EXTENDED REPORT

Bone mineral density in patients with recently diagnosed, active rheumatoid arthritis

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Objectives: Osteoporosis is a well-known extra-articular phenomenon in patients with uncontrolled, long-standing rheumatoid arthritis (RA). In the present study, the extent of osteoporosis and reduced bone mineral density (BMD) and the disease-related and demographic factors that are associated with osteoporosis and reduced BMD were examined in patients with recently diagnosed, active RA.

Methods: BMD of the total hip and the lumbar spine was measured using dual-energy x ray absorptiometry in 381 patients with recently diagnosed active RA, who had never been treated with DMARDs or corticosteroids. Osteoporosis was defined as a T score ≤ -2.5 SD and reduced BMD as Z score ≤ -1 SD. Multivariate logistic regression analyses were performed to detect associations of osteoporosis and reduced BMD with disease activity, functional disability, joint damage (Sharp-van der Heijde score) and demographic factors.

Results: Osteoporosis and reduced BMD were found in the spine and/or the hip in 11% and 25%, respectively, of the patients. Longer symptom duration and presence of rheumatoid factor (RF) were the only RA-specific markers for osteoporosis and reduced BMD. Further, postmenopausal status in women, a low body mass index, familial osteoporosis, and, remarkably, male gender, were independently associated with osteoporosis and reduced BMD.

Conclusion: In patients with recently diagnosed active RA who had never been treated with DMARDs or corticosteroids, BMD seems to be well-preserved and predominantly related to demographic factors. Longer symptom duration and a positive RF, but not higher disease activity or more joint damage, were related to osteoporosis and reduced BMD.

Generalised osteoporosis is a well-known extra-articular complication in uncontrolled, long-standing rheumatoid arthritis (RA).^{1–3} Underlining the clinical significance of low bone mineral density (BMD) in RA, the risk of hip^{4–6} and vertebral fractures^{6–8} and the associated morbidity, mortality and healthcare costs are increased in patients with RA.

It is thought that the pathogenesis of both periarticular and generalised osteoporosis and local bone erosions share common pathways.⁹ This hypothesis has been strengthened by the discovery that osteoclasts, stimulated mostly by the receptor activator of nuclear factor kappa B ligand (RANKL) pathway, play a central role in all of these processes.^{10–12} A clinical study on patients with early, untreated RA showed that the baseline ratio of RANKL to osteoprotegerin (its natural decoy receptor) is independently predictive for joint damage progression after 5 years of follow-up.¹³

Over the past few years, the extent of osteoporosis in patients with established RA has been clarified. The overall occurrence of generalised osteoporosis in patients with long-standing RA ranges from 7% to 26% in the hip and 19% to 32% in the spine.^{14–19} In a population-based study of patients with established RA, a twofold increase in osteoporosis was seen in 394 women¹⁹ and a twofold increase of reduced BMD in men,²⁰ compared with control groups. Previous studies, performed with patients with established RA, reported disease-related factors, such as long disease duration, high disease activity, joint damage, functional disability and corticosteroid use, as determinants of osteoporosis or reduced BMD.^{14–22} Hence, patients with long-standing RA with destructive disease, functional disability or immobilisation, or who are on long-term corticosteroid treatment are at high risk for osteoporosis.²³

Only a few studies focusing on BMD in patients with early RA have been performed; however the disease duration in some

was up to 5 years.^{24–26} Very little is known about the extent of osteoporosis and the influence of disease-associated factors on BMD in patients with recently diagnosed RA.^{27–28} These data are required in order to unravel the common mechanisms between generalised osteoporosis and RA.

In this paper we present data from the Behandel Strategieën (BeSt) study, a multicentre, randomised clinical trial with a large cohort of patients with recently diagnosed, active, RA, who had never been treated with DMARDs or corticosteroids.²⁹ We evaluated the frequency of osteoporosis in the lumbar spine and total hip and studied the influence of disease and demographic factors on osteoporosis and reduced BMD in recent onset RA that might indicate a common pathway between rheumatoid inflammation and generalised osteoporosis.

