Radiographic joint destruction in postmenopausal rheumatoid arthritis is strongly associated with generalised osteoporosis.

Forsblad D'Elia, H; Larsen, A; Waltbrand, E; Kvist, G; Mellström, D; Saxne, Tore; Ohlsson, C; Nordborg, E; Carlsten, H

Published in:
Annals of the Rheumatic Diseases

DOI:
10.1136/ard.62.7.617

2003

Radiographic joint destruction in postmenopausal rheumatoid arthritis is strongly associated with generalised osteoporosis

H Forsblad d'Elia, A Larsen, E Waltbrand, G Kvist, D Mellström, T Saxne, C Ohlsson, E Nordborg and H Carlsten

Ann. Rheum. Dis 2003;62;617-623
doi:10.1136/ard.62.7.617

EXTENDED REPORT

Radiographic joint destruction in postmenopausal rheumatoid arthritis is strongly associated with generalised osteoporosis

H Forsblad d'Elia, A Larsen, E Waltbrand, G Kvist, D Mellström, T Saxne, C Ohlsson, E Nordborg, H Carlsten

Ann Rheum Dis 2003;**62**:617–623

See end of article for authors' affiliations

Correspondence to: Dr H Forsblad d'Elia, Department of Rheumatology and Inflammation Research, Göteborg University, Guldhedsgatan 10, S-413 46 Göteborg, Sweden; helena.forsblad@rheuma.gu.se

Accepted 22 November 2002

Objectives: To investigate determinants of joint destruction and reduced bone mineral density (BMD) in postmenopausal women with active rheumatoid arthritis (RA) not treated with bisphosphonates or hormone replacement therapy and to evaluate if there are common markers of erosive disease and bone loss.

Methods: BMD was measured using dual *x* ray absorptiometry and joint damage was examined by *x* ray examination according to the Larsen method in 88 patients with RA. Associations between BMD and Larsen score, and between demographic and disease related variables, including proinflammatory cytokines, HLA-DR4 epitopes, and markers of bone and cartilage turnover, were examined bivariately by simple and multiple linear regression analyses.

Results: 49/88 (56%) patients had osteoporosis in at least one site. Reduced BMD and increased joint destruction were associated with: at the forearm and femoral neck, high Larsen score, low weight, and old age (R^2=0.381, p<0.001; R^2=0.372, p<0.001, respectively); at the total hip, low weight, high Larsen score, and dose of injected glucocorticosteroids (R^2=0.435, p<0.001); at the lumbar spine, low weight, reduced cartilage oligomeric matrix protein, and increased carboxyterminal propeptide of type I procollagen (R^2=0.248, p<0.001). Larsen score was associated with long disease duration and increased C reactive protein (CRP) (R^2=0.545, p<0.001).

Conclusions: Osteoporosis is common in postmenopausal patients with RA. Low weight and high Larsen score were strongly associated with BMD reduction. Increased CRP and long disease duration were determinants of erosive disease in postmenopausal women with RA. These findings indicate common mechanisms of local and generalised bone loss in RA.

Generalised osteoporosis is a well known phenomenon in rheumatoid arthritis (RA) as demonstrated by decreased bone mineral density (BMD) in several studies.[1–7] Consequently, the risk of fractures is also increased.[2 8 9] Two other forms of bone affection occur also: the focal bone loss affecting the immediate subchondral bone at the joint margins, the erosions and the periarticular osteopenia adjacent to inflamed joints.

The pathophysiological mechanisms of the three different types of bone involvement have previously largely been thought to be separate processes. However, present studies have suggested that both local and systemic bone destruction are mediated by osteoclast activation because it has been shown that several cells at the bone-pannus interface in RA express receptor activator of nuclear factor κB ligand (RANKL), a factor stimulating osteoclast differentiation.[10 11]

Recently it was shown that the presence of joint erosions in patients with RA was associated with generalised osteoporosis[12] and there were strong correlations between the Larsen score in the hand, the trabecular bone in the distal radius, and os calcis.[13] Hormone replacement therapy (HRT) is known to increase BMD in postmenopausal women,[14] and we have shown in a two year prospective study that HRT in postmenopausal women with RA had a beneficial effect on BMD in parallel with a joint protective effect in patients with progressive erosive disease[14a], suggesting that some of the disease mechanisms for generalised osteoporosis are common to those for local bone involvement.

The first aim of this study was to evaluate the frequency of osteoporosis in postmenopausal women with established RA not treated with bisphosphonates or HRT. The second aim was to determine the markers of low BMD and erosive disease among demographic and disease related variables and, thirdly, to identify common determinants of the two processes.

