Bone Mineral Density in Men with Rheumatoid Arthritis Is Associated with Erosive Disease and Sulfasalazine Treatment But Not with Sex Hormones

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ABSTRACT. ***Objective.*** To quantify bone mineral density (BMD) in men with rheumatoid arthritis (RA) and to evaluate the influence of various disease-specific and non-disease-specific variables on bone mass.
Methods. Dual energy x-ray absorptiometry was performed in 104 male patients with RA and BMD was measured in lumbar spine, femoral neck, trochanter, and Ward's triangle. Inflammatory activity, measured as Disease Activity Score including 28 joints (DAS28), degree of functional impairment measured with the Health Assessment Questionnaire, and sex hormones (bioavailable testosterone, DHEAS, estradiol, and estrone) were estimated. Presence of erosions, rheumatoid factor, and current treatment as well as body mass index and smoking habits were recorded. Correlations were performed with nonparametric tests and multiple regression analyses.
Results. BMD was reduced in both spine and hip compared to an age matched reference population. Erosive disease was the variable with the strongest correlation with BMD. Treatment with sulfasalazine correlated positively with BMD at 3 of the 5 measured bone sites. However, in multivariate analysis significance was sustained only in the trochanter region. There were no correlations between the degree of inflammation, levels of sex hormones, treatment with corticosteroids, or smoking and BMD at any site measured.
Conclusion. A large proportion of the men with RA had reduced bone mass. Sex hormone levels and treatment with corticosteroid did not influence BMD, nor did current degree of disease activity. Erosive disease was closely correlated with low BMD, whereas sulfasalazine was associated with high BMD at least in the trochanter region. (J Rheumatol 2002;29:2299–305)

Key Indexing Terms:
RHEUMATOID ARTHRITIS MEN BONE MINERAL DENSITY
TESTOSTERONE ESTRADIOL SULFASALAZINE

Rheumatoid arthritis (RA) is a disease that has been shown to affect bone metabolism. The first obvious sign of bone loss is periarticular osteoporosis evident by radiograph some months after onset of disease. Since the advent of bone densitometry measurement we have learned that bone loss in RA is indeed general and occurs in both the appendicular and the axial skeleton[1-3].

Studies of bone mineral density (BMD) in RA have focused on women in whom osteoporosis is an important health problem. This has been attributed to disease duration and to physical inactivity as well as to high inflammatory activity, as the proinflammatory cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor-α affect bone remodeling[4-9]. Further, treatment with corticosteroids has been shown to have a negative effect on bone tissue[10-14], although this effect can more or less be counteracted by the beneficial effect of corticosteroids on inflammation[15].

The skeletal situation in men with RA is considerably less studied. The few studies focused on men show low BMD at different sites in those with established disease, predominately in those treated with corticosteroids[16-19]. However, the extent and distribution of bone loss are controversial and are not apparent in all age groups[19]. In contrast to the studies of women with RA, disease activity has not been shown to be associated with reduced bone mass in men[19], whereas salivary testosterone is reported to correlate with BMD[17].

Testosterone has anabolic properties and thus affects muscle and bone cells. As men with RA have low concentrations of bioavailable testosterone[20-22], hypogonadism might contribute to low BMD in men with RA. However, other sex hormones such as estradiol and estrone are also of importance for bone turnover in men[23], although the effect of these hormones on BMD has not been studied in men with RA.

We investigated a predominantly Swedish male population with RA to determine the extent of bone loss and to analyze which factors had the largest influence on BMD.

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We correlated current degree of inflammation, degree of physical impairment, duration of disease, and treatment with corticosteroid and disease modifying antirheumatic drugs (DMARD) with BMD. We also analyzed if sex hormones or factors not related to the disease such as body mass index (BMI) and smoking had any influence on BMD.

