Reduced Bone Mineral Density in Early Rheumatoid Arthritis Is Associated with Radiological Joint Damage At Baseline and After 2 Years in Women

KRISTINA FORSLIND, CATHARINA KELLER, BJÖRN SVENSSON, and INGIÄLD HAFSTRÖM
for the BARFOT Study Group

ABSTRACT. ***Objective.*** Data suggest that reduced bone mass may be associated with radiological damage in rheumatoid arthritis (RA). We investigated if patients with reduced bone mineral density (BMD) at onset of RA had more radiological damage at onset and after 2 years than patients with normal BMD.
Methods. BMD at lumbar spine and hip was measured in 204 patients with recent RA at presentation. At baseline and after 2 years, radiographs of hands and forefeet were evaluated according to the Larsen method. At the same time-points, Disease Activity Score (DAS 28) and functional disability (the Stanford Health Assessment Questionnaire, HAQ) were assessed.
Results. The 134 women and 70 men had a mean age of 55 and 61 years, respectively. Reduced bone mass (RBM, Z score ≤ 1.0 SD) in at least one site was found in 46.0% of women and 62.5% of men. T and Z scores correlated significantly with Larsen scores both at baseline and after 2 years for the total patient cohort. Calculated separately for the sexes, significant correlations were found only for women. Women but not men with reduced bone mass and osteoporosis had higher Larsen scores at baseline and after 2 years than those without. From a stepwise multiple logistic regression analysis Z score trochanter and baseline C-reactive protein were selected as independent predictors of joint damage, measured as proportion over the median Larsen scores. This model could explain about 25% of the "variance" in outcome (Nagelkerke $R^2 = 0.27$).
Conclusion. Reduced BMD at onset of RA in women was associated with a higher Larsen score at baseline and after 2 years, indicating that the development of reduced bone mass and joint destruction in RA may have a common pathophysiological mechanism. (J Rheumatol 2003;30:2590–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS BONE MINERAL DENSITY JOINT DESTRUCTION GENDER

Generalized osteoporosis in rheumatoid arthritis (RA) has been considered to be a complication of the disease[1,2] with multifactorial causes. The most important determinants of this generalized bone loss are disease activity, functional disability, disease duration, and use of glucocorticoids[1,3-8]. The bone formation is reduced[9,10], but the dominant reason leading to generalized bone loss in RA is stimulated osteoclastic bone resorption[5,11]. The pathophysiology of generalized bone loss has been suggested to be different from that of focal bone erosions, where synovial invasion into adjacent cartilage and bone with activation of matrix degradation enzymes from fibroblasts and macrophages has been regarded to be the main cause[12].

However, the hypothesis has been put forward that there may be a common pathophysiological mechanism for the development of osteoporosis and bone erosions[13]. This hypothesis has been strengthened by the association between high prevalence of osteoporosis and presence of erosions found in a cross-sectional study of women with established RA[8].

In patients with very early RA, less than one year, bone mineral density (BMD) has been found not to be different from that of healthy people. In spite of that, a considerable number of the patients already had reduced bone mass at that time[14]. This might suggest that the disease had already affected bone in some patients, which raises the question whether reduced BMD is related to a more severe disease.

To test the hypothesis that reduced BMD at onset of disease may be associated with radiological damage we prospectively followed a cohort of patients with early RA for 2 years investigating primarily radiological joint damage.

From the Rheumatology Section, Department of Medicine, Helsingborg's lasarett, Helsingborg; and the Rheumatology Department, Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden.

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K. Forslind, MD; C. Keller, MD; B. Svensson, MD, Assistant Professor, Rheumatology Section, Department of Medicine, Helsingborg's lasarett; I. Hafström, MD, Assistant Professor, Rheumatology Department, Karolinska Institutet, Huddinge University Hospital.

Address reprint requests to Dr. I. Hafström, Rheumatology Department, R92, Huddinge University Hospital, 141 86 Stockholm, Sweden. E-mail: ingiald.hafstrom@hs.se

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MATERIALS AND METHODS

Two hundred four Caucasian patients with recent onset RA, satisfying the 1987 American College of Rheumatology (ACR) classification criteria[15], were enrolled into this prospective study. The patients were included in the "BARFOT" register, a Swedish multicenter observational study of early RA[16], and were recruited from those 227 consecutive patients who earlier participated in a study of assessment of BMD at disease onset[14] and whose radiographs of hands and feet at enrolment could be identified. The patients were between 21 and 85 years of age and were referred to the rheumatology departments at Huddinge and Helsingborg hospitals in Sweden from 1995 to 1999. To be included, disease duration was to be no more than 12 months and the patient should not have been treated with glucocorticoids or disease modifying antirheumatic drugs (DMARD). Neither should they have any other disease or medication that might affect bone metabolism. All patients gave their informed consent and the respective ethics committees approved the study.

