EXTENDED REPORT

Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density

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Ann Rheum Dis 2004;**63**:1576–1580. doi: 10.1136/ard.2003.016253

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Accepted 18 January 2004

Objective: To examine variables associated with bone mineral density (BMD) in patients with rheumatoid arthritis (RA).

Methods: We investigated 373 patients with low to moderately active RA. Patients with low disease activity were recruited from a cohort of patients in clinical remission. Patients with moderately active disease were included in a trial comparing the effects of long term high intensity exercise programme and conventional physical therapy. Demographic and clinical data were collected. Bone mineral density (BMD) was measured by means of dual *x* ray absorptiometry (DXA). Associations between demographic and clinical measurements on the one hand and BMD on the other were investigated in regression analyses.

Results: The patient group consisted of middle aged, mainly female, patients. The median (interquartile range) disease duration was 7 (4 to 13) years, the mean disease activity score (standard deviation) was 3.2 (1.4). Of the group, 66% was rheumatoid factor positive, and 83% (n = 304) had never used corticosteroids. The median Larsen score of hands and feet was 27 (5 to 61). Greater age and low body mass index were related to low BMD at the hip and spine. High Larsen score for hands and feet was significantly associated with low BMD at the hip. The use of corticosteroids was not independently associated with BMD. The results of the multiple regression analyses also applied to the subgroup of corticosteroid naive patients.

Conclusion: BMD data of patients with low to moderately active RA demonstrated an association between high radiological RA damage and low BMD at the hip, which suggests an association between the severity of RA and the risk of generalised bone loss, which also occurred in corticosteroid naive patients.

Generalised osteoporosis is an extra-articular complication of rheumatoid arthritis (RA).[1] Decreased bone mineral density (BMD) [2 3] plus an increased risk of both hip and vertebral fractures in patients with RA compared with patients without RA has been demonstrated in several studies.[4–6]

Previous studies helped to unravel the extent of osteoporosis and change in BMD in patients with RA. The occurrence of osteoporosis in these studies is 15–20% at the hip and the spine.[7 8] Haugeberg elegantly showed a twofold increase in osteoporosis in women with RA and a twofold increase of reduced bone mass in men with RA, compared with patients without RA in a population based study.[8 9] Numerous studies have investigated the relation between demographic and disease related variables on the one hand, and bone mass on the other, in patients with RA. These studies tried to identify patients at high risk of osteoporosis.[10–12] Studies investigating the variables associated with BMD[13–16] showed some inconsistencies, which might be caused by differences in methodological aspects, such as sample size and patient selection. Moreover, the complex interaction between inflammation, immobility, and corticosteroid use may contribute to the lack of unanimous results.

Our hypothesis was that disease related variables such as disease duration and physical disability contribute to BMD loss. In particular, we intended to confirm the association between cumulative disease activity (expressed as radiological damage) and low BMD[7 17] in 373 outpatient clinic based patients, including a subgroup of 304 corticosteroid naive patients. In contrast to Sambrook, we assessed the radiological damage of the hands as well as the feet.[17] Compared with the two previous investigations, the present cross sectional study investigates a larger number of patients, including many corticosteroid naive patients, with shorter disease duration.[7 17]

METHODS

Patients

All patients included fulfilled the American College of Rheumatology (ACR) 1987 revised classification criteria for RA.[18] In general, these patients with RA had a low to moderately active disease. Patients were participating in one of two research projects; the RAPIT trial (n = 300)[19] and a cohort of patients in clinical remission (n = 76).[20] The RAPIT study was a 2 year multicentre randomised clinical trial.[19] The patients included in this trial were between 20 and 70 years old and with ACR functional class I–III.[21] Patients were included if they were on a stable regimen of disease modifying antirheumatic drugs (DMARDs) in the 3 months prior to inclusion and able to exercise on a bicycle. Patients suffering from a serious cardiovascular and/or pulmonary disease contraindicating intensive exercise, and patients with a prosthesis of a weightbearing joint were excluded. The second project concerned a cohort of patients in clinical remission.[20] At inclusion in the cohort, the patients fulfilled

Abbreviations: ACR, American College of Rheumatology; BMD, bone mineral density; BMI, body mass index; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; DXA, dual *x* ray absorptiometry; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor

Pinal's modified criteria of clinical remission.[22] Retrospectively, patients had non-active RA during 6 months before inclusion in the cohort, and patients were excluded from participation in the remission cohort if they were using corticosteroids at the time of inclusion.