MATERIALS AND METHODS

One hundred four male patients diagnosed with RA according to the American College of Rheumatology criteria[24] were consecutively enrolled into the study. The patients attended the rheumatology clinic at Huddinge University Hospital and the local ethical committee approved the study protocol. Patients' characteristics are depicted in Table 1. Eighty-one patients were treated with DMARD, namely methotrexate (MTX) (n = 33), sulfasalazine (n = 26), injectable gold (n = 19), cyclosporin A (n = 9), chloroquine (n = 4), auranofin (n = 4), penicillamine (n = 2), or podophyllin (n = 2). Eighteen patients were treated with 2 DMARD and in 23 patients treatment with DMARD was not yet initiated, as they were included into the study at disease onset. Thirty-seven patients received corticosteroids.

Disease activity measures. The Disease Activity Score (DAS) composite index was used to assess disease activity and was calculated for 28 joints (DAS28)[25]. This includes number of swollen joints, number of tender joints, the patient's global assessment of disease activity measured on a visual analog scale, range 0–100 mm, and the erythrocyte sedimentation rate (ESR), and creates a score ranging from 0 to 10.

The patients also completed the Swedish version of the Stanford Health Assessment Questionnaire (HAQ), a self-reporting instrument[26]. This disability index comprises 20 questions, divided into 8 subcategories, each consisting of 2 to 3 activities of daily life. The response to each question ranges from 0 (no difficulty) to 3 (unable to perform). The created score for the disability index ranges from 0 to 3, where a higher score indicates a higher degree of disability[27].

BMD measurements. BMD was measured by dual energy x-ray absorptiometry (DEXA) with a Lunar densitometer at the lumbar spine (L1 and L2–L4) with anterior-posterior view and at the left hip (femoral neck, greater trochanter, and Ward's triangle). BMD was expressed as the number of standard deviations (SD) from the mean of young healthy people, the T score, and as the number of SD from the mean of healthy age and sex matched people, the Z score. Values were obtained from Lunar's combined European/US reference population[28]. Osteoporosis was defined as a T score > 2.5 SD below the mean value of young adults according to the World Health Organization definition[29,30], and reduced bone mass as a Z score ≤ 1.0 SD below the mean value of the age matched reference population[31].

Table 1. Demographic and clinical data of 104 men with RA.

Variables	N	Percentage	Means, Median
Age, yrs, mean (SD)			57.5 (9.3)
20–49	21		
50–59	33		
60–69	50		
BMI, mean (SD)			25.1 (3.4)
Current smokers		39	
Disease duration, yrs, median (range)			4 (0–43)
Current treatment with corticosteroid		36	
Current treatment with NSAID		79	
Current treatment with DMARD		78	
Positive RF		79	
Erosive disease		68	
DAS28, mean (SD)			4.5 (1.5)
HAQ, mean (SD)			0.9 (0.6)

Hip measurements were not performed in 6 patients because of bilateral hip prosthesis. Spine measurements were performed for all patients except 2.

Radiological examinations. Radiological examinations were performed on the hands, wrists, and feet according to the clinical routine of the department. For 3 patients examinations were available for only the hand and wrist. The investigations were done in the preceding year before inclusion in the study. Patients whose radiographs showed at least one erosion were considered erosive, but not patients with only periarticular osteoporosis.

Biochemical analysis. Blood was sampled in the morning between 8:00 and 10:00 AM for measurement of serum concentrations of total testosterone, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), estradiol 17ß, and estrone, as well as albumin and ESR.

Testosterone and SHBG analyses have been described in detail[22]. Briefly, serum concentrations of testosterone were determined by radioimmunoassay and SHBG by time resolved fluorescence assay (TRFIA). Non-SHBG bound testosterone (NST; the sum of free + albumin bound T) was used as an index of biologically active testosterone, as proposed by Pardridge[32].

DHEAS in serum was analyzed only in patients not undergoing corticosteroid treatment. Serum concentrations of DHEAS were determined by competitive chemiluminescence immunoassay using a commercial kit (Immulite® DHEA-SO4; Diagnostic Products Corp., Los Angeles, CA, USA). Serum concentrations of estradiol 17ß were determined by radioimmunoassay using a commercial kit (ESTR-US-CT; CIS Bio International, Gif-sur-Yvette, France) and serum concentrations of estrone were determined after extraction with diethyl ether using an in-house radioimmunoassay with minor modifications.