BMD was measured before start of DMARD therapy by dual-energy x-ray absorptiometry (DEXA) with a Lunar densitometer at the lumbar spine (L1 and L2–L4) and at the left hip (femoral neck, greater trochanter, and Ward's triangle). BMD was expressed as gram of bone mineral per square centimeter (g/cm^2), as the number of standard deviations (SD) from the mean of young healthy people, T score, and as the number of standard deviations (SD) from the mean of healthy age and sex matched people, Z score, values obtained from Lunar's combined European/US reference population[17]. Osteoporosis was defined as T score > 2.5 SD below the mean value of young healthy controls according to the World Health Organization definition[18,19], and reduced bone mass as a Z score ≤ 1.0 SD below the mean value of healthy age and sex matched people[7].

Posteroanterior radiographs were taken of hands, wrists, and forefeet at enrolment and after 2 years. Radiographic damage was classified by comparison with standard reference radiographs according to the method of Larsen, *et al*[20]. The joints assessed were the wrists (score multiplied by 5), all metacarpophalangeals (MCP) (= 10), all proximal interphalangeals (PIP) (= 8), both IP I in the hands (= 2), metatarsophalangeals II–V (= 8), and both IP in the great toe (= 2). Each joint was scored grade 0 to V. The Larsen score is the total sum of the grading in all 32 joints, range 0–200. As a control we also calculated Larsen score by summing only grades II–V, as grade I, picturing soft tissue swelling and osteoporosis, does not indicate structural damage. We called this measure "Larsen –1". The radiographs were read in chronological order by one blinded observer (KF). The intraobserver reliability was assessed by calculating the intraclass correlation coefficient (ICC) from a random sample of 20 pairs of radiographs from baseline and endpoint. The films were read twice with an interval of 2 weeks. The ICC for the baseline films was 0.9783 (95% CI 0.9452 to 0.9914) and 0.9963 (95% CI 0.9907 to 0.9985) for the radiographs taken after 2 years.

Disease activity was measured by the Disease Activity Score (DAS) composite index, using a 28-joint score (DAS 28)[21]. This includes number of swollen joints, number of tender joints, patient's global assessment of disease activity, and erythrocyte sedimentation rate (ESR). C-reactive protein (CRP) and rheumatoid factor (RF) were also determined.

Functional disability was evaluated using the Swedish version of the Stanford Health Assessment Questionnaire (HAQ)[22], a self-reporting instrument measuring disability of daily life activities. The score created for the disability index ranges from 0 to 3, where a higher score indicates a higher degree of disability[23].

Statistical methods. For the ICC a 2-way mixed effects model was used. The Mann-Whitney test was used for between-group comparisons, the Wilcoxon signed-rank test for test of changes over time, and the chi-square test for differences between proportions. Correlations were assessed by the Spearman correlation coefficient.

Larsen scores at 2 years and the various measures of BMD were not linearly associated. Therefore, linear regression was not an applicable method for prediction. Instead, a multivariate stepwise logistic regression model was used to select independent predictors of joint damage, measured as proportion over the median Larsen scores.

All significance tests were 2-tailed and conducted at the 0.05 significance level. Analyses were performed using SPSS 11.0 software.

RESULTS

Patients' demographic and clinical characteristics. The baseline characteristics of the 204 patients (134 women, 70 men) are shown in Table 1. The mean age at diagnosis was 57 years and the mean disease duration was 6 months. Men were significantly older and had higher body mass index (BMI) compared with women, but otherwise there was no statistically significant difference in demographic and clinical characteristics between the sexes. Of the 134 women, 79 were postmenopausal, of whom 11 were using hormone replacement therapy (HRT).