PATIENTS AND METHODS

Study design

All measurements were performed in the setting of the BeSt study.²⁹ This was a multicentre, randomised clinical trial designed to compare the effectiveness of four different treatment strategies in patients with recently diagnosed, active RA. The BeSt study was conducted by rheumatologists participating in the Foundation for Applied Rheumatology Research in 18 peripheral and 2 university hospitals in the western part of the Netherlands. The medical ethics committee at each participating centre approved the study protocol and all

Abbreviations: BeSt, Behandel Strategieën; BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; HRT, hormone replacement therapy; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor kappa B ligand; RF, rheumatoid factor

patients gave written informed consent prior to participation in the study.

In total, 508 patients who met the definition of RA as defined by the American College of Rheumatology 1987 revised criteria, were included in the trial. Other inclusion criteria were age at least 18 years, symptom duration <2 years, and active disease with ≥ 6 swollen joints out of 66 possible and ≥ 6 tender joints out of 68 possible, and either an erythrocyte sedimentation rate ≥ 28 mm/hour or a score on the Visual Analogue Scale for Global Health, reported by the patient, of ≥ 20 mm on a scale of 0–100 mm (0, best; 100, worst). Exclusion criteria were previous treatment with DMARDs other than antimalarials, concomitant treatment with an experimental drug, malignancy within the previous 5–6 years, bone marrow hypoplasia, levels of serum liver enzymes (aspartate/alanine aminotransferases) >3 times the upper limit of normal, serum creatinine >150 mmol/l or estimated creatinine clearance <75%, diabetes mellitus, alcohol and/or drug misuse, pregnancy, planning conception during the study period or inadequate contraception.

BMD measurements

In 381 patients, BMD of the lumbar spine (L2–L4 anteroposterior view) and total hip was measured at baseline in 14 of 20 centres participating in the BeSt trial, in which dual energy x ray absorptiometry was available. The BMD measurements were carried out using a densitometer (Hologic 4500 QDR (Hologic, Waltham, Massachusetts, USA) in eight centres and a Lunar DPX-L (Lunar, Madison, Wisconsin, USA) in six centres). Osteoporosis, defined as T score (number of SD from the mean of young, healthy people) ≤ -2.5 SD and reduced BMD, defined as Z score (number of SD from the mean of healthy age-matched and gender-matched people) ≤ -1 SD were determined according to locally used reference populations provided by the manufacturers. In the centres with Lunar equipment, the UK or US spine and hip references were used, and in centres with Hologic equipment, the Hologic spine reference group and the National Health and Examination Survey femur reference population were used. Absolute values of BMD, measured with the two densitometers, are not comparable because of calibration differences.³⁰ However, if there are no differences in the mean T and Z scores between the different equipments and reference populations, the two measurement methods are probably reliable and interchangeable.³¹

Demographic and clinical variables

Sociodemographic and clinical data were obtained partly by self-report questionnaires and partly by interview and clinical examinations that were performed by specially trained research nurses. The following variables were collected: age, gender, race, height, weight, symptom duration, body mass index (BMI), menopausal status, age at menopause and premature menopause (<40 years), current smoking and alcohol status, previous clinical fractures, osteoporosis in first-degree relatives, estimated daily calcium intake and use of calcium and vitamin D supplements, hormone replacement therapy (HRT) and bisphosphonates. Disease assessment was made using the Disease Activity Score (DAS), based on the number of swollen joints and the Ritchie Articular Index for pain in tender joints, the visual analogue scale for patient global assessment of disease activity (0–100 mm) and the erythrocyte sedimentation rate. Functional ability as measured by the Dutch validated Health Assessment Questionnaire (HAQ) and laboratory tests (C-reactive protein (CRP), 25-OH vitamin D level and serum IgM rheumatoid factor (RF), defined as positive or negative according to locally applied assays and cut-off points) were obtained. Radiographic joint damage according to the Sharp–van der Heijde score was rated independently by two

physicians, who remained blinded to patient-specific data and treatment group, was assessed. The intraobserver coefficients were 0.93 and 0.94, and the interobserver coefficient was 0.93. For this study, the mean of the baseline scores of the two assessors was used for analysis. A patient was classified as having erosive disease if the mean erosion score was >0.5.

