Data driven attempt to create a clinical algorithm for identification of women with rheumatoid arthritis at high risk of osteoporosis

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Abstract

Objectives—To examine relations between osteoporosis and low bone mass and demographic and clinical variables in patients with rheumatoid arthritis (RA), in an attempt to develop a data driven clinical tool for identification of patients at high risk of osteoporosis.

Methods—All patients were recruited from a county based register and were examined cross sectionally with a variety of clinical and health status measures as well as bone density measures (anteroposterior spine L2–4, total hip, and femoral neck). Associations between osteoporosis (T score ≤ -2.5 SD) and low bone mass (T score ≤ -1 SD), on the one hand, and demographic and clinical measures, on the other, were examined bivariate and by logistic regression analyses.

Results—394 patients with a mean age of 54.8 years were examined. The percentages having osteoporosis/low bone mass were 16.8/45.8, 14.7/54.5 and 14.7/55.5 in spine L2–4, total hip, and femoral neck, respectively. Osteoporosis and low bone mass were bivariate related to age, body mass index (BMI), disease duration, disease process measures, presence of deformed joints, physical disability, current use of corticosteroids, and history of non-vertebral fracture. In multivariate analyses, age >60 years, low BMI, and current use of corticosteroids were consistently related to osteoporosis and to low bone mass at all sites. The presence of deformed joints was associated with osteoporosis at the total hip, and a history of previous non-vertebral fracture with osteoporosis at the femoral neck. The Modified Health Assessment Questionnaire (MHAQ) ≥ 1.5 and non-vertebral fracture were also independently associated with low bone mass at the hip. The logistic regression analyses models could, however, only predict osteoporosis with a sensitivity of about 50–60% and a specificity of 80–90% at the various measurement sites, and low bone mass with a sensitivity and specificity of about 70%.

Conclusion—Consideration of demographic and disease markers may be of some help in predicting presence of osteoporosis or low bone mass, but a combination of markers cannot be used as a clinical tool with sufficient sensitivity and

specificity for the identification of osteoporosis or low bone mass in patients with RA.

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Osteoporosis is recognised as a complication of rheumatoid arthritis (RA) (see review¹). Several studies have explored the relation between osteoporosis, on the one hand, and demographic and disease related variables, on the other.^{2–3} Use of corticosteroids has been found to be related to osteoporosis in RA,⁴ and several studies have also indicated that the development of bone loss (osteoporosis) is related to disease activity, especially early in the disease course.^{5–6}

Guidelines have been issued on the management of osteoporosis with corticosteroids.^{7–8} These guidelines have also included directions on which patients to select for diagnostic osteoporosis procedures, including bone mineral densitometry (BMD). Such guidelines have partly been based on published scientific data, partly on expert opinions, and partly on consenting group processes.

Longitudinal data are generally required to make statements about causal relations. However, for the clinician facing individual patients retrospective evaluation of a series of markers of disease activity and severity is usually not available. Thus the clinician must often rely on cross sectional data to identify patients at high risk of osteoporosis being candidates for diagnostic procedures. Recently, the need for a clinical algorithm for osteoporosis in patients with RA has been discussed.⁹ A preliminary proposal was made to measure bone density in patients with RA fulfilling two out of three of the following criteria: (a) age above 60, (b) immobility, and (c) high disease activity, defined as mean C reactive protein (CRP) above 20 mg/l or persistently raised erythrocyte sedimentation rate (ESR) above 20 mm/1st h.⁹

Previous studies on the identification of clinical and demographic variables predicting high risk of osteoporosis have been performed in rather limited patient numbers recruited from clinical settings, with a possible overrepresentation of patients with RA using corticosteroids and with active and severe disease. Our present approach was to examine a large number of patients recruited from a county based RA register in an attempt to develop a clinical tool to identify female patients who require diagnostic procedures and treatment.

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Materials and methods

SETTING AND INCLUSION CRITERIA

A register of patients with RA has been established in the county of Oslo since 1994.¹⁰ Inclusion criteria are a diagnosis of RA¹¹ and a residential address in Oslo. The register is continuously updated with new cases and also withdrawals due to death or new addresses outside Oslo.

