausal phase of bone loss (39-41) and in patients taking steroids (42,43). Our data do not conclusively support a positive effect of calcium, but suggest a slowing of femoral bone loss, particularly in older patients and in those taking steroids. These results support those of Sambrook et al, who found that calcium was no less effective than calcitriol or calcitonin in the prevention of steroid-related femoral bone loss, whereas it was inferior in preventing spinal bone loss (43). The rheumatoid hip is especially vulnerable to bone loss (1,5), and in view of the reported impaired absorption of calcium in RA (44), calcium supplementation may be of added importance in this disease and merits further attention.

Future randomized studies of bone loss in RA need to explore any possible dose-related, or interactive, effect of either estrogen or calcium supplementation, particularly at the hip. Studies of preventive interventions should include patients with early dis-

ease, in whom high rates of bone loss have been reported (45). In summary, the beneficial effects of HRT on bone mass in normal postmenopausal women have been reproduced in a heterogeneous group of women with RA, demonstrating its efficacy in patients with inflammatory disease as well as those taking low-dose corticosteroids. We believe that all postmenopausal women with RA, especially those receiving corticosteroids, should be considered for HRT.

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