Statistical analysis

The demographic and disease-related variables in relation to the occurrence of osteoporosis and reduced BMD in the different measurement sites were analysed by regression analyses adjusted for possible confounders. Potential contribution of the variables, as independent risk factors of osteoporosis or reduced BMD, was evaluated by stepwise multivariate regression analyses, performed as forward (conditional) procedures. All results were adjusted for age, gender, race, menopausal status, current smoking and alcohol status, except adjustment for themselves. Additionally, symptom duration, joint damage, RF status, DAS and HAQ were adjusted for each other. The adjusted odds ratios (ORs) obtained by regression analyses were corrected into relative risks using the formula of Zhang *et al* to interpret the magnitude of the associations more appropriately.³² All tests were two-tailed and $p \leq 0.05$ was considered significant.

RESULTS

Patient characteristics

BMD measurements were available for 381 patients: lumbar spine for 378, left total hip for 329 and right total hip for 30 patients. For 22 patients, no total hip measurement was performed; two of these due to bilateral hip prosthesis and others due to logistic reasons. Three patients did not have spine measurements taken.

Table 1 shows the characteristics of the 381 patients with BMD measurements. There were no significant differences in the demographic and disease variables between the group of patients with BMD measurements and the group without BMD measurements ($n = 127$) (data not shown). There were no significant differences in the mean T and Z scores and in the frequencies of osteoporosis and reduced BMD as a result of measurements with different equipments and references (data not shown). The study population consisted mainly of postmenopausal women, aged 55 years, with recent onset RA and median symptom duration of 23 weeks. All patients had active disease with a mean (SD) DAS of 4.4 (0.9), and 72% of the patients had erosive disease. The mean calcium intake per day was 926 mg, and 7% and 2% of the patients received calcium and vitamin D supplements, respectively. Five patients (1%) used bisphosphonates and 21% of the women (had) used HRT. The mean T score was -0.4 SD and the mean Z score was 0.3 SD in both the hip and the spine.

Prevalence of osteoporosis/reduced BMD

The overall frequency of osteoporosis was 9% in the spine, 4% in the total hip and 11% in either the spine or the hip. The proportion of all patients having reduced BMD was 19% for the spine, 14% for the hip and 25% for either the spine or the hip (table 2). More men than women had reduced BMD and more postmenopausal than premenopausal women had osteoporosis in the measured sites. With increasing age, the frequency of osteoporosis and reduced BMD also increased, except for the highest age group.

Determinants of osteoporosis/reduced BMD

All variables listed in table 1 were entered into regression analyses and adjusted for possible confounders. Longer symptom duration before inclusion was associated with

Table 1 Demographic, laboratory and clinical characteristics of the 381 patients who received BMD measurement