The register has been shown to be about 85% complete in the age range 18–79 years, and it has been successful in providing data on incidence,¹² prevalence, and disease severity of RA.¹⁰

Inclusion criteria for the present study were enrolment in the Oslo RA register, female sex, and age between 18 and 70 years (born 1926 or later). The number of patients with RA fulfilling the inclusion criteria was 721. Of these 721 patients, 394 white subjects were willing to meet for clinical examination and BMD measurement (attendance rate 55%).¹³ All patients were younger than 70 years when completing the data collection (clinical data and BMD).

COLLECTION OF CLINICAL DATA

The collection of data was performed during a 15 month period between September 1996 and December 1997. Clinical data were collected partly by questionnaire, partly by interview and examination by trained research nurses under the supervision of a rheumatologist.

The following demographic variables were assessed: age, disease duration, body weight (light indoor clothing), and height. From the two last measures the body mass index (BMI) was computed. Comorbidities, exposure to oestradiol (current or not current user), menopause status, and previous oophorectomy were recorded as well as a history of previous non-vertebral fracture. Lifestyle variables included smoking (current, previous, never).

Disease activity was assessed by the following eight variables: 28 tender and 28 swollen joint counts, patients' and investigators' global assessment of disease activity (on a five point categorical scale and 100 mm visual analogue scale (VAS), respectively), pain severity and fatigue on 100 mm VAS, and acute phase reactants by ESR and CRP. The disease activity score (DAS) was computed using 28 joint counts.¹⁴

Damage was assessed by the number of deformed joints (score 0–18), and functional health status by the Modified Health Assessment Questionnaire (MHAQ) (range 1–4).¹⁵

Use of corticosteroids was assessed as a categorical variable (never user, previous user, current user).

BMD MEASUREMENTS

The BMD measurements of the hip (total hip and femoral neck) and the anteroposterior lumbar spine (L2–4) were performed by three trained technicians using the same dual energy x ray absorptiometry equipment (Lunar Expert, Madison, Wisconsin). The machine was calibrated daily with a spine phantom supplied by Lunar. Measurements of the left hip and spine were done according to standardised

procedures.¹³ In 14 patients no hip measurement was performed as they had had two hip replacements, and in 14 patients the right hip only was measured owing to replacement of severe destruction of the left hip. No spine measurement was performed in one patient.

To ensure uniformity of the results all the scans were reanalysed by one of the experienced technicians after all the data had been collected. The spine phantom precision error calculated as a coefficient of variation (CV%) was 0.9% for the whole measurement period (15 months). The in vivo reproducibility of BMD measurements was assessed from duplicate measurements in 31 healthy female hospital workers (mean age 56.1 years, range 50–66). The CV was 2.2% at the lumbar spine, 1.5% at the total hip, and 1.5% at the femoral neck. The interobserver variation for the three trained technicians performing measurements and analyses was assessed by pairwise comparisons of analyses of 30 randomly selected patients with RA. The precision varied from 0.7 to 1.4% at the spine L2–4, from 0.4 to 0.5% in the total hip, and from 0.5 to 0.8% in the femoral neck.

The BMD measurements in the RA population were compared with a pooled European/US reference population aged 20–69, based on different normal data from Europe and US, containing 9505 women with hip and 10 281 with spine measurements.^{16–24} The variation of mean BMD values among the geographical sites in this pooled population was about 1.3% (SD/mean).¹⁶ The reference database comprised measures of ambulatory subjects generally free from earlier fractures, chronic diseases, and drugs influencing bone metabolism (for example, corticosteroids, anti-convulsant drugs, and thyroxine).¹⁶

The BMD data for the pooled European/US reference population were provided by Lunar Corporation, Madison, including the data for T score estimations. For T score estimations the following mean (SD) BMD results for young adults (age 20–39) were used: femoral neck 0.98 (0.12) g/cm², total hip 1.00 (0.12) g/cm², and spine L2–4 1.20 (0.12) g/cm².

ETHICS AND LEGAL ASPECTS

The local ethic committee approved this study. The Data Inspectorate had approved the register of patients with RA in Oslo.

DATA ANALYSES

Data analysis was performed in the total female patient group (n=394) and, separately, for patients aged over 50 (n=271). All analyses were performed with SPSS, version 8.0.