Treatment with DMARD and glucocorticoids. After inclusion all but 16 patients started with DMARD therapy. The doses and agents were adjusted according to the physicians' decision based upon disease activity and side effects. A summary of treatments is given in Table 2. Glucocorticoid treatment was initiated in 25% of the patients at disease start, and 28% of patients were using this medication at 2 years with no difference between women and men. The doses [mean (SD)] were at baseline 7.7 (1.32), range 5–15, and after 2 years, 6.9 (1.67), range 1.25–10. The doses did not differ between sexes. Further, 6 patients were treated with bisphosphonates and 120 with calcium supplementation with or without vitamin D.

BMD at baseline. BMD and Z scores are given in Table 3. For the female patients the mean Z scores were similar to those of age matched women at all sites except L1, whereas the mean Z scores for the male patients were low at most sites, and were most pronounced at L1 and L2–L4.

Radiological scores at baseline and after 2 years. Larsen scores at baseline and after 2 years are shown in Table 4. Thus, the damage scores increased significantly during the 2 years with no difference between women and men, and a similar increase was found when calculating frequency of patients with Larsen score > 1 in any joint (Table 4). At baseline there was a significantly higher frequency of women with no radiographic changes (Larsen score = 0) compared with men, a difference that was not significant after 2 years.

Correlations between Z and T scores and Larsen scores. Z scores at all measured sites correlated significantly with Larsen scores both at baseline and after 2 years for the total patient cohort (Table 5), correlations that were also significant when using "Larsen –1" scores (data not shown). When calculated separately for both sexes, significant correlations were found only for women.

This difference between sexes was also seen when calculating correlations between T scores and Larsen scores at baseline and after 2 years, where significant correlations were found for T scores at all sites and Larsen scores for

Table 1. Demographic and clinical characteristics of the 204 patients with RA.

	Total, n = 204	Women, n = 134	Men, n = 70	Difference, Women/Men p
Age, yrs, mean (SD)	57 (15)	55 (16)	61 (13)	0.009
BMI, mean (SD)	24.5 (4.1)	24.1 (4.0)	25.2 (4.1)	0.036
Disease duration, mo, mean (SD)	5.8 (3.3)	5.6 (3.3)	6.1 (3.3)	NS
Number of RA criteria, mean (SD)	4.8 (0.8)	4.8 (0.8)	4.8 (0.8)	NS
RF positive, n (%)	117 (57)	76 (57)	41 (59)	NS
DAS 28, mean (SD)	5.38 (1.18)	5.45 (1.18)	5.25 (1.17)	0.195
CRP, mean (SD)	39 (39)	37 (41)	42 (37)	0.096
HAQ score, mean (SD)	1.11 (0.67)	1.18 (0.68)	0.99 (0.64)	0.056
Smoking status, %				0.095
Never smokers	32.5	34.6	28.6	
Ex-smokers	39.9	34.6	50.0	
Current smokers	27.6	30.8	21.4	

NS: non significant.

Table 2. Number of patients with DMARD and glucocorticoid treatment started at baseline and undergoing treatment after one and 2 years.

	Baseline	1 Year	2 Years
No DMARD	16	29	29
Sulfasalazine	96	57	35
Methotrexate	56	65	66
Antimalarials	15	14	7
Parenteral gold	15	14	10
Auranofin	4	4	1
Combinations	2	8	28
Other DMARD	0	2	4
Glucocorticoids	50	63	57

Table 3. BMD and Z scores in L1, L2–L4, femoral neck, Ward's triangle, and trochanter for all 204 patients at baseline.

	Women		Men	
	BMD	Z score	BMD	Z score
L1	0.95 (0.19)	–0.53 (1.12)	1.00 (0.14)	–0.77 (1.15)
L2–L4	1.09 (0.20)	0.01 (1.38)	1.12 (0.14)	–0.49 (1.07)
Femoral neck	0.88 (0.16)	0.04 (0.93)	0.92 (0.12)	–0.23 (1.00)
Ward's triangle	0.74 (0.20)	–0.11 (1.01)	0.75 (0.13)	–0.18 (1.06)
Trochanter	0.75 (0.15)	0.11 (1.07)	0.89 (0.13)	–0.01 (1.16)

Values are mean (SD).

women. After 2 years, significant weak correlations were found at L1 and L2–L4 for men also (data not shown).

Correlations between Z and T scores and clinical variables. Z scores and T scores did not correlate significantly with the disease variables DAS 28 or CRP or with the HAQ score at baseline or 2 years for women or for men (data not shown).