Sociodemographic variables	
Mean (SD) age, years (n = 381)	55 (13)
Mean (SD) BMI, kg/m ² (n = 378)	26 (4)
Women, % (n = 381)	71
Postmenopausal, % (n = 269)	68
Mean (SD) age at menopause, years	47 (5)
Premature menopause, %	7
Surgical ovariectomy, %	33
Premature ovarian failure, %	67
Caucasian, % (n = 381)	93
Current smoker, % (n = 381)	36
Median (IQR) number of cigarettes/day	13 (18–20)
Current alcohol user, % (n = 381)	52
Median (IQR) number of glasses of alcohol/day	7 (3–14)
Previous clinical fractures >30 years, % (n = 381)	14
Postmenopausal fractures, % (n = 269)	4
Familial (first-degree relatives) osteoporosis, % (n = 379)	15
Disease-related variables	
Median (IQR) symptom duration, weeks (n = 381)	23 (13–53)
Positive IgM rheumatoid factor, % (n = 381)	64
Mean (SD) DAS ₄₄ (n = 381)	4.4 (0.9)
Mean (SD) HAQ score, 0–3 scale (n = 370)	1.4 (0.7)
Median (IQR) total SHS, 0–448 scale (n = 375)	4.0 (1.5–8.5)
Erosive disease, % (n = 375)	72
Mean (SD) CRP, mg/L (n = 352)	37 (42)
Mean (SD) calcium intake, mg/day (n = 378)	924 (356)
Calcium supplementation, % (n = 381)	2
Mean (SD) 25-OH vitamin D level, nmol/L (n = 323)	51 (30)
Vitamin D supplementation, % (n = 381)	1
HRT, % (n = 271)	21
Median (IQR) duration used, years	5 (2–14)
Bisphosphonates use, % (n = 381)	1
Spine L2–4 (n = 378)	
Mean (SD) T score SD	–0.44 (1.5)
Mean (SD) Z score	0.29 (1.5)
Total hip (n = 359)	
Mean (SD) T score	–0.43 (1.3)
Mean (SD) Z score	0.26 (1.2)

BMI, body mass index; CRP, C-reactive protein; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; HRT, hormone replacement therapy; SHS, Sharp–van der Heijde Score.

Table 2 Prevalence of osteoporosis and reduced BMD in the spine L2–4, total left hip or either

	Osteoporosis			Reduced BMD		
	Spine L2–4	Total hip	Either	Spine L2–4	Total hip	Either
All (n = 381)	9.0	4.0	11.3	19.1	14.2	24.7
Men (n = 109)	9.3	3.3	11.0	31.0	19.0	32.1
Women						
All women (n = 272)	8.9	4.3	11.5	14.2	12.3	21.8
Premenopausal (n = 83)	2.3	0	1.3	9.9	2.5	6.7
Postmenopausal (n = 187)	12.0	6.3	16.5	16.4	12.1	24.5
Age, years						
20–49 (n = 126)	2.4	0	2.4	16.4	15.5	21.6
50–59 (n = 118)	11.0	4.8	15.2	24.0	15.8	29.5
60–69 (n = 80)	13.8	9.0	17.9	23.0	15.9	30.6
70–89 (n = 54)	13.0	4.1	14.3	8.7	4.9	12.2

BMD (bone mineral density).

osteoporosis and reduced BMD in the hip and the presence of RF was associated with reduced BMD in the spine. DAS, HAQ and SHS were not related to osteoporosis or reduced BMD in the spine or the hip (table 3). Postmenopausal status, a low BMI and current smoking were associated with osteoporosis, and male gender, a low BMI, familial (first-degree relative) osteoporosis and current smoking were associated with reduced BMD in the measured sites (data not shown). Variables that showed significant associations in the regression analyses, adjusted for possible confounders, were entered into a multiple regression analyses. Longer symptom duration and positive RF were independently associated with osteoporosis and reduced BMD in the hip and with reduced BMD in the spine, respectively. Postmenopausal status and low BMI remained related with osteoporosis in the spine or the hip. Male gender, low BMI and familial osteoporosis were independently associated with reduced BMD in the spine or the hip (table 4).

DISCUSSION

In this large cross-sectional study, we examined BMD in a large group of patients with recent onset, active RA, who had never been treated with DMARDs or corticosteroids. We found that approximately 11% of both men and women with RA had an osteoporosis (T score ≤ -2.5 SD) and 32% of the men with RA and 22% of the women with RA had reduced BMD (Z score ≤ -1 SD). The independent disease-related determinants of

osteoporosis and reduced BMD in these patients were longer symptom duration and the presence of RF.