PATIENTS AND METHODS

Patients

Five hundred and ninety two female patients with RA aged between 45 and 65 years were identified from rheumatology clinic patient registers in Göteborg and Borås. They were invited to participate in a cross sectional study evaluating the frequency and determinants of osteoporosis and joint destruction. The patients were later randomised in a two year HRT study.

The participants were postmenopausal, fulfilled the American Rheumatism Association 1987 revised criteria for adult RA,[15] and had an active disease which met at least two of the following criteria: more than six painful joints; more than three swollen joints; erythrocyte sedimentation rate (ESR)

Abbreviations: BMD, bone mineral density; COMP, cartilage oligomeric matrix protein, CRP, C reactive protein; DAS28, 28 joint count disease activity score; DMARDs, disease modifying antirheumatic drugs; DXA, dual *x* ray absorptiometry; ELISA, enzyme linked immunosorbent assay; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HRT, hormone replacement therapy; ICTP, telopeptide of type I collagen; IGF-I, insulin-like growth factor-I; IL, interleukin; IL1Ra, interleukin 1 receptor antagonist; OPG, osteoprotegerin; PICP, propeptide of type I procollagen; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor κB ligand; sIL6R, interleukin 6 soluble receptor; TNFα, tumour necrosis factor α

>20 mm/1st h; and/or C reactive protein (CRP) >10 mg/l. Patients were not excluded owing to high disease activity. Patients were not receiving, and had not used in the past two years, drugs affecting the bone metabolism (HRT or bisphosphonates), except calcium and vitamin D_3, which were allowed. The patients had no contraindications to HRT, treatment with disease modifying antirheumatic drugs (DMARDs) and glucocorticosteroids orally were stable for the past three months, and all patients understood Swedish.

Of the 592 patients, 478 (81%) responded. Seventy two of the women were not postmenopausal and 19 did not fulfil the diagnostic criteria of RA. Two hundred and ninety nine patients were not able to participate for the following reasons: 159 patients had been treated with HRT during the past two years and 6 with bisphosphonates; 26 had a history of deep venous thrombosis or embolism and 23 of cancer in the breasts, uterus, or ovaries; 18 had recently started treatment with DMARDs or glucocorticosteroids, had language problems, or had moved away; and 67 did not want to participate. Finally, 88 women wanted to take part and fulfilled the inclusion criteria of the study. All patients gave informed consent and the ethics committee at Göteborg University approved the study.

Assessment of outcome variables

The patients answered a questionnaire about age at menarche and menopause, smoking habits, milk and cheese consumption, previous and present use of glucocorticosteroids, present use of DMARDs, and disease duration. A control group, consisting of 72/299 postmenopausal women with RA who did not fulfil the inclusion criteria, answered the same questionnaire. These 72 patients had not been included in the study for varying reasons: 39 were treated with HRT and 1 with bisphosphonate; 5 had had deep venous thrombosis or embolism and 7 cancer in the breasts, uterus or ovaries; 14 did not want to participate; and 6 had moved to other parts of Sweden or had another severe disease.

The cumulative dose of oral prednisolone and glucocorticosteroids injected intra-articularly and intramuscularly converted to the quantity of prednisolone was calculated for each participant.

The disease activity was estimated by calculating the 28 joint count disease activity score (DAS28)[16] using the following formula:

$$DAS28 = 0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.70\ln ESR + 0.014GH$$

where TJC = tender joint count; SJC = swollen joint count; GH = patient's assessment of general health using a visual analogue scale of 100 mm.

The physical disability was evaluated by the Health Assessment Questionnaire (HAQ), where 0 implies no handicap and 3 severe disability.[17 18]

The BMD at the left forearm, left total hip, left femoral neck, and lumbar spine (L1–4) was measured by dual *x* ray absorptiometry (DXA; Hologic QDR-4500A). The precision was 0.4% both at the lumbar spine and the total hip. It was not possible to measure all skeletal sites in every patient because of the presence of prostheses and osteosynthetic materials. The results were presented as absolute values (g/cm^2) but also as the number of standard deviations (SD) above or below the mean results of young female adults (T score) and an age matched female population (Z score) of the NHANES (National Health and Examination Survey) reference population provided by the manufacturer. Osteoporosis was defined according to the WHO[19] (World Health Organisation, 1994) as a value for BMD that is more than 2.5SD below, and osteopenia as a BMD that lies between 1 and 2.5SD below, the young adult mean value measured at any site using DXA.

Radiographs of the hands, wrists and forefeet were evaluated according to Larsen.[20] Briefly, 40 joints were scored in each patient from 0 (normal) to 5 (maximal destruction). The scores for each patient were summed and then divided by the number of examined joints to give the mean Larsen score for each patient ranging from 0 to 5.