In the current study, we investigated baseline data of 300 RAPIT patients and data from 3 years after inclusion in the cohort of patients in clinical remission. Therefore, a small number of the patients from the remission cohort were reported as current users of corticosteroids. Of the 187 patients originally participating in the remission cohort, 76 were available for the current study. The patients from the remission cohort were selected based on persistent remission and willingness to participate in the present study. Three patients participated in both the RAPIT trial and the remission cohort. The data of these three patients were counted in the remission cohort group. At the time of clinical examination, all patients underwent a BMD measurement, unless (in case of the remission cohort) they had had a BMD measurement within the previous year.

Demographic and clinical variables

The demographic and clinical variables of the patients were systematically retrieved by interview and clinical examination. The demographic variables collected were age, body weight, height, and disease duration. Other data collected concerned menopause status, smoking status, use of anti-osteoporotic drugs and DMARDs, and history of corticosteroid use. Three corticosteroid variables were investigated (current use (yes or no), previous use (yes or no), and never versus ever use). Owing to the small number of current users, never versus ever use was chosen as the corticosteroid variable in the multiple regression. The fracture history of the patient (fracture after 25 years of age) and their first degree relatives (fracture after 50 years of age not caused by accident involving motorised traffic) was also recorded.

RA disease activity core measures were collected: pain; patient's and investigator's global disease activity assessment measured on a visual analogue scale (0–100 mm); physical disability by means of the Health Assessment Questionnaire (HAQ),[23] Ritchie score; 44 swollen joint count; and the acute phase reactant (erythrocyte sedimentation rate; ESR). The disease activity score (DAS) was calculated.[24]

The radiological damage to the joints of the hands and feet was assessed by a trained rheumatologist according to the Scott modification of the Larsen method.[25] As a further modification, the wrists were evaluated as a single unit and the score of each wrist was multiplied by 5. The intra-observer variability was calculated by means of the intraclass correlation coefficient (ICC = 0.97) and Cronbach's α (0.99) on a sample of 15 randomly chosen *x* rays.

BMD measurements

BMD measurements of the hip (femoral neck) and lumbar spine L1–4 in anteroposterior view were carried out by trained technicians at each centre. Several quality aspects of the BMD data collected on the four different dual energy *x* ray absorptiometry (DXA) machines were examined. In vitro reproducibility, expressed as a coefficient of variation (CV), was 0.8%, 0.3%, 0.3%, and 1.3% using the Hologic 2000, two Hologic 4500 machines, and the Lunar DPX, respectively. At the femoral neck, the corresponding figures were 3.7%, 2.6%, 2.6%, and 2.3%.

To prevent systematic error of the BMD caused by the use of different DXA machines, we performed cross calibration of the four different DXA machines. The centre where the BMD of the majority of the patients was measured was chosen as the reference centre. The raw BMD values of the reference centre and the adjusted BMD values of the other centres were compared with the Hologic (L1–4) and NHANES (femoral neck) reference populations for T and Z score estimation.

Ethics

The study protocols of the original research projects and the current study were approved by the medical ethical committees at the respective centres.

