

## OSTEOPOROSIS IN RHEUMATOID ARTHRITIS

### A Monozygotic Co-Twin Control Study

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**Objective.** To quantify the magnitude and distribution of osteoporosis in rheumatoid arthritis (RA).

**Methods.** Bone mineral density (BMD) was measured by dual x-ray absorptiometry, in a monozygotic co-twin control study.

**Results.** BMD was reduced at most skeletal sites in the twin with RA compared with the co-twin (lumbar spine 4.6%, femoral neck 9.7%, total body 5.7%). Differences in lean soft tissue (5.6% for total body) correlated with differences in BMD between twins at multiple sites.

**Conclusion.** Osteoporosis in RA is generalized and may be related to loss of mobility or muscle mass associated with the disease.

Localized osteoporosis is a well-recognized radiologic feature of rheumatoid arthritis (RA). Generalized osteoporosis is also commonly observed in RA, but the extent and distribution of reductions in bone mineral density (BMD), particularly in the axial skel-

eton and at sites removed from involved joints, are controversial. Some studies have demonstrated ~10-15% reductions in BMD at axial sites in RA patients compared with age-matched controls (1,2), whereas others have failed to show significant reductions (3,4). Although some of these discrepancies may be due to differences in the methods used for assessment of bone density or differences in disease characteristics of the subjects studied, they could also be due to genetic factors.

Twin studies provide an effective tool for examining the influence of genetic factors on quantitative human traits such as bone density, and such studies have confirmed strong genetic effects on bone density at both peripheral and axial bone sites (5-8). Twin studies using metacarpal morphometry have provided heritability estimates of between 0.7 and 0.8 (6), and twin studies of lumbar spine and femoral neck bone density suggest that genetic factors explain up to 80% of the population variation in bone density (7). This strong genetic effect on bone density could confound any differences due to RA itself. To examine the extent and distribution of BMD deficits in RA while controlling for this large genetic effect, BMD was measured in the present study in monozygotic/identical twins who were either discordant for RA or, if concordant, had a discordant disease duration.

### PATIENTS AND METHODS

Identical twin pairs in which at least 1 member had RA were recruited from sources in Australia and the UK. In Australia, twins identified by a National Health and Medical Research Council Twin Registry questionnaire were initially followed up by telephone interview by a rheumatologist (9). The UK group consisted of twin pairs in southern England who were identified by a national twin survey (10). Identical

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twin pairs were invited to undergo an interview, clinical examination, and bone densitometry.

At the interview, details of disease and treatment characteristics (including corticosteroid and estrogen use) were obtained. At the same visit, a physical examination of both affected and unaffected twins was performed. Radiographs of the hands and feet and results of tests for rheumatoid factor were reviewed to verify disease features and American College of Rheumatology (formerly, the American Rheumatism Association) RA criteria (11). Zygosity was established by self reporting and a standardized questionnaire and was confirmed by DNA typing.

Three pairs were excluded because 1 or both twins were currently receiving estrogen therapy. However, another pair in which both twins had used estrogen in the past, for <12 months, was included, leaving 16 pairs (15 female pairs, 1 male pair) for analysis. One RA-affected twin had taken low-dose prednisone (<5 mg/day) for 3 months in the past, but no subject was currently receiving corticosteroids. Two pairs were concordant for RA but with differing disease duration, and the remainder were discordant. The mean  $\pm$  SD age of the twins was  $56.8 \pm 8.3$  years, and the mean disease duration was  $13.8 \pm 9.6$  years. All female pairs were concordant for menopausal status. Functional class gradings (12) were as follows: grade I  $n = 6$ , grade II  $n = 10$ , grade III  $n = 2$ ; functional class gradings in the 2 concordant pairs were identical between twins.

BMD ( $\text{gm}/\text{cm}^2$ ) in the lumbar spine, femoral neck, and total body was measured by dual x-ray absorptiometry (DXA). Total body scans allowed investigation of changes in different parts of the skeleton as well as changes in lean soft tissue and fat. The radiation dose with DXA is <100  $\mu\text{Gy}$  to the skin and <200  $\mu\text{Gy}$  to the ovaries. The coefficient of variation with this technique is <1% for lumbar spine BMD and total body calcium (13). Body composition data are presented for total body and lower limbs only, because the precision error becomes relatively high at other sites such as the upper limbs and thorax, where bone is a larger proportion of the total mass (14).