Osteoporosis was defined as a T score ≤ -2.5 SD,²⁵ low bone mass as T score ≤ -1 . After computing the number of patients with osteoporosis and low bone mass, bivariate comparisons of demographic, disease activity, and disease severity measures between patients with and without osteoporosis/low bone mass were performed, using two sided *t* tests (continuous variables) and χ^2 tests (counts).

Independent variables to be used in the multivariate analyses were dichotomised as

Table 1 Demographic variables and measures of disease activity and severity in the study samples. Mean (SD) for continuous variables, % for counts

	All patients (n=394)	50–70 years (n=271)
Demographic variables		
Age (years)	54.8 (11.6)	61.5 (6.2)
BMI* (kg/m ²)	24.0 (4.2)	24.5 (4.4)
Menopause (%)	66.0	91.9
Menopause age (years)	47.9 (5.5)	48.1 (5.4)
Oophorectomy (%)	4.3	4.8
Current users of oestradiol (%)	28.5	35.4
Bisphosphonates (%)	2.6	3.8
Smoking		
Non-smoker (%)	33.0	30.5
Previous smoker (%)	30.5	32.4
Current smoker (%)	36.5	37.0
Disease variables		
Disease duration (years)	13.0 (9.4)	14.3 (10.2)
Rheumatoid factor positive (%)	52.0	54.3
Investigator's global assessment (VAS* 0–100 mm)	28.7 (24.1)	32.0 (25.3)
Patient's global assessment (1–5)	2.63 (0.88)	2.72 (0.91)
MHAQ* (range 1–4)	1.61 (0.50)	1.70 (0.51)
Pain (VAS 0–100 mm)	36.1 (21.9)	39.7 (22.0)
Fatigue (VAS 0–100 mm)	44.9 (27.8)	46.4 (28.0)
28 Swollen joint count	7.84 (6.11)	8.48 (6.28)
28 Tender joint count	6.84 (6.36)	7.53 (6.67)
18 Deformed joint count	2.15 (3.70)	2.63 (4.05)
ESR* (mm/1st h)	21.6 (16.5)	23.2 (17.4)
CRP* (mg/l)	16.2 (11.9)	16.5 (12.3)
DAS*	4.49 (1.37)	4.70 (1.33)
Corticosteroids		
Never user (%)	36.3	30.7
Previous user (%)	23.2	23.4
Current user (%)	40.5	46.0
Non-vertebral fracture (%)	21.2	26.5

*BMI = body mass index; VAS = visual analogue scale; MHAQ = Modified Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C reactive protein; DAS = disease activity score.

follows: age over and under 60 years, BMI and DAS divided by the two highest and lowest quartiles, presence and absence of deformed joints, MHAQ score ≥ 1.5 (indicating physical disability), corticosteroids into current versus not users, and presence versus absence of previous non-vertebral fracture.

The occurrence of such possible predictors of osteoporosis (age ≥ 60 years, low BMI, high DAS, deformed joints, MHAQ ≥ 1.5 , current user of corticosteroids, previous non-vertebral fracture) were compared between patients with and without osteoporosis/low bone mass. These possible predictors were subsequently entered into a logistic regression analysis applying osteoporosis/low bone mass at different sites as dependent variables. The logistic regression analyses were run with the enter procedure.

Table 2 Comparison of demographic and disease activity/severity variables between patients with and without osteoporosis. Means for continuous variables, % for counts