Statistical analysis. Analysis was performed using Statistica for Windows (version 4.2). Spearman rank order correlations were used for continuous data. For comparisons between groups, Student's t test was used for normally distributed data and Mann Whitney U test for data not normally distributed. In multiple regression analysis normal distribution was obtained with transformation of the independent variable by logarithm when appropriate. When current DMARD treatment was a dependent variable in regression analysis, all patients were included in the analysis and coded to presence or absence of a specific DMARD. We did not introduce more than one DMARD as dependent variable in the analysis. The maximum number of dependent variables in the different regression models tested was 4. The best models, i.e., with the highest R value, are presented here, but we found no independently significant variables in weaker models.

RESULTS

The men with RA we studied were heterogeneous for age and disease duration. They exhibited varying inflammatory activity, with a mean DAS28 value of 4.5 (range 1.0–8.3). The degree of functional impairment by HAQ ranged from 0 to 2.25 (mean 0.9). For detailed demographic and clinical data see Table 1.

The patients had small but significant reductions in their BMD compared with an age and sex matched reference population (Z score). The mean BMD was lowered 6% ($p < 0.01$) in femur neck and trochanter, 7% ($p < 0.01$) in the region of Ward's triangle, 3% ($p < 0.05$) in L2–L4, and 6% ($p < 0.01$) in L1. The reductions were recorded in all age groups at all sites except for the oldest at trochanter and L2–L4 (Table 2). Reductions of BMD did not differ statistically between the age groups; the correlation coefficient for age and Z scores is shown in Table 4. The bone loss in L1 was higher compared with L2–L4 for all age groups ($p < 0.001$).

Table 2. BMD in percentage of expected values, mean (95% confidence interval), in all patients and in different age groups compared with the matched reference population. Mean (median) disease durations were 4.4 (3) years in age group 20–49, 7.5 (5) years in age group 50–59, 8.5 (4) years in age group 60–69.

Age groups, yrs	Femur neck	Trochanter	Ward	L2–L4	L1
All patients	93.8 (90.8–96.7)	93.7 (91.0–96.5)	92.9 (89.3–96.4)	96.6 (93.6–99.5)	93.7 (91.0–96.5)
20–49	91.9 (87.8–96.0)	88.4 (81.4–95.3)	90.8 (84.1–97.5)	93.9 (88.5–99.3)	92.3 (86.7–97.8)
50–59	93.5 (89.9–97.2)	93.0 (88.4–97.5)	91.3 (85.0–97.6)	95.3 (91.4–99.2)	92.8 (88.7–96.9)
60–69	93.7 (90.0–97.5)	96.1 (91.5–100.7)	93.8 (88.0–99.5)	98.0 (92.7–103.4)	94.5 (89.8–99.2)

Table 3. Frequency of reduced bone mass and of osteoporosis at any measured site in all patients and in different age groups as well as at specified locations.

Age Groups, yrs	Reduced Bone Mass, % (n)	Osteoporosis, % (n)
Any site		
All patients	63 (66/104)	34 (35/104)
20–49	57 (12/21)	29 (6/21)
50–59	73 (24/33)	24 (8/33)
60–69	62 (31/50)	42 (21/50)
Femur neck	28	13
Trochanter	34	11
Ward	30	24
L2-L4	39	10
L1	42	12

A substantial proportion of the patients had reduced bone mass defined as Z score ≤ 1 SD and osteoporosis defined as a BMD < 2.5 SD (compared with young adults, T score). These reductions were observed in all age groups and at all measured sites (Table 3).

Correlations of BMD (Z score) with disease dependent and disease independent variables are shown in Table 4. The best regression model, with BMD in trochanter as the dependent variable, explained 29% of the variance and included presence of erosions, treatment with sulfasalazine, HAQ, and BMI. Duration of disease lost its significance in all models when presence of erosions was considered. Thus, with the exception of BMI, disease dependent variables that reflect structural damage seemed to be important for bone tissue whereas inflammatory activity, measured as DAS28, blood levels of bioavailable testosterone, estradiol and estrone, and smoking habits were insignificant.