Statistical analysis

Data of all patients as well as subgroups of men and women separately, corticosteroid naive patients, and patients with radiological damage (Larsen score>0), were analysed. The independent variables associated with BMD at different measurement sites were investigated by means of linear regression. In the crude analysis, relations between demographic and clinical variables listed in table 1 and BMD were investigated. Based on the results of the corresponding crude analysis ($p<0.20$) and presumed clinical relevance, variables were added to the respective multiple regression models. In all multiple regression models, we adjusted for participation in original study protocol (RAPIT or remission), thus controlling for the heterogeneity between the respective original patient groups. The models for the total patient group were then further refined by tentatively adding first order interactions, squared terms investigating curve of the regression, and single variables initially excluded from the model based on the results of the crude analysis. A two sided p value of $\leqslant 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of the 373 patients included in the study are shown in table 1. The patient group consisted of middle aged, mainly female, patients with RA. Most of the women were postmenopausal. The patients had a moderate disease duration and a low disease activity. Most of the patients were rheumatoid factor (RF) positive and had little radiological damage. The demographic and clinical variables of the patients per subgroup, based on original study, differed in accordance with the inclusion criteria of the respective study protocols. The patients from the remission cohort were older, had a longer disease duration, a lower DAS at clinical examination, a more favourable distribution of the ACR functional classes, and less current corticosteroid use, compared with the patients participating in the RAPIT trial. There was a tendency towards less RA damage, as expressed by HAQ and Larsen score, in the remission cohort patients. Although several demographic and clinical characteristics had missing values, there was no difference in hip and spine BMD between patients in whom the respective characteristics were present or absent (data not shown).

BMD, frequency of osteoporosis, and reduced bone mass

The frequencies of osteoporosis (T score $\leqslant -2.5$ SD)[26] and reduced bone mass (Z score $\leqslant -1$ SD), according to subgroup and BMD measurement site, are presented in table 2. In the total patient group, osteoporosis occurred in 6.5% and 12.6% in the femoral neck and spine, respectively. Reduced bone mass occurred in 18.9% in the femoral neck and in 20.7% in the spine (all patients). In all (sub)groups presented, the group of premenopausal women excepted, osteoporosis occurred more frequently in the spine compared with the hip. In two patients from the remission cohort, no hip measurement was performed owing to bilateral hip replacement.

Table 1 Demographic variables, disease related and therapy variables, damage, bone mineral density, and fractures

	All patients (n = 373)	RAPIT (n = 297)	Remission (n = 76)
Demographic variables			
Age (years)	53.8 (11.9)	52.0 (11.1)	60.9 (12.3)
Sex (women/men) (%)	77/23	79/21	68/32
BMI (kg/m^2)	26.4 (4.8)	26.7 (5.0)	25.3 (3.5)
Menopause (%)	63.5	60.7	75.0
Menopause age (years)	46.8 (5.3)	46.8 (5.0)	46.9 (6.6)
Current smoker (%)	24.6	23.8	27.6
Disease variables			
Disease duration (years)	7.0 (4.0 to 13.0)	6.0 (3.0 to 12.0)	9.0 (6.0 to 18.0)
Rheumatoid factor positive (%)	66	72	43
Investigator's global assessment (VAS 0–100 mm)	20.0 (7.0 to 34.8)	24.0 (10.0 to 37.5)	12.0 (3.0 to 19.0)
Pain (VAS 0–100 mm)	30.0 (10.0 to 54.0)	32.0 (13.0 to 57.0)	14.0 (4.8 to 37.0)
Disease activity (VAS 0–100 mm)	27.0 (10.0 to 51.0)	32.0 (13.0 to 52.5)	16.0 (4.0 to 29.5)
HAQ (range 0–3)	0.6 (0.3 to 1.0)	0.6 (0.3 to 1.0)	0.5 (0.0 to 1.1)
Ritchie score	2 (2 to 13)	8 (4 to 14)	2 (0 to 5)
44 swollen joint count	10 (5 to 16)	12 (6 to 18)	4 (2 to 8)
ESR (mm/1st hour)	15.0 (8.0 to 27.0)	17.0 (8.0 to 29.0)	11.0 (5.0 to 22.0)
DAS	3.2 (1.4)	3.5 (1.3)	2.0 (1.1)
ACR functional class (I/II/III) (%)	31.4/40.2/28.4	18.2/48.5/33.3	82.9/7.9/9.2
Therapy variables			
Corticosteroids (%)			
Never user	82.8	84.2	71.1
Previous user	9.3	4.7	26.3
Current user	7.9	9.1	2.6
Ever user of DMARDs (%)	95.6	96.2	93.4
Current user of HRT (%)	3.8	2.2	9.6
Current user of bisphophonates (%)	3.0	2.4	5.3
Current user of anti-osteoporotic drugs (%)	12.5	9.5	22.4
Damage variable			
Larsen score hands and feet (0–200)	27.0 (5.0 to 61.0)	31.0 (5.5 to 62.5)	15.0 (2.0 to 51.0)
BMD variables			
BMD femoral neck (g/cm^2)	0.78 (0.13)	0.78 (0.13)	0.80 (0.14)
BMD spine L1–4 (g/cm^2)	0.99 (0.16)	1.00 (0.16)	0.98 (0.16)
Z score femoral neck	−0.06 (1.08)	0.09 (1.04)	−0.64 (1.06)
Z score spine L1–4	0.59 (1.88)	1.01 (1.79)	−1.07 (1.23)
T score femoral neck	−0.76 (1.15)	−0.78 (1.17)	−0.67 (1.04)
T score spine L1–4	−0.87 (1.40)	−0.82 (1.42)	−1.07 (1.34)
Fractures			
Fracture 1st degree relative (%)	15.3	15.9	13.2
Fracture patient>age 25 (%)	18.2	16.7	23.7