	Spine L2–4			Total hip			Femoral neck		
	T $\leq$ –2.5 (n=66)	T>–2.5 (n=327)	p Value	T $\leq$ –2.5 (n=56)	T>–2.5 (n=324)	p Value	T $\leq$ –2.5 (n=56)	T>–2.5 (n=324)	p Value
Age (years)	62.8	53.2	<0.001	63.9	53.0	<0.001	63.7	53.1	<0.001
Disease duration (years)	15.9	12.3	0.007	16.9	11.8	<0.001	16.0	11.9	0.005
Body mass index	22.9	24.2	0.006	22.5	24.2	0.002	22.7	24.2	0.005
Number of swollen joints	9.92	7.44	0.01	11.19	7.16	<0.001	11.46	7.11	<0.001
Number of deformed joints	4.16	1.77	<0.001	4.89	1.49	<0.001	4.63	1.54	<0.001
CRP* (mg/l)	18.0	15.8	0.17	20.9	14.7	0.001	19.9	14.9	0.005
ESR* (mm/1st h)	24.7	21.1	0.16	26.6	20.1	0.008	26.5	20.1	0.01
MHAQ*	1.74	1.59	0.06	1.81	1.56	0.002	1.74	1.57	0.02
DAS*	4.88	4.42	0.02	5.08	4.37	0.001	5.05	4.37	0.001
Current use of corticosteroids (%)	66.1	35.3	<0.001	64.8	35.2	<0.001	66.7	34.9	<0.001
Ever use of corticosteroids (%)	80.6	60.3	0.002	85.2	58.7	<0.001	83.3	59.0	0.001
Rheumatoid factor positive (%)	58.3	50.6	0.32	68.6	48.9	0.01	67.3	49.0	0.02
Non-vertebral fracture (%)	33.9	18.6	0.007	37.0	17.3	0.001	44.4	16.0	<0.001

*CRP = C reactive protein; ESR = erythrocyte sedimentation rate; MHAQ = Modified Health Assessment Questionnaire; DAS = disease activity score.

Results

PATIENTS

Table 1 shows the demographic and clinical characteristics of the 394 female patients with RA finally included in the study, born 1926 and later, and the 271 patients aged between 50 and 70.

Of all the women with RA from the register, born 1926 or later (n=721), there were no statistically significant differences in age, disease duration, and rheumatoid factor positivity between those measured and not measured. A group of 109 patients had clinical examinations, without bone mass measurement. The clinical and disease characteristics, including disease activity and severity measures, in these patients did not differ from those whose BMD was measured. Thus, the final sample of 394 patients with RA seems to be representative of the overall RA population in the county.

BMD MEASURES

The BMD values (mean (SD) in g/cm²) for the whole patient group were 1.10 (0.21) at the spine L2–4, 0.87 (0.16) at the total hip, and 0.85 (0.16) at the femoral neck. Corresponding values in the 50–70 age group were 1.05 (0.20), 0.83 (0.16), and 0.80 (0.15).

The percentages (95% confidence interval (CI)) having osteoporosis (T score $\leq$ –2.5SD) were in the total patient group 16.8 (13.1 to 20.5) at L2–4, 14.7 (11.1 to 18.3) at the total hip, and 14.7 (11.1 to 18.3) at the femoral neck. Among those aged 50–70 the percentages were as expected higher (23.3 (18.3 to 28.3), 21.1 (16.2 to 26.0), and 20.7 (15.9 to 25.5)). The percentages (95%CI) with low bone mass (T score $\leq$ –1SD) were 45.8 (40.9 to 50.7), 54.5 (49.5 to 59.5), and 55.5 (50.5 to 60.5) in the spine L2–4, total hip, and femoral neck, respectively.

COMPARISON OF PATIENTS WITH AND WITHOUT OSTEOPOROSIS/LOW BONE MASS

Table 2 gives bivariate comparisons of demographic and disease activity and severity variables between patients with and without osteoporosis. Osteoporosis was statistically associated with increasing age, longer disease duration, lower BMI, increasing disease activity, and use of corticosteroids at all sites of measurement. The computed DAS also

Table 3 Possible risk factors of osteoporosis at the spine L2–4. Occurrence and logistic regression analysis

	Occurrence (%)			Logistic regression analysis			
	$T \leq -2.5$ (n=66)	$T > -2.5$ (n=327)	p Value	β	SE	OR	CI
Age ≥ 60	77.3	33.9	<0.001	1.87	0.36	6.46	3.18 to 13.13
BMI* 2 lowest quartiles	62.1	47.7	0.04	1.26	0.35	3.52	1.77 to 6.99
Deformed joints	54.8	35.6	0.006	0.50	0.33	1.65	0.87 to 3.14
MHAQ* ≥ 1.5	59.0	50.2	0.21	-0.26	0.36	0.77	0.38 to 1.56
DAS* 2 highest quartiles	65.5	47.9	0.02	0.27	0.36	1.31	0.64 to 2.67
Current use of corticosteroids	66.1	35.3	<0.001	1.07	0.34	2.91	1.50 to 5.65
Non-vertebral fracture	33.9	18.6	0.007	0.50	0.36	1.65	0.82 to 3.32
Constant				-4.32	0.51		
Sensitivity/specificity (%)						52/87	

*BMI = body mass index; MHAQ = Modified Health Assessment Questionnaire; DAS = disease activity score.