Venous blood samples were obtained after an overnight fast and were stored at −70°C until needed for analysis. ESR, CRP, haemoglobin, and rheumatoid factor were measured by standard laboratory techniques. Quantitative sandwich enzyme linked immunosorbent assay (ELISA) kits were used for measurement of the proinflammatory cytokines, tumour necrosis factor α (TNFα), interleukin 1β (IL1β), interleukin 1 receptor antagonist (IL1Ra), interleukin 6 (IL6), interleukin 6 soluble receptor (sIL6R) (Quantikine HS, R&D Systems, Minneapolis, USA), and the inhibitor of osteoclastogenesis, osteoprotegerin (OPG; Immundiagnostic, Bensheim, Germany). The cartilage remodelling marker, cartilage oligomeric matrix protein (COMP) was measured by a novel sandwich ELISA based on two monoclonal antibodies (AnaMar, Medical, Lund, Sweden). Radioimmunoassay was used for the quantitative determination of the bone anabolic factor, insulin-like growth factor-I (IGF-I) (Mediagnost, Teubingen, Germany); the bone remodelling markers, carboxyterminal crosslinked telopeptide of type I collagen (ICTP) and carboxyterminal propeptide of type I procollagen (PICP) (Orion Diagnostica, Espoo, Finland); and s-oestradiol (Clinical Assays, DiaSorin, Vercelli, Italy).

The presence of HLA-DR4, DRB1:70–74:QKRAA/QRRAA and two HLA-DR4 subtypes DRB1*0401 and DRB1*0404 was determined by indirect immunofluorescence and flow cytometry (Terra Nova, Biotechnology, St John's, Newfoundland, Canada). Patients were divided into risk groups (1–5) according to the terra nova severity risk test in patients with RA derived from previous studies.[21–23]

Statistical analysis

Fisher's permutation test[24] was used comparing the z values of the BMD of the study patients and the control group. Simple regression analyses were calculated with BMD, Larsen score, and cumulative glucocorticosteroids as dependent variables and potentially demographic and disease related determinants, listed in table 1, as independent factors. Multiple linear regression analyses were then used by a stepwise (forward) method to explore the relationships between BMD, radiological status, and cumulative dose of glucocorticosteroids and the demographic and disease related variables which had shown significant correlations in the simple regression. All tests were two tailed and $p<0.05$ was considered significant.

RESULTS

Patient group

Table 1 shows demographic and disease related characteristics. The most common DMARD was methotrexate used by 30 (34%) patients. Nineteen patients (22%) were receiving prednisolone at a mean (SD) dose of 4.6 (1.5) mg/day.

Demographic data of the 72 controls not fulfilling the study inclusion criteria did not show any differences in age, height, weight, body mass index, disease duration, age at menarche and menopause, milk and cheese consumption, smoking habits, use of DMARDs, non-steroidal anti-inflammatory drugs, and glucocorticosteroids and of the prevalence of fractures compared with the study group. A larger proportion of the controls (61%), however, had previously been treated with glucocorticosteroids orally for >3 months compared with the study group (43%), $p=0.026$, and 54% of the controls were receiving HRT compared with none of the study patients, $p<0.001$.

Bone mineral density

Table 2 shows the results of the DXA measurements and the proportion of patients who had osteoporosis, osteopenia, and normal BMD, at different skeletal sites. Forty nine (56%) of

Table 1 Demographic variables, clinical and laboratory measurements of disease activity, proinflammatory cytokines, and biochemical markers of bone and cartilage turnover in postmenopausal women with rheumatoid arthritis. Values are means (SD) [numbers of patients with available data]