Erosive disease was thus strongly negatively correlated with BMD at all sites except femur neck (Table 4). Excluding patients with disease duration less than one year did not attenuate the correlation between BMD and erosive disease. Eleven patients had a nonerosive disease despite disease duration of more than one year. These patients had normal BMD: femur neck 96.5%, trochanter 104.5%, Ward 103.5%, L2–L4 102%, and L1 102% of the reference population.

Corticosteroid treated patients had lower BMD than the control population at all sites measured, but these differences were small and not statistically significant (Table 4). The only site with a clinically relevant larger loss of bone

Table 4. Correlation coefficients (R) for age matched BMD at different sites and clinical and laboratory variables.

	Femoral Neck	Trochanter	Ward	L2–L4	L1
Age	–0.03	0.04	–0.01	–0.03	–0.07
Duration of disease	–0.14	–0.25, p < 0.05	–0.22, p < 0.05	–0.18	–0.25, p < 0.05
Presence of erosions	NS (p = 0.07)	p < 0.001 [–]	p < 0.01 [–]	p < 0.05 [–]	p < 0.01 [–]
RF	NS	NS	NS	NS	NS
DAS28	–0.08	–0.12	–0.06	–0.02	+0.04
HAQ	–0.12	–0.23, p < 0.05	–0.13	–0.09	–0.05
Treatment with SSZ	NS (p = 0.08)	p < 0.001 [+]	p < 0.05 [+]	NS	p < 0.05 [+]
Treatment with MTX	NS	p < 0.01 [–]	NS	NS	NS (p = 0.07)
Treatment with glucocorticoids	NS	NS	NS	NS	NS
DHEAS	0.00	–0.05	+0.03	–0.02	–0.08
Bioavailable testosterone	+0.03	–0.02	+0.03	–0.05	–0.12
Estradiol	+0.05	–0.01	+0.15	+0.08	0.00
Estrone	+0.07	0.00	+0.15	+0.03	+0.05
Smoking, pack-yrs	+0.02	–0.09	+0.02	–0.04	0.00
BMI	+0.04	+0.32, p < 0.01	+0.09	+0.18	+0.23, p < 0.05

Statistical analyses were performed with Spearman rank order correlations for continuous data and Mann-Whitney U test for categorical data. The table shows the R coefficient for continuous data. The p values are shown if the correlations were statistically significant. Trend values are indicated in brackets. NS: not statistically significant. Signs within brackets [+] and [–] denote positive and negative correlations, respectively. SSZ: sulfasalazine, MTX: methotrexate.

mass was in the trochanter, where the corticosteroid treated group had a mean 90.9% of predicted BMD versus mean 95.1% in the nontreated group ($p = 0.17$). However, the corticosteroid group had more erosive disease ($p < 0.001$) and longer disease duration ($p < 0.05$) and in a regression analysis with these variables, corticosteroid lacked influence on bone density.

The effect on BMD of 4 DMARD was analyzed for each drug, namely MTX, sulfasalazine, cyclosporin A, and injectable gold, against the total patient population. The other DMARD were not used in a sufficient number of patients to make statistical analysis meaningful. We found no effect of cyclosporin A or injectable gold on bone tissue. MTX was associated with low BMD in trochanter in univariate analysis, but the correlation was not significant in a regression model including BMI and presence of erosions. Sulfasalazine was correlated with higher BMD in trochanter, Ward, and L1. The correlation in trochanter was highly significant in different regression models, but the correlations in Ward and L1 lost their significance in multiple regression analysis. Sulfasalazine treated patients thus had 8–10% higher BMD in trochanter than patients not treated with sulfasalazine. The best regression models (i.e., the models with the highest R^2 value) for sulfasalazine and MTX are shown in Table 5. For both drugs the best model was obtained with BMI, HAQ, and presence of erosions.

Serum levels of NST, DHEAS, estradiol 17ß, and estrone were analyzed and correlated with BMD. The correlation coefficients were very close to zero (Table 4). As NST and DHEAS decline by age, we also performed correlation analyses between Z score and NST and DHEAS in each age group separately. This did not change the results — there was no correlation at any site measured. There was no correlation between bioavailable testosterone and corticosteroid treatment, as we have described[22].

Eighty percent of patients were current or previous smokers; data were lacking for 4 patients. We found no correlation with BMD and smoking, for either current smoking or cumulative smoking calculated as pack-years (see correlation coefficients, Table 4).