Because the prevalence of osteoporosis is dependent on many population-specific factors, such as genetics, race, age and gender, it is important to compare our data on the prevalence of osteoporosis with data in the general Dutch population. Versluis *et al* showed in a cohort of 449 Dutch postmenopausal women, with a mean age of 67 years, that osteoporosis was present in the femoral neck in 7%, which is in accordance with our results (osteoporosis in the hip in 6% of postmenopausal women, mean age 61 years).³³ In addition, Smeets-Goovaers showed the presence of osteoporosis in the lumbar spine in 13% of 1079 Dutch postmenopausal women with a mean age of 51 years, which matches the prevalence of osteoporosis in the spine in our postmenopausal women (12%).³⁴ These agreements might suggest that the prevalence of osteoporosis in our patients with recently diagnosed, untreated RA is not increased compared with the general Dutch population; however, comparison of these populations should be treated with caution, owing to differences in demographic characteristics, especially in age. In accordance with our results, Keller *et al* showed in 227 patients with RA with a mean disease duration of 6 months, who had never been treated with DMARDs, that BMD values did not differ significantly between patients with RA and controls.²⁷ However, the proportion of patients with reduced BMD (Z score ≤ -1 SD; 45% of women and 51% of men) was higher than in the reference population (16%), even in this early stage of the disease. Unfortunately, no data exist on the prevalence of reduced BMD in the general Dutch population; however, compared with the population of Keller *et al*, reduced BMD in our population seems to be less frequent (32% of men and 22% of women). In addition, Forslind *et al* showed in 134 women with RA with mean disease duration of 6 months, who had never been treated with DMARDs, that BMD was similar to that of age-matched controls, whereas the BMD in the 70 men with RA was lower than the controls.²⁸ Hence, despite the poor prognostic markers in our study, with RF present in 64% and erosions in 72% of the patients after a median symptom duration of 23 weeks, BMD is fairly well preserved in the very early stages of the disease. This could be explained by the fact that generalised osteoporosis is more associated with long-standing, destructive and disabling RA,³⁵ whereas early RA is associated with periarticular osteoporosis.³ This is further supported by the fact that longer symptom duration is independently associated with more generalised osteoporosis in studies, including the present one.¹⁴ In contrast, other studies have found lower BMD in patients with early RA

Table 3 Regression analysis of osteoporosis and reduced BMD in the spine and the hip (dependent variables) and disease variables (independent variables)

RR (95% CI)	Osteoporosis		Reduced BMD	
	Spine L2–4	Total hip	Spine L2–4	Total hip
Symptom duration, weeks	1.001 (0.99 to 1.00)	1.004 (1.00 to 1.01)	1.001 (0.99 to 1.00)	1.002 (1.00 to 1.00)
Positive RF	1.17 (0.87 to 1.38)	1.24 (0.64 to 1.48)	1.31 (1.09 to 1.45)	1.07 (0.83 to 1.43)
DAS	0.89 (0.64 to 1.15)	0.89 (0.48 to 1.36)	0.89 (0.70 to 1.08)	1.10 (0.85 to 1.34)
HAQ	1.02 (0.70 to 1.36)	0.94 (0.43 to 1.54)	1.12 (0.85 to 1.39)	0.93 (0.63 to 1.27)
Total SHS	1.00 (0.98 to 1.02)	0.96 (0.91 to 1.02)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.03)

BMD, bone mineral density; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; RR, relative risk; SHS, Sharp–van der Heijde Score.

All variables were adjusted for age, gender, menopausal status, race, smoking and alcohol status, except for themselves. Symptom duration, RF status, DAS, HAQ and total SHS were additionally adjusted for each other.

than in the reference population.^{24–26} However, in these studies, methodological aspects varied, such as the sample size, the selection of patients (with disease duration up to 5 years) and the (non-)treatment of RA and osteoporosis. In our study, none of the patients had been treated for RA (at baseline) and only 5 of the 381 patients had been using bisphosphonates for a few months, which did not affect the analyses.