	Characteristics
Age (years)	57.6 (5.1)) [88]
Height (cm)	162.9 (6.3)) [88]
Weight (kg)	66.5 (12.6)) [88]
Body mass index (kg/m^2)	25.0 (4.2)) [88]
Disease duration (years)	15.9 (11.7)) [88]
Age at menarche	13.6 (1.7)) [87]
Age at menopause	49.2 (3.4)) [78]
Milk (glasses/day)	1.8 (1.6)) [88]
Cheese (slices/day)	3.3 (2.5)) [86]
Smoking status (%)	[87]
Non-smoker	38
Previous smoker	30
Current smoker	32
Disease modifying antirheumatic drugs (%)	81 [88]
Non-steroidal anti-inflammatory drugs (%)	77 [88]
Calcium and vitamin D_3 (%)	6 [88]
Previous treatment with glucocorticosteroid >3 months (%)	43[87]
Glucocorticosteroid treatment at present (%)	22 [88]
Cumulative oral prednisolone dose (g)	2.6 (5.1)) [88]
Cumulative injected glucocorticosteroid dose, expressed as prednisolone (g)	1.1 (1.3)) [88]
Low energy peripheral fractures or vertebral fractures (%)	19 [84]
Larsen score (0–5)	1.36 (1.06) [83]
Erosive disease (%)	89 [83]
Risk group according to HLA-DR4 subtyping (1–5)	3.3 (1.2) [80]
Health Assessment Questionnaire (0–3)	1.0 (0.7) [88]
28 Joint count disease activity score	5.3 (1.0) [87]
Positive serum test for rheumatoid factor (%)	83 [88]
Haemoglobin (g/l)	129 (12) [88]
Erythrocyte sedimentation rate (mm/1st h)	29 (17) [87]
C reactive protein (mg/l)	17 (17) [87]
Tumour necrosis factor α (pg/ml)	4 (3) [85]
Interleukin 1β (pg/ml)	0.4 (1.2) [87]
Interleukin 1 receptor antagonist (pg/ml)	542 (647) [87]
Interleukin 6 (pg/ml)	23 (32) [87]
Interleukin 6 soluble receptor (pg/ml)	789 (236) [86]
Osteoprotegerin (pg/ml)	112 (97) [83]
Carboxyterminal crosslinked telopeptide of type I collagen (ng/ml)	4.8 (1.9) [77]
Carboxyterminal propeptide of type I procollagen (ng/ml)	133 (41) [78]
Insulin-like growth factor-I (ng/ml)	80 (30) [77]
Cartilage oligomeric matrix protein (U/l)	11 (3) [86]
Oestradiol (pmol/l)	51 (85) [72]

the women had osteoporosis in at least one site, 35 (40%) in at least two, 24 (27%) in at least three, and, finally, 8 (9%) had osteoporosis at all sites measured. BMD was significantly lower at all sites than in the reference population provided by the manufacturer, forearm $p=0.006$, lumbar spine $p<0.001$, total hip $p<0.001$ and femoral neck $p<0.001$. BMD of the whole body was also measured but the findings are not shown because 14 patients had at least one prosthesis, which may influence the results of the bone mass.

Markers of low BMD

Table 3 shows BMD at different measurement sites that significantly correlated with the demographic and disease related variables listed in table 1. In the multiple regression analyses (BMD at other measure sites excluded as independent variables) high Larsen score, low weight, and old age remained significantly connected with low BMD in the forearm. Low weight, high Larsen score, and high cumulative injected glucocorticosteroids were significant markers of low BMD of the total hip. Low weight, high Larsen score and increasing age were significantly connected with low BMD in the femoral neck, whereas low weight, low COMP, and high PICP remained significantly associated with low BMD in the lumbar spine (table 4).

To test whether joint destruction had an effect beyond that of disease duration and the DAS28, disease duration and DAS28 were inserted in the multiple stepwise regression analyses with BMD at different measure sites as dependent

Table 2 Bone mineral density (BMD), mean (SD) and percentage of patients with osteoporosis, osteopenia, and normal BMD

	BMD (g/cm^2)	T score (SD)	Z score (SD)	Osteoporosis (%)	Osteopenia (%)	Normal BMD (%)
Forearm (n=81)	0.47 (0.10)	−1.82 (2.02)	−0.60 (1.96)	35	26	40
Total hip (n=87)	0.77 (0.16)	−1.69 (1.31)	−0.72 (1.27)	26	45	29
Femoral neck (n=87)	0.65 (0.13)	−2.43 (1.31)	−0.93 (1.26)	48	38	14
Lumbar spine, L1–4 (n=87)	0.86 (0.13)	−1.74 (1.20)	−0.46 (1.18)	26	46	28

Table 3 Correlation coefficients (*r*) obtained by regression analyses of bone mineral density (BMD) (dependent variables) and demographic and disease related factors (independent variables). Only statistically significant variables are shown

	BMD, forearm		BMD, total hip		BMD, femoral neck		BMD, lumbar spine	
	r	p Value	*r*	p Value	*r*	p Value	*r*	p Value
Age (years)	–0.27	0.016			–0.28	0.008		
Height (cm)	0.35	0.001	0.27	0.012	0.28	0.008	0.26	0.016
Weight (kg)	0.41	<0.001	0.55	<0.001	0.49	<0.001	0.35	0.001
BMI (kg/m^2)	0.29	0.008	0.48	<0.001	0.40	<0.001	0.28	0.008
Disease duration (years)	–0.31	0.005						
Injected glucocorticosteroid (g)	–0.30	0.006	–0.35	0.001	–0.30	0.005		
Larsen score (0–5)	–0.44	<0.001	–0.46	<0.001	–0.39	<0.001		
HAQ (0–3)			–0.27	0.013	–0.29	0.007		
Haemoglobin (g/l)			0.25	0.020				
Il1β (pg/ml)	–0.22	0.046						
Il1β/IL1Ra	–0.27	0.016						
ICTP (ng/ml)	–0.27	0.023	–0.31	0.006	–0.28	0.015		
PICP (ng/ml)							–0.23	0.045
COMP (U/l)							0.28	0.010
BMD forearm (g/cm^2)			0.75	<0.001	0.72	<0.001	0.70	<0.001
BMD total hip (g/cm^2)	0.75	<0.001			0.93	<0.001	0.70	<0.001
BMD femoral neck (g/cm^2)	0.72	<0.001	0.93	<0.001			0.67	<0.001
BMD lumbar spine (g/cm^2)	0.70	<0.001	0.70	<0.001	0.67	<0.001		