Correlations between clinical variables and Larsen scores. CRP correlated significantly with Larsen scores at baseline and after 2 years when calculated for all patients and for women separately but not for men, whereas DAS 28 and HAQ score did not correlate significantly with Larsen scores at any time-point, apart from a significant correlation between DAS 28 and Larsen score at 2 years for men only ($p = 0.045$) (Table 5).

Differences in demographic and clinical variables and Larsen scores between patients with and without reduced bone mass and with and without osteoporosis. The relation of presence of reduced bone mass and presence of osteoporosis in women and men to disease dependent and disease independent variables at baseline and after 2 years is shown in Table 6. Thus, women but not men with reduced bone mass had higher Larsen scores at baseline and after 2 years than those with normal bone mass, and this difference was statistically significant for baseline Larsen score. Also, women with osteoporosis at baseline, but not men, had significantly higher Larsen scores both at baseline and after 2 years compared to those without osteoporosis. As could be expected, both women and men with osteoporosis were significantly older than those without, and the women with osteoporosis also had a lower BMI. Concerning clinical variables, baseline DAS 28 was significantly higher in women with osteoporosis compared with women without. Otherwise, clinical variables were not found to be associated with osteoporosis or reduced bone mass.

Predictive value of BMD for radiological damage at 2 years. The Z scores from all measured sites were highly intercorrelated. As stated, significant correlations were found between the Z scores and Larsen scores for women only. Thus, the prediction analysis was limited to women. Z scores from the trochanter site were selected for the regression analysis since this site had one of the highest correlations with the Larsen scores at 2 years.

Z scores for trochanter, patient age, disease duration, presence of RF, baseline CRP, DAS 28, HAQ score, and glucocorticoid treatment between baseline and 2 years were entered into the regression model as possible predictors for joint damage (Larsen scores above median 11 at 2 years). From the stepwise logistic regression analysis, Z score

Table 4. Larsen scores at baseline and after 2 years and frequency of patients with Larsen score = 0.

	All Patients		Women		Men	
	Baseline	2 Years	Baseline	2 Years	Baseline	2 Years
Larsen scores (0–200)						
Mean (SD)	9.5 (11.0)	17.4 (16.1)**	9.6 (11.1)	16.5 (16.6)**	9.4 (11.0)	19.3 (15.1)**
Median	7.0	13.0	7	11	7	15
25–75 percentile	0–14	5–26	0–16	4–25	2–12	9–29
Range	0–68	0–82	0–40	0–82	0–68	0–66
Larsen score > 1 in at least one joint, percentage of patients	36.3	62.7	37.3	60.0	34.3	62.7
Larsen score = 0, percentage of patients	26.5	10.7	32.1*	13.0	15.7	6.5

* p = 0.012 compared with frequency at baseline for men. ** p < 0.001 compared with baseline scores.

Table 5. Correlations between Z scores at different sites or clinical variables at baseline and Larsen scores at baseline and after 2 years.

		All Patients		Women		Men	
		Larsen Baseline	Larsen 2 Years	Larsen Baseline	Larsen 2 Years	Larsen Baseline	Larsen 2 Years
L1	r*	–0.267	–0.243	–0.332	–0.201	–0.034	–0.267
	p	0.000	0.002	0.000	0.034	0.808	0.064
L2–L4	r	–0.284	–0.287	–0.360	–0.259	0.045	–0.241
	p	0.000	0.000	0.000	0.007	0.747	0.103
Ward's triangle	r	–0.232	–0.253	–0.344	–0.287	0.022	–0.165
	p	0.001	0.001	0.000	0.002	0.857	0.199
Trochanter	r	–0.275	–0.276	–0.391	–0.340	–0.017	–0.129
	p	0.000	0.000	0.000	0.000	0.892	0.318
Femoral neck	r	–0.211	–0.200	–0.316	–0.223	0.044	–0.134
	p	0.003	0.008	0.000	0.017	0.717	0.298
DAS 28	r	0.090	–0.016	0.147	0.125	–0.062	–0.255
	p	0.200	0.832	0.091	0.185	0.611	0.045
CRP	r	0.168	0.232	0.208	0.289	0.015	0.075
	p	0.017	0.002	0.016	0.002	0.904	0.565
HAQ	r	0.062	0.007	0.097	0.067	–0.053	–0.103
	p	0.388	0.933	0.270	0.485	0.671	0.439

* Spearman's rho.

trochanter and baseline CRP were selected as independent predictors (Table 7). This model was able to explain about 25% of the "variance" in outcome (Nagelkerke $R^2 = 0.27$).