Bone density measurements in Sydney, Melbourne, Brisbane, and Adelaide, Australia were performed using a Lunar DPX densitometer. Bone density measurements in Perth, Australia and London, England were made using a Hologic QDR machine. Although these machines use a different technique to measure BMD and have different control population data (13), the data were combined by comparing each twin with his or her co-twin, and each individual twin pair was measured with the same machine.

Paired *t*-tests were used to examine intra-pair differences, and multiple regression analysis was used to examine factors related to bone density differences.

## RESULTS

Intra-pair differences in BMD at different regions and in body composition are shown in Table 1. Compared with their co-twins, the RA-affected twins had reductions in BMD at most sites. These reductions were statistically significant (4.6–9.7%) at all sites

**Table 1.** Differences in bone density and body composition in twin pairs in which 1 member had rheumatoid arthritis

	Intra-pair difference, Mean $\pm$ SEM %*	<i>P</i>
Lumbar spine	4.6 $\pm$ 2.2	0.03
Femoral neck	9.7 $\pm$ 2.7	0.002
Total body	5.7 $\pm$ 1.5	0.0014
Regions of total body		
Upper limbs	8.6 $\pm$ 2.4	0.003
Lower limbs	7.1 $\pm$ 2.0	0.003
Ribs	7.4 $\pm$ 1.6	0.002
Pelvis	5.9 $\pm$ 1.9	0.006
Skull	2.8 $\pm$ 2.0	0.15
Fat	-1.7 $\pm$ 6.6	0.68
Lean soft tissue		
Total	5.6 $\pm$ 1.7	0.007
Lower limbs	5.8 $\pm$ 2.6	0.02
Weight	3.2 $\pm$ 3.3	0.21
Height	0.3 $\pm$ 0.6	0.56

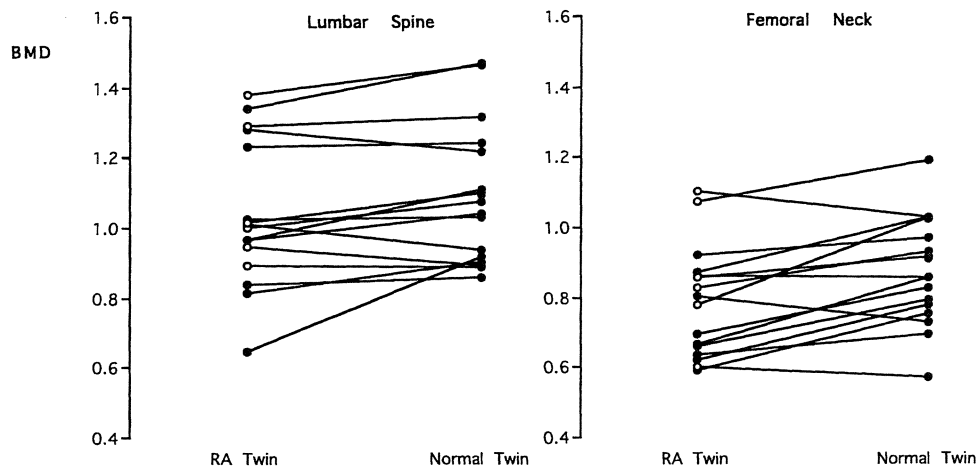
\* Percent difference calculated as [(Unaffected - affected)/unaffected]  $\times$  100. A positive value indicates that the unaffected twin has a higher value than the affected twin.

except the skull, where the difference was 2.8%. The distribution of differences in BMD at the lumbar spine and femoral neck for individual pairs is shown in Figure 1. The presence or absence of lower extremity RA involvement did not determine differences in BMD between twins. Total lean soft tissue and lower limb lean soft tissue were also significantly reduced (range 5.2–12.3%) in the twins with RA. There were no statistically significant differences in body weight, fat, or height.