BMI, body mass index; HAQ, Health Assessment Questionnaire; IL1β, interleukin 1β; Il1β/IL1Ra, interleukin 1β/interleukin 1 receptor antagonist; ICTP, carboxyterminal crosslinked telopeptide of type I collagen; PICP, carboxyterminal propeptide of type I procollagen; COMP, cartilage oligomeric matrix protein.

variables. The results changed slightly (R^2 decreased a little in the forearm, total hip, and femoral neck), but no additional variables were shown to be significant markers except for disease duration, which was shown be an important determinant of BMD in the lumbar spine. The R^2 value of the regression equation of BMD in the lumbar spine increased from 0.25 to 0.33.

Markers of joint destruction

The correlations between radiographic erosion score, according to the Larsen method, as dependent variable and the factors listed in table 1 and bone mass, as independent variables were examined by simple regression. Body weight, haemoglobin, IGF-I and BMD in the forearm, total hip, and femoral neck were negatively correlated with the erosion score, whereas disease duration, cumulative oral and injected glucocorticosteroid dose, risk group according to the HLA-DR4 subtype analyses, HAQ score, DAS28, ESR, CRP, IL6, sIL6R, ICTP, and COMP were positively correlated with the erosion score. Previous treatment with glucocorticosteroids for >3 months was connected with a higher erosion score (table 5). In the multiple regression analysis disease duration and CRP were found to be significantly associated with joint destruction (table 6).

Glucocorticosteroids

The cumulative doses of oral and injected glucocorticosteroids were calculated for each participant and were correlated with the variables listed in table 1 and BMD by simple and multiple linear stepwise regression analyses. In the multiple regression analysis the oral prednisolone dose was associated with the level of IL1Ra (unstandardised regression coefficient β=0.46, p<0.001), previous use of oral corticosteroids for at least three months (β=0.40, p<0.001), and Larsen score (β=0.21, p=0.014), R^2=0.54. The injected dose of glucocorticosteroids was connected with ICTP (β=0.33, p=0.003), BMD in the forearm (β=–0.24, p=0.029), DAS28 (β=0.24, p=0.032), and previous use of oral corticosteroids for at least three months (β=0.24, p=0.047), R^2=0.37.

DISCUSSION

This study showed that osteoporosis is a common finding; 56% of postmenopausal women with RA, not treated with

Table 4 Multiple stepwise regression analyses of bone mineral density (BMD) at different sites of measurements (dependent variables) and demographic and disease related variables (independent variables). The regression equation of BMD in the forearm was= $0.71–4.08\times10^{-2}\times$Larsen score$+2.90\times10^{-3}\times$weight (kg)$–6.57\times10^{-3}\times$age (years) and so on for the other sites

	Forearm			Total hip			Femoral neck			Lumbar spine, L1–4		
	0.71			0.53			0.83			0.62		
Control	β	SE	p Value	β	SE	p Value	β	SE	p Value	β	SE	p Value
Age (years)	-6.57×10^{-3}	0.002	0.002				-6.99×10^{-3}	0.002	0.005			
Weight (kg)	2.90×10^{-3}	0.001	0.001	4.93×10^{-3}	0.001	<0.001	4.14×10^{-3}	0.001	<0.001	3.25×10^{-3}	0.001	0.007
Injected corticosteroid (g)				-2.79×10^{-5}	<0.001	0.028						
Larsen score (0–5)	-4.08×10^{-2}	0.011	0.001	-3.71×10^{-2}	0.015	0.018	-3.75×10^{-2}	0.012	0.002			
PICP (ng/ml)										-9.92×10^{-4}	<0.001	0.006
COMP (U/l)										1.43×10^{-2}	0.005	0.005
R^2	0.38			0.44			0.37			0.25		

Beta values are unstandardised regression coefficients. The multiple R^2 is equal to the variance explained in the model. SE=standard error
PICP, carboxyterminal propeptide of type I procollagen; COMP, cartilage oligomeric matrix protein; Injected corticosteroid, cumulative injected glucocorticosteroid expressed as prednisolone