DISCUSSION

This is the first prospective study evaluating the possible importance of reduced BMD for disease severity in RA. We found that BMD expressed as T and Z scores was significantly correlated with Larsen scores both at baseline and after 2 years of disease, but when analyzing the sexes separately, significant correlations were found only for women. Larsen scores were also significantly higher in the groups of women having osteoporosis or reduced bone mass, i.e., a Z score ≤ 1.0 SD at any of the measured sites.

Previous prospective studies to identify possible factors associated with poor radiological outcome in RA have not included BMD[24-27]. In our study, BMD measurements showed a high proportion of patients with reduced bone mass just a few months after disease onset, which indicates that there is already a subgroup of patients with reduced bone mass early in the disease.

Radiological damage occurs early in the disease course and the proportion of patients with joint destruction after 2 years in this study was consistent with earlier reports[25,28,29]. Thus, the majority of patients developed radiological damage within the first 2 years, with no significant difference between the sexes.

The observed correlations between bone mineral measures at disease onset and radiological score at baseline and after 2 years support the suggestion that these events may be related[13]. The identification of mature bone-resorbing osteoclasts rich in lysosomal enzymes and their

Table 6. Differences in demographic and clinical variables and Larsen scores between patients with and without reduced bone mass (RBM) and with and without osteoporosis (OP). Values are medians (25–75 percentile). p values are differences between patients with and without RBM, and with and without OP for each sex.

	Women				Men			
	No RBM	RBM	No OP	OP	No RBM	RBM	No OP	OP
Patients, %	54.0	46.0	66.2	33.8	37.8	62.5	68.5	31.5
Age, yrs	52 (41–67)	56 (44–68)	48 (38–55)	69 (64–74) p < 0.001	60 (55–67)	58 (48–69)	56 (48–66)	66 (56–71) p < 0.05
BMI	24 (22–27)	23 (21–25)	24 (22–26)	22 (21–24) p < 0.01	25 (23–29)	24 (21–27)	24 (22–27)	25 (21–27)
DAS 28, baseline	5.54 (4.63–6.36)	5.48 (4.58–6.34)	5.35 (4.44–6.05)	6.09 (5.30–6.64) p < 0.01	5.06 (4.33–6.37)	5.23 (4.49–5.96)	5.05 (4.23–6.09)	5.42 (5.10–6.40)
DAS 28, 2 yrs	3.17 (2.44–3.62)	3.00 (2.09–4.50)	3.17 (2.26–3.64)	3.01 (2.44–4.70)	2.05 (1.83–3.29)	2.37 (1.80–3.28)	2.16 (1.74–3.28)	2.77 (2.03–3.84)
CRP, baseline	22 (10–38)	20 (12–49)	20 (10–37)	21 (10–53)	28 (11–57)	28 (12–67)	26 (10–57)	53 (17–86)
CRP, 2 yrs	10 (9–12)	10 (8–14)	10 (9–14)	10 (9–13)	10 (10–22)	10 (9–16)	10 (9–16)	10 (9–18)
HAQ, baseline	1.00 (0.80–1.60)	1.10 (0.50–1.80)	1.00 (0.70–1.59)	1.30 (0.60–2.00)	0.90 (0.60–1.10)	0.90 (0.57–1.10)	0.90 (0.60–1.15)	0.90 (0.50–1.15)
HAQ, 2 yrs	0.50 (0.00–0.95)	0.50 (0.13–1.00)	0.38 (0.00–0.90)	0.75 (0.22–1.19)	0.13 (0.00–0.69)	0.40 (0.00–0.88)	0.13 (0.00–0.69)	0.25 (0.12–0.84)
Larsen score, baseline	2 (0–11)	10 (2–19) p < 0.001	2 (0–9)	13 (7–21) p < 0.05	8 (3–19)	6 (3–10)	8 (3–13)	6 (3–11)
Larsen score, 2 yrs	8 (3–19)	16 (5–26) p = 0.078	9 (3–22)	16 (5–31) p < 0.05	14 (7–32)	17 (10–29)	12 (7–29)	17 (12–30)

Table 7. The stepwise logistic regression analysis shows that Z score trochanter and baseline CRP are selected as independent predictors of joint damage in women, defined as median Larsen score > 11 after 2 years.