Mean (SD) for continuous variables with normal distribution. Median (IQR) for continuous variables with non-normal distribution. ACR, American College of Rheumatology; BMD, bone mineral density; BMI, body mass index; DAS, disease activity score; DMARD, disease modifying anti rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; HRT, hormone replacement therapy; anti-osteoporotic drugs, hormone replacement therapy, bisphosphonates, calcium, and/or vitamin D supplementation; VAS, visual analogue scale.

Variables associated with BMD in all patients

The demographic and disease related variables listed in table 1 were investigated in a crude single regression analysis with BMD. In the crude analysis, the following variables were associated with BMD at both the lumbar spine and the femoral neck ($p<0.20$): age, body mass index (BMI), menopause, age at menopause, disease duration, ESR, ever use of DMARDs, use of bisphos-phonates, use of anti-osteoporotic drugs, Larsen score of hands and feet, fractures in first degree relative, and fractures at >25 years of age. In addition, sex was associated with BMD in the lumbar spine and the number of swollen joints was associated with BMD in the femoral neck.

Table 2 Frequency of osteoporosis and reduced bone mass in hip (femoral neck) and spine, L1–4 among all patients with RA and the respective subgroups according to sex, menopausal state, and original study in which they participated (%)

	Osteoporosis*		Reduced bone mass†	
	Femoral neck	Spine L1–4	Femoral neck	Spine L1–4
All (n = 373)	6.5	12.6	18.9	20.7
Men (n = 87)	3.5	8.0	23.3	40.2
Women				
All women (n = 286)‡	7.4	14.0	17.6	14.7
Premenopausal (n = 96)	3.1	3.1	22.9	17.7
Postmenopausal (n = 167)	10.3	21.7	16.4	13.3
RAPIT (n = 297)	7.1	12.1	15.2	13.8
Remission (n = 76)	4.1	14.7	34.2	48.0

*T score $\leqslant -2.5$ SD; †Z score $\leqslant -1$ SD; ‡Owing to missing values the total differs from the sum of subgroups of women.

The variables finally investigated as independent variables associated with BMD in the total group of patients are shown in table 3. Greater age and lower BMI were independently associated with low BMD in both the femoral neck and spine. Sex was also significantly associated with both hip and spine BMD. Participation in the RAPIT trial and high total Larsen score were associated with low BMD in the hip. None of the corticosteroid variables was significantly related to BMD in either the hip or the spine. The confidence intervals of the β coefficient of corticosteroid use (never versus ever) just exceeded zero in the positive direction, suggesting a lack of power in demonstrating an association between corticosteroid use and low BMD. The association between age and BMD