Table 4 Possible risk factors of osteoporosis at the total hip. Occurrence and logistic regression analysis

	Occurrence			Logistic regression analysis			
	$T \leq -2.5$ (n=56)	$T > -2.5$ (n=324)	p Value	β	SE	OR	CI
Age ≥ 60	82.1	33.3	<0.001	2.58	0.44	13.23	5.58 to 31.33
BMI* 2 lowest quartiles	66.1	47.5	0.01	1.82	0.41	6.16	2.76 to 13.75
Deformed joints	59.3	32.7	<0.001	0.75	0.37	2.12	1.03 to 4.36
MHAQ* ≥ 1.5	66.0	47.8	0.02	0.42	0.41	1.52	0.68 to 3.39
DAS* 2 highest quartiles	68.6	47.6	0.006	0.01	0.42	1.01	0.45 to 2.29
Current use of corticosteroids	64.8	35.2	<0.001	1.00	0.39	2.71	1.27 to 5.78
Non-vertebral fracture	37.0	17.3	0.001	0.67	0.40	1.96	0.90 to 4.27
Constant				-5.63	0.65		
Sensitivity/specificity (%)						56/89	

*BMI = body mass index; MHAQ = Modified Health Assessment Questionnaire; DAS = disease activity score.

discriminated between patients with and without osteoporosis. Osteoporosis was more consistently related to disease activity and severity measures at the hip location than at the spine L2–4 site of measurement (table 2).

Similar patterns of differences were seen for demographic and disease variables between patients with and without low bone mass (data not shown).

RISK FACTORS FOR OSTEOPOROSIS

Tables 3–5 present bivariate comparisons and logistic regression analyses of the associations

between osteoporosis and categorised risk factors (age, BMI, joint deformity, disability, DAS, current use of corticosteroids, and previous non-vertebral fracture). Table 6 presents the multivariate relations between low bone mass and the categorised risk factors.

Patients with osteoporosis differed for all tested variables (table 4) from those without osteoporosis of the total hip, whereas group differences were not found for physical disability (MHAQ ≥ 1.5) between patients with and without osteoporosis at the spine L2–4 (table 3) and femoral neck (table 5). The same trends

Table 5 Possible risk factors of osteoporosis at the femoral neck. Occurrence and logistic regression analysis

	Occurrence (%)			Logistic regression analysis			
	$T \leq -2.5$ (n=56)	$T > -2.5$ (n=324)	p Value	β	SE	OR	CI
Age ≥ 60	78.6	34.0	<0.001	2.17	0.42	8.80	3.88 to 19.98
BMI* 2 lowest quartiles	66.1	47.5	0.01	1.76	0.41	5.82	2.60 to 13.00
Deformed joints	57.4	33.0	0.001	0.67	0.37	1.96	0.95 to 4.02
MHAQ* ≥ 1.5	60.4	48.7	0.14	-0.10	0.40	0.91	0.41 to 2.00
DAS* 2 highest quartiles	70.6	47.2	0.002	0.37	0.42	1.44	0.64 to 3.27
Current use of corticosteroids	66.7	34.9	0.001	1.12	0.38	3.05	1.44 to 6.48
Non-vertebral fracture	44.4	16.0	<0.001	1.29	0.39	3.63	1.71 to 7.73
Constant				-5.46	0.63		
Sensitivity/specificity (%)						68/90	

*BMI = body mass index; MHAQ = Modified Health Assessment Questionnaire; DAS = disease activity score.