Symptom duration and the presence of RF were the only RA-specific markers for osteoporosis and reduced BMD in this study. It is known that seropositive RA is associated with more aggressive joint disease and is more commonly complicated by extra-articular manifestations than is seronegative RA.^{36–40} Previous studies showed an independent association between the presence of RF and osteoporosis or reduced BMD in established and recent onset RA.^{20–27} This suggests that there might be a common pathway between (future) local bone involvement in RA and generalised osteoporosis with osteoclasts, stimulated mostly by the RANKL pathway playing a crucial role in the pathogenesis.^{11–13} However, although joint damage, disease activity and functional disability were related to lower BMD in several studies of patients with established^{14–15–17–19} and early^{24–26} RA, these were not associated with osteoporosis or reduced BMD in the present study of patients with recently diagnosed RA. This could be explained by the very short disease duration of our patients, and follow-up might reveal associations between these disease-related variables and BMD.

In agreement with previous studies, osteoporosis and reduced BMD were independently associated with the well-known risk factors of low BMI, postmenopausal status and familial osteoporosis.^{1–14–16–19–41} In this study, we also, remarkably, found greater reduction in BMD in the spine in men than in women. After adjustment was made for confounders, such as

menopausal status for women, age was not associated with osteoporosis or reduced BMD in both men and women. However, it was remarkable that the highest age group had a lower prevalence of BMD reduction than the younger groups. This could be due to degenerative changes in the lumbar spine, the smaller number of patients and selection of the fittest patients.

In our large cohort of patients with early, active and mostly erosive RA, who had never been treated with DMARDs or corticosteroids, we found that longer symptom duration and the presence of RF, predictive for aggressive joint disease, was associated with osteoporosis and reduced BMD, suggesting that these events might share a common pathway. However, a comparison with Dutch population-based cohorts suggests that the prevalence of osteoporosis in our patients overlaps with that of the Dutch population, indicating that generalised osteoporosis in recently diagnosed RA is predominantly related to the well-known risk factors unrelated to disease, such as postmenopausal status, presence of familial osteoporosis and a low BMI. Further studies will be performed in the BeSt cohort to evaluate the effect of disease activity, joint damage progression and antirheumatic medication, including the use of corticosteroids and TNF inhibitors, on BMD loss.

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Table 4 Multivariate regression analysis of osteoporosis and reduced BMD in the spine and the hip (dependent variables) and demographic and disease variables (independent variables)

RR (95% CI)	Osteoporosis		Reduced BMD	
	Spine L2–4	Total hip	Spine L2–4	Total hip
Male gender	2.54 (0.88 to 6.16)	2.05 (0.73 to 4.56)	1.80 (1.23 to 2.41)	1.43 (0.74 to 2.47)
Postmenopausal status	1.93 (1.17 to 3.07)	1.60 (0.78 to 3.85)	2.05 (0.99 to 4.55)	1.45 (0.66 to 3.15)
BMI, kg/m ²	0.90 (0.84 to 0.96)	0.74 (0.58 to 0.90)	0.99 (0.94 to 1.04)	0.92 (0.87 to 0.97)
Familial osteoporosis	1.54 (0.93 to 2.02)	1.15 (0.44 to 3.20)	2.16 (1.23 to 3.39)	2.47 (1.30 to 4.00)
Symptom duration, weeks	1.001 (0.99 to 1.00)	1.004 (1.00 to 1.01)	1.001 (0.99 to 1.00)	1.002 (1.00 to 1.00)
Positive RF	1.17 (0.87 to 1.38)	1.24 (0.64 to 2.48)	1.31 (1.09 to 1.45)	1.07 (0.83 to 1.43)

BMD, bone mineral density; BMI, body mass index; RF, rheumatoid factor; RR, relative risk.

All variables were adjusted for age, gender, menopausal status, race, smoking and alcohol status, except for themselves. Symptom duration, rheumatoid factor status, Disease Activity Score, Health Assessment Questionnaire and total Sharp–van der Heijde score were additionally adjusted for each other.

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