Table 5. Regression analyses with the best R value for age and sex matched BMD, percentage of expected value, in trochanter versus treatment with sulfasalazine (A) and methotrexate (B).

A	B	Standard Error of B	p
Sulfasalazine	8.8	3.1	< 0.01
BMI	1.0	0.4	< 0.05
Erosive disease	–8.1	2.8	< 0.01
HAQ	–3.6	2.1	NS (0.09)
$R = 0.54$, $R^2 = 0.29$			
B	B	Standard Error of B	p
MTX	–4.9	2.9	NS (0.10)
BMI	1.1	0.4	p< 0.01
Erosive disease	–8.2	2.9	p < 0.01
HAQ	–4.9	2.1	p < 0.05
$R = 0.52$, $R^2 = 0.26$.			

DISCUSSION

This study reports that men with RA had lower BMD in spine and hip than a healthy age matched reference population. BMD was significantly negatively associated with erosive disease and positively correlated with sulfasalazine treatment, whereas no correlation was determined with current degree of inflammation or sex hormones.

Our data confirms previous findings of bone loss in both spine and hip in men with established RA disease from clinical cohorts[17,18]. However, in a Norwegian study of 94 male patients with RA recruited from a community based register no bone loss in L2–L4 was found and the mean reduction in hip reached statistical significance only in the 60–70 age group[19]. However, the largest mean reductions of BMD in femoral neck and total hip were recorded in the youngest age group (30–39 yrs), 8.5% and 7.1%, respectively, but the lack of significance in this age group was probably due to the small number of observations (11 patients).

The proportion of patients with reduced bone mass in the Norwegian study[19] was similar to our data, with about 30% of the patients having a Z score < 1. This proportion with reduced bone mass was also found in the spine, while mean BMD in spine did not differ from the reference population. The reductions in mean BMD in our population (Table 2) correspond to roughly 0.5 SD, which will result in about 30% below –1 SD if the values are normally distributed. A rather large proportion with reduced bone mass is thus to be expected with a modest mean reduction in BMD. Our data in hip were normally distributed with least skewness in trochanter (skewness 0.14).

BMD measures in L2–L4 and L1 in our population were not normally distributed, indicating that additional factors influence BMD in the spine. A skew distribution may be one explanation of the findings in the Norwegian study[19] of a large proportion with reduced BMD in spine in spite of the same mean BMD as the reference population. Our study and the 2 clinical cohorts[17,18] also showed reduced low bone mass in spine, but we assume this reflects a population with more advanced disease. A great variation of disease severity is expected in the Norwegian patients, as for example only 53% in that population were RF positive versus 79% in our population.

The WHO proposals for diagnostic categories in osteoporosis are based on the relation between BMD and the prospectively evaluated fracture risk and apply only for postmenopausal women[29]. As the fracture risk seems to be

similar in both sexes for the same absolute area BMD level, the WHO definition for osteoporosis has also been considered appropriate for men[33-36]. Looker, *et al* calculated the prevalence of osteoporosis in American men using a male reference population and T score < –2.5 SD as the cutoff level. Non-Hispanic white men older than 50 years had a prevalence of osteoporosis of 6% in femur neck and 3% in trochanter[33]. The corresponding figures in our study for men above 50 years of age were 14% and 9%, respectively, and are thus higher than in healthy Americans.

Male osteoporosis has often been considered a disease of the elderly, but it was also present in 29% of the youngest age group of men with RA. This highlights the necessity for increased knowledge of the bone mineral situation in men with a disease associated with an increased risk of affecting bone metabolism.

In the spine only L2–L4 is validated as a risk factor for vertebral fractures, and studies of BMD in spine are therefore generally confined to L2–L4. However, these vertebrae are often affected by spondylosis, which elevates BMD, and a diagnosis of osteoporosis may be overlooked[37]. Spondylosis is less common in the first lumbar vertebra. Our findings of larger reductions in BMD in L1 compared with L2–L4 suggest that BMD measurements of spine in patients with RA should include L1. As shown here, the disease seems to influence BMD in L1 and trochanter more than other sites.