Table 6 Possible risk factors of low bone mass (T score ≤ -1) at the spine L2–4, total hip, and femoral neck

	Spine L2–4			Total hip			Femoral neck		
	β	OR	CI	β	OR	CI	β	OR	CI
Age ≥ 60	1.29	3.62	2.21 to 5.92	1.13	3.10	1.81 to 5.29	1.42	4.13	2.43 to 7.01
BMI* 2 lowest quartiles	0.89	2.43	1.49 to 3.97	1.43	4.17	2.45 to 7.11	0.86	2.37	1.44 to 3.92
Deformed joints	-0.08	0.93	0.57 to 1.50	0.48	1.62	0.97 to 2.70	0.48	1.61	0.98 to 2.66
MHAQ* ≥ 1.5	0.48	1.62	0.97 to 2.71	0.84	2.31	1.35 to 3.97	0.62	1.86	1.10 to 3.14
DAS* 2 highest quartiles	0.19	1.20	0.72 to 2.00	-0.04	0.96	0.56 to 1.65	0.12	1.13	0.67 to 1.91
Current use of corticosteroids	0.89	2.44	1.51 to 3.93	0.75	2.11	1.27 to 3.53	0.55	1.74	1.05 to 2.86
Non-vertebral fracture	0.47	1.59	0.89 to 2.85	1.17	3.23	1.63 to 6.37	0.69	2.00	1.05 to 3.83
Constant	-1.97			-2.06			-1.63		
Sensitivity/specificity (%)		69/70			74/69			73/65	

*BMI = body mass index; MHAQ = Modified Health Assessment Questionnaire; DAS = disease activity score.

were found for patients aged 50–70, but owing to the lower sample size not all differences reached statistical significance (data not shown).

Age over 60, low BMI, and current use of corticosteroids were the most consistent risk factors in multivariate analyses for osteoporosis and low bone mass (tables 3–6). The presence of deformed joints was associated with osteoporosis at the total hip, and a history of previous non-vertebral fracture with osteoporosis at the femoral neck (tables 4 and 5). MHAQ ≥ 1.5 and non-vertebral fracture were independently associated with low bone mass at the hip.

The classification tables showed that models generally reached a sensitivity between 50 and 60% and specificity between 80 and 90% for osteoporosis (tables 3–5) and a sensitivity and specificity of about 70% for low bone mass (table 6).

In addition to the model examining the main effects, an expanded model which included all first order interactions was fitted. The overall test for all the interactions turned out to be non-significant. Consequently, the main effects model had an adequate fit.

Discussion

This study confirms that patients with RA with osteoporosis and low bone mass generally have a more active and severe disease than patients without osteoporosis. Thus markers of disease activity and severity as well as treatment with corticosteroids indicate an increased risk of osteoporosis. However, this study also highlights that these associations with clinical markers are weak, as increasing age and low BMI were the strongest and most consistent predictors of osteoporosis at all sites, both in the total patient group and in the analyses of patients aged 50–70. Age and BMI are also consistent predictors in postmenopausal osteoporosis,²⁶ suggesting that these demographic variables may be more important at a group level than the disease factors.

However, clinical markers are also important, even if the logistic regression models used had rather low sensitivity in detecting patients with osteoporosis. The most important clinical factor was the current use of corticosteroids, and then the presence of deformed joints, indicating structural joint damage. In this cross sectional approach the DAS and the MHAQ score did not turn out to be independent predictors of osteoporosis, and the MHAQ score only reached borderline statistical significance at one measurement site. Analyses were also performed with low bone mass as the dependent variable because the threshold of the T score ≤ -1 SD may be as important when advocating treatment, especially in patients using corticosteroids.⁸

The results can be used to compute algorithms of some help in clinical practice. The predicted probabilities for a combination of clinical variables can be calculated by adding the parameter estimates from any combinations. For example, the results in table 4

indicate that the odds of having total hip osteoporosis for women in the oldest age group and lowest BMI group with inactive and not severe disease is:

logit (constant, age ≥ 60 , BMI two lowest quartiles, not deformed joints, MHAQ ≤ 1.5 , DAS two lowest quartiles, no use of corticosteroids, and no previous non-vertebral fracture) = logit ($-5.63 + 2.58 + 1.82 + 0 + 0 + 0 + 0 + 0$),

while the odds for having osteoporosis for women with the same age and BMI characteristics, but with severe and active disease and previous non-vertebral fracture is:

logit (constant, age ≥ 60 , BMI two lowest quartiles, deformed joints, MHAQ ≥ 1.5 , DAS two highest quartiles, current use of corticosteroids, and previous non-vertebral fracture) = logit ($-5.63 + 2.58 + 1.82 + 0.75 + 0.42 + 0.01 + 1.00 + 0.67$).