Table 5 Correlation coefficients (*r*) obtained by linear regression analyses of the Larsen score (dependent variable) and demographic and disease related factors (independent variables). Only statistically significant variables are shown

	r	p Value
Weight (kg)	–0.24	0.027
Disease duration (years)	0.50	<0.001
Previous treatment with glucocorticosteroids for >3 months*	0.31	0.004
Cumulative oral prednisolone (g)	0.38	<0.001
Cumulative injected glucocorticosteroid (g)	0.52	<0.001
Risk group (1–5)	0.24	0.037
HAQ (0–3)	0.46	<0.001
DAS 28	0.34	0.002
Haemoglobin (g/l)	–0.39	<0.001
ESR (mm/1st h)	0.51	<0.001
CRP (mg/l)	0.44	<0.001
IL6 (pg/ml)	0.40	<0.001
sIL6R (pg/ml)	0.28	0.012
IGF-I (ng/ml)	–0.23	0.049
ICTP (ng/ml)	0.54	<0.001
COMP (U/l)	0.26	0.020
BMD forearm (g/cm^2)	–0.44	<0.001
BMD total hip (g/cm^2)	–0.46	<0.001
BMD femoral neck (g/cm^2)	–0.39	<0.001

*Yes=2, no=1.
HAQ, Health Assessment Questionnaire; DAS28, 28 joint count disease activity score; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; IL6, interleukin 6, sIL6R, interleukin 6 soluble receptor; IGF-I, insulin-like growth factor-I; ICTP, carboxyterminal crosslinked telopeptide of type I collagen; COMP, cartilage oligomeric matrix protein; BMD, bone mineral density.

Table 6 Multiple stepwise regression analysis of radiological erosion score according to the Larsen method (dependent variable) and demographic and disease related variables (independent variables). The regression equation was: radiological erosion score=0.191+4.043×10^{-2}×disease duration (years)+2.265×10^{-2}×CRP (mg/l)

	Larsen score		
Constant	0.19		
	β	SE	p Value
Disease duration (years)	4.04×10^{-2}	0.007	<0.001
CRP (mg/l)	2.26×10^{-2}	0.005	<0.001
R^2	0.54		

β Values are unstandardised regression coefficients. The multiple R^2 is equal to the variance explained in the model. SE=standard error. CRP, C reactive protein.

bisphosphonates or HRT, had osteoporosis at one or more measured sites. Of the patients with RA, 48% had osteoporosis in the femoral neck and 26% in the lumbar spine. Corresponding figures for healthy postmenopausal Swedish women, 50–59 years old, are 7% and 13%, respectively.[25] Our results are in accordance with some previous studies,[12] whereas others have found a lower prevalence[7] in RA. Different rates might be explained by the disparate ways of recruiting the study group, and the diverse equipment for DXA with different reference populations, which may also influence the classification.[26 27]

The participants were later included in an HRT study; consequently there was a selection of patients enrolled. Data of 72 RA women not fulfilling the inclusion criteria were also recorded. No significant differences in the demographic and disease related variables were found between the included patients and the controls, except that more controls had previously been treated with glucocorticosteroids orally for >3 months and 54% were receiving HRT. Thus, it is not possible to generalise the results in this study to the whole population of postmenopausal women with RA attending rheumatology clinics. However, the clinical impression was that the patients enrolled represented ordinary postmenopausal women with RA attending our rheumatology clinics. No adjustment for multiple testing was done because most of the variables explored were significant at an extreme level, which could not be assumed to be falsely significant, and the remaining tested parameters were subsequently relatively few.

Whereas, some previous reports showed reduced bone mass at appendicular sites and the hip of patients with RA, they failed to demonstrate decreased bone mass in the lumbar spine.[2 3 7 13] The reason for such a discrepancy is unclear but might be due to incorrectly recorded increased bone mass owing to osteoarthritis and/or vertebral fractures or to a genuine predominance of bone loss in the hip compared with the spine. It has also been proposed that femoral BMD is relatively low compared with the spine owing to poor mobility,[3 4] which is in line with the present results displaying a negative correlation between HAQ and BMD in the femoral neck and total hip. In addition, HAQ was positively correlated with the Larsen score, also in accordance with previous findings in established RA.[28]

Low body weight is a potent risk factor for osteoporosis[29 30] and is associated with both reduced BMD[7 12 13] and fractures in RA.[2 31] Indeed, osteoporotic women in our study weighed almost 10 kg less than the non-osteoporotic controls (data not shown). Furthermore, weight was negatively correlated with the Larsen score, implying that thinness in itself is also associated with joint destruction. In the multiple regression analysis body weight was the strongest independent determinant of decreased BMD at all measurement sites. The connection between low body weight and osteoporosis after menopause may be due to the fact that most of the circulating oestrogen derived from androgens is converted to oestrogens, especially in fat tissue. Interestingly, we found significantly lower serum levels of oestradiol in the women with osteoporosis in the femoral neck than in the non-osteoporotic patients (data not shown). Also, fat tissue has a direct absorbing effect, protecting against fractures when a patient falls.