The clinical variable that had the largest influence on BMD was erosive disease. This variable was, for obvious reasons, closely associated with disease duration, but in multiple regression analysis erosions correlated independently with BMD in trochanter and in Ward. The effect of erosive disease on BMD in men with RA has not been described previously, but deformed joint count, which might indicate joint destruction, was the only clinical disease measure that was independently associated with reduced bone mass in the study by Haugeberg, *et al*[19]. Additionally, the presence of erosions in women with RA has been associated with high prevalence of osteoporosis[38]. This association has raised the hypothesis that there may be common mechanisms for bone erosions and osteoporosis[39]. Such an association may also explain why the patients with nonerosive disease had normal BMD in our study. The fact that disease activity did not affect BMD can probably be explained by rapid variations of inflammation from time to time, whereas low bone mass and erosive disease are variables that reflect structural damage. We had no data on the degree of inflammation over time in this cross sectional study.

The lack of any correlation between current treatment with corticosteroids and BMD is in contrast with other investigations of men with RA[16-18]. Two studies[16,18] found a significant negative effect on L2–L4, while Mateo, *et al*[17] also found the same in femur neck. It is difficult to draw any conclusions of differences in BMD between corticosteroid treated versus nonsteroid treated patients with RA, however, because steroid treated patients often have worse disease, and thus several other factors besides steroid treatment might affect BMD. For example, in the studies of Garton, *et al*[16] (current treatment) and Stafford, *et al*[18] (ever treated) the steroid treated groups had more active or severe disease than the nontreated groups. In the study of Mateo, *et al*[17], the mean age in the steroid treated patients was 7 years higher, which probably influenced the BMD, as they used absolute values (g/cm^2) and not age matched values for comparisons. Further, the steroid treated group was more functionally incapacitated[17]. To evaluate the importance of corticosteroid on BMD several factors must be considered, and when this was done in a regression model, steroid treatment was found not to have an independent association with BMD in men with RA[19]. In the present study the lack of data on previous corticosteroid treatment and cumulative doses of corticosteroid makes it impossible to draw any conclusions about the effect of corticosteroid over time.

MTX is known to cause severe osteopenia and fractures when used in high doses in cancer therapy[40,41]. It has been debated if the drug also contributes to osteoporosis in patients with RA when used in low doses. This could not be confirmed in our study, where MTX certainly was associated with low BMD in trochanter but was not an independent factor when tested in a regression model. MTX treatment has not been found to affect BMD in women with RA[42,43].

Patients treated with sulfasalazine had higher BMD, at least in trochanter. The difference was of large statistical significance. We have searched throughout our data without finding any confounding variables. This finding warrants further investigation, as it has not been reported before.

The lack of correlation between levels of bioavailable testosterone and BMD confirms results of a study in which the correlations were made for total testosterone in 50 men with RA[18]. Free testosterone also has not been correlated with BMD and vertebral fractures in men with ankylosing spondylitis[44]. This is in contrast to the correlation between salivary testosterone as a measure of free testosterone and femur BMD in men with RA[17]. However, absolute values of BMD (g/cm^2) were used in that study and not age matched values. As both BMD and bioavailable testosterone decline with age, a comparison of BMD and bioavailable testosterone will be positively correlated if age is not considered. When age was taken into consideration in a study of elderly men, no association was determined between free testosterone and BMD[45].

We also found no correlation between levels of DHEAS, estradiol, or estrone and BMD. This has not been studied previously in men with RA. Estradiol but not DHEAS has been reported to correlate to BMD in women[46].

Levels of free testosterone and estradiol, considered to be

important anabolic hormones for bone tissue in elderly men[47-49], were thus insignificant for BMD in the present study. Results of cross sectional studies of the role of testosterone as an independent factor in BMD in healthy men have been ambiguous[50].

Thus we have confirmed that men with RA have low BMD. The BMD showed a strong negative correlation with erosive disease, indicating that the pathogenesis of erosions and osteoporosis may be similar. Conversely, sulfasalazine had a positive correlation with BMD. This was an unexpected finding, and further studies are needed to evaluate the mechanism of this association.

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