The log odds ratio (OR) for women over 60 and with low BMI with active and severe disease and with previous non-vertebral fracture compared with those without active disease and with no previous non-vertebral fracture is:

(logit ($-5.63 + 2.58 + 1.82 + 0.75 + 0.42 + 0.01 + 1.00 + 0.67$)) – (logit ($-5.63 + 2.58 + 1.82 + 0 + 0 + 0 + 0 + 0$)) = $1.62 - (-1.23) = 2.85$.

Thus the OR for having total hip osteoporosis for those with compared with those without active and severe disease and a previous history of non-vertebral fracture is: $e^{2.85} = 17.29$, where e is the base of the natural logarithms, approximately 2.718.

It can be argued that other disease activity measures should have been included in the model. A lot of exploratory analyses were done before we decided to use the present model, which incorporates various dimensions of measures that are recommended for longitudinal observational studies²⁷ and also may be used in the routine clinical care of patients with RA.

For corticosteroids we chose to use current instead of ever use of corticosteroids as the independent variable as corticosteroid induced bone loss may be reversed when corticosteroid treatment is stopped.²⁸ In the exploratory analyses we found that acute phase reactants, number of swollen joints, and rheumatoid factor were not independent predictors. From the group comparisons it was also shown that only marginal differences were seen for these variables between the patients with and without osteoporosis (table 2). This result partially contradicts the results of a previous study showing that the mean ESR measured during the six months before the BMD measurement was negatively associated with hip BMD.²⁹ We had expected a stronger effect of the MHAQ level on osteoporosis, as this previous Dutch study also found an association between physical disability and BMD.²⁹ The level of MHAQ is, however, closely related to age, and age came out as the strongest overall predictor.

Previous studies on osteoporosis in RA have mainly focused on selected groups of patients recruited from referral centres.^{2 3 30 31} In our study we had a different approach, examining patients from a county based RA register. This register has been examined for its completeness and includes about 85% of the total underlying patient population,¹⁰ and prevalence data have shown a twofold increase in osteoporosis in patients with RA.¹³ Furthermore, the patients examined did not differ significantly from the patients on the register who were eligible for this study. Thus our results are relevant for all patients with RA as a group, but different results might have been found if similar analyses had been performed in selected patients with active and severe disease, or in a selected group of patients who were not receiving hormone replacement therapy. It should be noted that more than one quarter of the patients in this study were current users of oestradiol. However, the results were similar when we repeated the analyses in a subsample excluding users of oestradiol (data not shown).

The effect of inflammatory markers on osteoporosis might also have been different if longitudinal data had been analysed.^{6 29} For radiographic progression it is well known that the level of acute phase reactants correlates with structural damage.³² This correlation has been shown to be even stronger if, for example, a series of CRP measurements are related to radiographic damage.³³

The important clinical outcome of low bone mass is symptomatic fracture. The incidence of hip and vertebral fractures is increased in patients with RA, but the relation between bone mass and subsequent fractures remains to be established.³⁴ It is not certain whether data from patients with postmenopausal osteoporosis, showing a double risk of fracture for each SD reduction in BMD,^{35 36} is also applicable to patients with RA. In our study a history of non-vertebral fracture was used as a possible predictor, showing an independent relation with osteoporosis and low bone mass in the hip, but not in the lumbar spine.

Our aim was to develop a clinical tool which would be helpful in the identification of patients with RA who were likely to develop osteoporosis. We found that osteoporosis and low bone mass in RA are more consistently associated with age, BMI, and current use of corticosteroids than disease variables. Osteoporosis could be predicted with an average sensitivity of only 50–60% and a specificity of 80–90% when the predictors were combined into logistic regression models. This indicates that consideration of risk factors may be helpful in clinical practice, but that many patients with osteoporosis will be missed if only those with known risk factors, including high disease activity and severity, are considered.

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