Differences in BMD between twins were examined in relation to disease duration and the difference in lean soft tissue. Disease duration did not correlate with the difference in BMD at any site. Multiple regression analysis showed the difference in lower limb and total lean soft tissue to be significant predictor variables, independent of age, of the difference in femoral neck BMD ( $P = 0.02$  and  $P = 0.005$ , respectively), but they were not significantly related to the difference in lumbar spine or total body BMD.

## DISCUSSION

There have been several studies of bone mass or density in RA at peripheral sites, such as the distal radius, but few studies of bone loss at sites removed from affected joints. Moreover, among the few previous studies of generalized bone loss in RA, there have been conflicting results regarding the effects of RA on BMD in non-steroid-treated patients. For example,



**Figure 1.** Distribution of the differences in bone mineral density (BMD) at the lumbar spine and femoral neck in twin pairs in which 1 twin had rheumatoid arthritis (RA). Open circles indicate absence of lower extremity involvement.

reported deficits have ranged from 5.3% to 15% for total body calcium (15,16) and from 0% to 11% for lumbar spine BMD (1-4). Although our method of recruiting twins may have led to some selection bias toward subjects with more severe RA, the present study, which examined non-steroid-treated patients, suggests that reductions in BMD can be substantial and involve multiple regions throughout the skeleton in RA patients. Although BMD measurements were, in absolute terms, marginally lower in twins measured using a Hologic machine as opposed to a Lunar machine, as has been reported previously (13), each individual twin pair was measured on the same machine, and differences in software algorithms for different skeletal sites would influence these results only marginally.

Osteoporosis in RA is generally considered to be multifactorial, and factors that have been suggested to be important include reduced physical activity (1), corticosteroid therapy (15), and disease mechanisms (17). Physical activity is strongly associated with BMD in normal subjects, and it has previously been shown that reduced physical activity and functional ability are factors in spinal and femoral osteopenia in RA (1,4). In the present study, total and lower limb lean soft tissue were significantly reduced in RA-affected twins and the difference was related to the difference in femoral neck BMD, suggesting that muscular activity has a positive effect on bone density, at least in the hip. Roubenoff et al (18) found that reductions in total body potassium correlated with disease severity and

with production of the cytokine tumor necrosis factor  $\alpha$  in RA and suggested that the underlying inflammatory process could promote osteoporosis in RA independent of reduced physical activity. However, reductions in total body potassium could also reflect altered physical activity since body potassium is found predominantly in lean tissue such as muscle. Like the study by Roubenoff and colleagues, however, the recent findings of Gough et al (17) suggest that inflammation *per se* plays a major role in bone loss in RA. In the latter study, bone loss was associated with disease activity measures, and improvements in bone density were seen in patients whose disease remitted and became inactive.

An alternative explanation for the reduced bone density in the RA-affected twins is their antirheumatic drug therapy. For example, the use of nonsteroidal antiinflammatory drugs is widespread in RA, and these drugs have been shown to affect bone metabolism. However, *in vitro* studies suggest that these drugs act to inhibit bone resorption, although potency differs between agents (19,20). *In vivo* studies also suggest that they can prevent post-ovariectomy bone loss in the rat (21) and suppress markers of bone resorption such as urinary cross-linked N-telopeptides in postmenopausal women (22). These effects of nonsteroidal antiinflammatory drugs to inhibit bone resorption therefore would not be expected clinically to result in reduced bone density. Moreover, the findings of Gough et al (17) suggest that suppression of inflammation by antirheumatic therapy would protect against

bone loss and, as such, would be expected to reduce any differences in bone density between RA-affected and nonaffected monozygotic twins.

Although some of the observed reductions in upper and lower limb bone density will undoubtedly reflect juxtaarticular osteoporosis, significant reductions were seen at sites unaffected by juxtaarticular bone loss (such as the ribs, lumbar spine, and pelvis), suggesting that relatively widespread osteopenia is associated with RA in the absence of corticosteroid therapy. Assuming that bone density predicts fracture as it does in other forms of osteoporosis, these findings indicate that RA patients are at significantly increased risk of osteoporotic fractures at all sites. Preventive strategies aimed at preserving both bone mass and lean muscle mass, by controlling inflammation and enabling the patient to maintain physical activity, should be explored.

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