	α	ß	SE	p	Exp (ß)	95% CI for Exp (ß) Lower	Upper
Step 1							
Z score trochanter		–0.683	0.205	0.001	0.505	0.338	0.755
Constant	0.142		0.203	0.484			
Step 2							
Z score trochanter		–0.683	0.212	0.001	0.505	0.333	0.766
Baseline CRP		0.022	0.008	0.005	1.022	1.007	1.038
Constant	–0.572		0.306	0.061			

SE: standard error.

precursors not only in bone but also in the rheumatoid synovium in areas of bone erosions[30,31] may explain that osteoporosis and erosions develop in parallel. The osteoclasts recruited to the pannus region and the osteoclasts localized in osteoporotic bone synthesize and secrete high concentrations of the inflammatory cytokine interleukin 8[32], which acts as an important regulatory signal for bone, immune cell recruitment, and amplification of the inflammatory disease[33]. Thus, osteoclasts present in both synovial tissue and bone may be the link between development of erosions and generalized reduced bone mass as osteoclast activation, rather than reduced bone formation, causes bone loss in early RA[5].

Various factors may influence the link between bone degradation and erosions. Inflammation stimulates bone degradation through inflammatory cytokines[34,35], but no single clinical inflammatory variable has been found to predict radiological damage early in the disease[36]. In this study, disease activity measures such as DAS 28 and HAQ score were not associated with Larsen scores at baseline or after 2 years. However, significant associations have been found when relating time-integrated values of inflammatory markers to radiological outcome[37-39], findings that undermine the hypothesis that synovial inflammation and erosions are independent phenomena[40]. The presence of reduced bone mass and erosions in a subgroup of patients only a few months after disease onset suggests that low grade inflammation may have existed before clinical symptoms developed.

Another factor that might be of importance to the link

between low BMD and erosions is age. Osteoporosis increases with age and RA is more destructive in older patients[41,42]. However, we found an association between osteoporosis and radiological damage only in women, thus other factors must also be considered. This is further strengthened by the fact that in women with reduced bone mass there was also an association with Larsen scores. Low Z scores indicate causes of reduced bone mass other than age and sex, as Z scores are the number of SD from the mean of healthy age and sex matched people. Such causes could include reduced sex hormones, which may have pathogenic roles in RA[43]. However, the physiological estrogen reduction after menopause, which is the main cause of osteoporosis in older women[44], was taken into account in the Z scores.

The interesting observation that the association between reduced BMD and joint damage was found only in women indicates that the different sex hormones are involved in bone and joint destruction in different ways. In women with RA, estrogen concentrations have not been found to be significantly different from those of healthy women[45], but the suppressive effect of hormone replacement therapy on disease activity[46] suggests a relative estrogen deficiency in RA. Estrogen deficiency has bone resorptive effects, mainly through upregulation of osteoclast formation by increased production of osteoclastic cytokines such as interleukin 1 and tumor necrosis factor-α and increased responsiveness of osteoclast precursors[47]. The resulting increase in osteoclast number and activity might explain the relation between reduced bone mass and erosions in women with RA observed here.

In men with RA bioavailable testosterone concentrations are low[48], as well as BMD, but no relation between these variables has been found[49]. Relatively few data are available concerning the effect of androgens on bone cells, but in aging men the importance of increased osteoclastic activity has been found to be less prominent for the age-related bone loss[50]. This lack of major influence of androgens on osteoclasts may explain why we found no significant correlation between bone mineral and Larsen score in this cohort of men with early RA, in contrast to the association between bone mineral and presence of erosive disease found in a study of men with long-standing disease[49].

Most patients were prescribed DMARD within the first month after presentation to the clinic, according to the ACR guidelines[51]. Early active treatment of RA reduces the progression of radiographic damage and bone turnover[52,53], which suggests that both focal and generalized bone loss can be affected by treatment.

Our finding of a relationship between reduced bone density and joint damage in women with early RA may support recent assumptions of a common pathophysiological mechanism[13]. Increasing awareness of generalized and focal bone loss in RA suggests possible specific therapies. Estrogen therapy and specific osteoclast-targeting agents, which have prevented osteoclast mediated bone destruction of joints in animal models[54], may be promising therapeutic tools in the future.

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