was different for men and women; the interaction term of age and sex contributed significantly to the final regression models of hip and spine. From the β coefficients presented in table 3, it was calculated that with increasing age, BMD in women decreases more than in men. For example, the BMD in women decreased 0.005 g/cm^2 per year in this model, whereas in men the decrease was 0.001 g/cm^2 per year. Consequently, at 50 years of age, men had 0.02 g/cm^2 more bone than women. At 70 years of age the difference increased: men had 0.10 g/cm^2 more bone than women. The final model for hip BMD explained 22% of the variation in BMD; for the spine model this percentage was 17%. None of the squared terms contributed significantly to the model. A number of other variables, including age, smoking status, disease duration, RF status, DAS, HAQ, and ESR, did not show an independent association with BMD in the multivariate analysis.

Variables associated with BMD in subgroups of patients

Multivariate analyses of men and women separately showed results in line with the results for the total patient group (data not shown). The final model found for the total patient group was applied to these subgroups, with sex omitted as a variable from the two respective subgroup analyses. Duration of menopause was added to the analysis of the subgroup of women. In women, longer duration of menopause and lower BMI were associated with low BMD at both hip and spine. At the hip, participation in the RAPIT trial and joint damage as expressed by the Larsen score were also independently associated with low BMD. The percentage of variance explained (R^2) was 31% for the femoral neck model and 30% for the spine model. In men, participation in the RAPIT trial was the only variable significantly associated with low BMD at the hip and the spine. At the femoral neck, low BMI was associated with low BMD. The R^2 of the models were 17% and 11% at the femoral neck and spine, respectively.

The subgroup analysis of the corticosteroid naive patients also showed results in line with the results for the total patient group (data not shown). The same variables were independently associated with BMD at both measurement sites. At the hip, the R^2 of the model increased from 22% to 24%, whereas at the lumbar spine, the R^2 of the model remained 17%. None of the added squared terms and initially excluded single variables (including age, smoking status, disease duration, RF status, DAS, HAQ, and ESR) contributed significantly to the model.

Finally, we investigated the association between radiological damage and BMD in a subgroup of 308 patients with radiological damage (Larsen score>0), in an attempt to improve the power of the data (data not shown). The final model found for the total patient group was applied to the 308 patients. The only marked difference from the results of the total patient group was that ever use of corticosteroids was now independently associated with a lower BMD at the lumbar spine ($\beta = -0.0467$, $p = 0.04$). The R^2 of the models changed to 20% and 19% for the femoral neck and spine, respectively.

DISCUSSION

The present study confirmed the hypothethetical association between a high Larsen score and low BMD in the femoral neck in a large sample of patients with RA with low to moderately active disease. Moreover, the well known associates of high age and low BMI were independent variables associated with low BMD at all measurement sites. With increasing age, BMD decreased more in women than in men im both the hip and the spine. The current results were confirmed in a large subgroup of corticosteroid naïve patients. This is interesting as these associations had not been studied previously in a large group of corticosteroid naive patients.[7 17]

Previous studies[7 17] showed an inverse association between joint damage, expressed by the Larsen score, and BMD measured by DXA in patients with a disease duration of more than 10 years in relatively small patient groups. With the present study, we confirmed these findings in a large population that was heterogeneous for disease duration and joint damage. The repeatedly observed association between severe joint damage and low BMD suggests an association between cumulative disease activity and low BMD, because the Larsen score, in our view, appears to be an appropriate measure of past fluctuating disease activity in cross sectional studies on BMD in RA. An alternative explanation of the association between severe joint damage and low BMD might be that joint damage contributes to physical inactivity with subsequent decrease in muscle strength, and thereby leads to less loading of the bone, resulting in low BMD. However, approaching this alternative explanation by adding physical disability, as expressed by the HAQ score, to the final regression models did not show an independent effect of HAQ on BMD.