The use of glucocorticosteroids and their influence on BMD is widely debated. Most cross sectional studies agree that the cumulative dose of prednisone is an important determinant of osteopenia in RA.[12 29 32 33] However, longitudinal studies have given inconclusive results.[34 35] In our study we demonstrate the importance of considering the intra-articular and intramuscular cumulative dose of corticosteroids because there was a negative correlation between the total amount of injected corticosteroids and bone mass of the forearm, total hip, and femoral neck. In the multiple regression models, the total amount of injected corticosteroids was a marker of low bone mass in the total hip.

Some previous trials have shown a protective effect of prednisone on joint destruction in patients with early and active RA.[36 37] In retrospective studies the use of corticosteroids was associated with more erosive disease,[12 38] probably reflecting the non-random assignment to the drug. In the present study the cumulative oral and injected dose correlated positively with the Larsen score. However, the independent effect of corticosteroids on joint destruction as well as on bone mass is questionable as the use of corticosteroids may be related to more severe disease.

In this study the common use of corticosteroids seemed to be associated with more severe disease demonstrated by the associations between the high cumulative dose of oral prednisolone, on the one hand, and ILIRa and the Larsen score, on the other, and between the injected dose of glucocorticosteroids and ICTP, bone mass in the forearm, and DAS28. ILIRa, is produced in response to infection and

inflammation,[39] indicating a connection between oral corticosteroids and more active RA.

Localised bone loss in RA is thought to be a result of an increase in the number and activity of osteoclasts owing to an immune response. The proinflammatory cytokines, TNFα, IL1, and IL6 are raised in the synovial tissue in RA. IL1Ra competitively inhibits the effects of IL1. The cytokines stimulate osteoclasts directly and mostly by the RANKL/OPG pathway.[40 41] Interestingly, we found a clear association between joint destruction and signs of inflammation: high ESR, CRP, IL6, sIL6R, DAS28, and low haemoglobin, and in the multiple regression analysis CRP, besides long disease duration, was the strongest marker of joint damage. Low BMD was also to some extent connected with inflammation.

The generalised bone loss in RA is principally caused by increased osteoclast activation and the theory about a common mechanism for bone erosions and osteoporosis is becoming increasingly accepted. Martin *et al* found strong correlations between the Larsen score in the hand and the trabecular bone mass in the ultradistal radius and BMD in os calcis,[13] indicating that the same inflammatory mechanisms causing joint damage also affect BMD. In agreement, we found that the Larsen score was the strongest disease related determinant of bone mass in the forearm, total hip, and femoral neck

Biochemical markers of bone resorption have been shown to be raised[42 43] and connected with the disease activity in RA.[44] In this study bone resorption measured by ICTP was inversely correlated with BMD and positively with the Larsen score. There is also some evidence of increased bone turnover in RA.[42] In our study, PICP was a determinant of bone mass in the lumbar spine, probably reflecting a high bone turnover.

COMP, a major non-collagenous matrix protein, synthesised by chondrocytes and released from cartilage during the erosive process,[45] has been shown to be increased in serum at disease onset in patients with RA who developed marked joint destruction.[46] In another study, serum COMP was measured at study inclusion in early RA and correlated with the Larsen score at inclusion and after one year but failed to identify patients prone to small joint destruction after five years.[47] In patients with established RA, using another assay, we found a positive correlation between the, Larsen score and COMP. In contrast, low bone mass in the spine was associated with reduced COMP. An interpretation might be that because joint destruction is strongly connected with low bone mass, the cartilage in the joints of the most osteoporotic patients may be severely damaged and, consequently, the COMP level decreased.

To summarise, we demonstrate in this cross sectional study that 56% of the postmenopausal RA women not treated with HRT or bisphosphonate have osteoporosis. Body weight, disease duration, cumulative dose of injected corticosteroids, functional disability, laboratory signs of inflammation, and markers of bone resorption were common connections between osteoporosis and joint damage and demographic and disease related variables. BMD in the lumbar spine was less influenced by RA. Altogether, low bone mass was strongly associated with increasing age, low weight, and large joint damage, whereas raised CRP and long disease duration were the best determinants of a high Larsen score. We suggest that by treating RA more efficiently—by preventing joint destruction and inflammation—patients in the future will possibly suffer less from osteoporosis and its consequences. However this proposition can only validly be proved by a prospective study, comparing BMD and joint damage in patients receiving aggressive and less aggressive treatment.