The absence of a significant association between Larsen score and BMD of the spine in our population could be ascribed to osteoarthritis of the spine, atherosclerosis of the aorta, and vertebral deformities, which increase the measured BMD and thus obscure a possible relation between potential predictors and 'true' BMD. The same mechanism might explain the lower percentage of variance explained by the final model of spine BMD compared with hip BMD. Because of the difficult interpretation of a spine BMD measurement, recent recommendations prefer the measurement

Table 3 Multiple linear regression analysis of BMD (g/cm^2) at different sites of measurement (dependent variable), demographic and disease variables (independent variables)

	Femoral neck			Spine L1–4		
	β	SE	95% CI	β	SE	95% CI
Original study	−0.061	0.017	−0.095 to −0.027‡	−0.007	0.021	−0.049 to 0.035
Sex	−0.18	0.084	−0.34 to −0.016§	−0.41	0.10	−0.61 to −0.21‡
Age (years)	−0.005	0.001	−0.006 to −0.004‡	−0.006	0.001	−0.007 to −0.004‡
Interaction (age × sex)	0.004	0.001	0.001 to 0.007‡	0.008	0.002	0.005 to 0.012‡
BMI (kg/m^2)	0.006	0.001	0.004 to 0.009‡	0.005	0.002	0.002 to 0.009‡
Corticosteroid use	−0.028	0.023	−0.062 to 0.007	−0.038	0.021	−0.080 to 0.005
Larsen score: hands and feet	−0.0004	<0.001	−0.001 to 0.000‡	−0.0002	<0.001	−0.001 to 0.000
R^2			22			17

BMD, bone mineral density; SE, standard error; CI, confidence interval; BMI, body mass index; R^2, percentage of total variance explained in the model. Numbers needed for regression equation: original study: 1 = remission cohort, 2 = RAPIT trial; sex: 0 = women, 1 = men; corticosteroid use: 0 = never, 1 = ever. §P<0.05; ‡P<0.01.

of BMD in the hip to other sites.[27] Furthermore, the low percentage of explained variance of the final regression models might have been caused by the selection of patients with low to moderate disease activity.

Some previous reports did find an association between corticosteroid use and low BMD,[16 28] whereas others,[13 29] including our main analyses, did not. There are several explanations for the lack of a significant association between corticosteroid use and low hip or spine BMD in the main multivariate analyses in our study; firstly, the low number of corticosteroid users among the patients and secondly, the relatively imprecise data collected on corticosteroid use (never, previous, or current use). Both explanations yield a lack of power to discriminate an existing negative association (table 3) between corticosteroid use and BMD. The subgroup analysis of patients with radiological joint damage was an attempt to increase the discriminatory power, and showed a significant negative association between previous corticosteroid use and low BMD at the lumbar spine, thus apparently confirming these explanations.

RF status, disease duration, and HAQ score, variables related to BMD in other studies,[2 8 13] did not independently predict low BMD in the present study. An explanation for the divergent findings may be the incorporation of the (effects of) RF status, disease duration, and HAQ score on the Larsen score, a variable not investigated in the aforementioned studies.

The association between joint damage and low BMD found in (corticosteroid naive) patients with RA suggests that some of the pathophysiological processes involved in generalised osteoporosis appear to be common to those for local bone loss consisting of juxta-articular osteoporosis and bone erosions of individual joints. If cytokines, for instance tumour necrosis factor α (TNFα), are involved in the development of generalised osteoporosis, treatment with anti-TNFα should not only reduce disease activity and joint damage in RA but also prevent or slow down the development of generalised bone loss.

All eligible patients attending the outpatient clinic were consecutively enrolled in the respective original studies. Due to the inclusion and exclusion criteria applied, the two patient samples might not be representative of the respective clinic populations. Notwithstanding the limitations regarding representation, the large sample studied, which contains premenopausal women, postmenopausal women, and men, with heterogeneous disease duration and joint damage, yields interesting results.

In summary, the consistent findings of a relationship between high cumulative disease activity and low BMD suggest an association between the severity of RA and the risk of generalised bone loss.

ACKNOWLEDGEMENTS

We would like to thank all patients and professionals who participated in the study, particularly B Oud, I Henkes, I Perquin, A Jansen, M Gulijk, and M Fluit for assessing the patients participating in the RAPIT trial.

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