ACKNOWLEDGEMENTS

Supported by grants from regional research sources from Västra Götaland, Novo Nordisk Research Foundation, Rune och Ulla Amlövs foundation for Rheumatology Research, the Research Foundation of Trygg-Hansa, the Swedish and Göteborg Association Against Rheumatism, Reumaforskningsfond Margareta, King Gustav V:s 80-years foundation, the Medical Society of Göteborg, and the Medical Faculty of Göteborg (LUA).

We are grateful to all patients in the study and we thank Laila Håkansson, Anna Jacobsson, Maud Pettersson, and Lena Svensson for their assistance with the patients and laboratory help, and Anders Oden for statistical advice.

Authors' affiliations

H Forsblad d'Elia, E Nordborg, H Carlsten, Department of Rheumatology and Inflammation Research, Göteborg University, Sweden
A Larsen, Department of Rheumatology, Kongsvinger, Norway
E Waltbrand, G Kvist, Department of Rheumatology, Borås, Sweden
D Mellström, Department of Geriatrics, Göteborg University, Sweden
T Saxne, Department of Rheumatology, University of Lund, Sweden
C Ohlsson, Department of Internal Medicine, Göteborg University, Sweden

REFERENCES

1 **Deodhar A**, Woolf A. Bone mass measurement and bone metabolism in rheumatoid arthritis: a review. Br J Rheumatol 1996;35:309–22.
2 **Verstraeten A**, Dequeker J. Vertebral and peripheral bone mineral content and fracture incidence in postmenopausal patients with rheumatoid arthritis: effect of low dose corticosteroids. Ann Rheum Dis 1986;45:852–7.
3 **Hall GM**, Spector TD, Griffin AJ, Jawad AS, Hall ML, Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum 1993;36:1510–16.
4 **Sambrook PN**, Eisman JA, Champion GD, Yeates MG, Pocock NA, Eberl S. Determinants of axial bone loss in rheumatoid arthritis. Arthritis Rheum 1987;30:721–8.
5 **Kroger H**, Honkanen R, Saarikoski S, Alhava E. Decreased axial bone mineral density in perimenopausal women with rheumatoid arthritis—a population based study. Ann Rheum Dis 1994;53:18–23.
6 **Sambrook PN**, Spector TD, Seeman E, Bellamy N, Buchanan RR, Duffy DL, *et al*. Osteoporosis in rheumatoid arthritis. A monozygotic co-twin control study. Arthritis Rheum 1995;38:806–9.
7 **Haugeberg G**, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. Arthritis Rheum 2000;43:522–30.
8 **Hooyman JR**, Melton LJ 3rd, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. A population-based study. Arthritis Rheum 1984;27:1353–61.
9 **Spector TD**, Hall GM, McCloskey EV, Kanis JA. Risk of vertebral fracture in women with rheumatoid arthritis. BMJ 1993;306:558.
10 **Gravallese EM**, Manning C, Tsay A, Naito A, Pan C, Amento E, *et al*. Synovial tissue in rheumatoid arthritis is a source of osteoclast differentiation factor. Arthritis Rheum 2000;43:250–8.
11 **Takayanagi H**, Iizuka H, Juji T, Nakagawa T, Yamamoto A, Miyazaki T, *et al*. Involvement of receptor activator of nuclear factor kappaB ligand/osteoclast differentiation factor in osteoclastogenesis from synoviocytes in rheumatoid arthritis. Arthritis Rheum 2000;43:259–69.
12 **Sinigaglia L**, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, *et al*. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. J Rheumatol 2000;27:2582–9.
13 **Martin JC**, Munro R, Campbell MK, Reid DM. Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. Br J Rheumatol 1997;36:43–9.
14 **Lufkin EG**, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW, *et al*. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992;117:1–9.
14a **Forsblad d'Elia H**, Larsen A, Mattsson L-A, Waltbrand E, Kvist G, Mellström D, *et al*. The impact of hormone replacement therapy on disease progression and bone mineral density in rheumatoid arthritis. J Rheumatol (in press).
15 **Arnett FC**, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
16 **Prevoo ML**, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
17 **Fries JF**, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
18 **Ekdahl C**, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. Use of a Swedish version of the Stanford Health Assessment Questionnaire. Scand J Rheumatol 1988;17:263–71.
19 **Kanis JA**, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994;9:1137–41.

20 **Larsen A**. How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in long-term studies. J Rheumatol 1995;22:1974–5.
21 **Wordsworth P**, Pile KD, Buckely JD, Lanchbury JS, Ollier B, Lathrop M, *et al*. HLA heterozygosity contributes to susceptibility to rheumatoid arthritis. Am J Hum Genet 1992;51:585–91.
22 **Weyand CM**, Hicok KC, Conn DL, Goronzy JJ. The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. Ann Intern Med 1992;117:801–6.
23 **Nepom GT**, Nepom BS. Prediction of susceptibility to rheumatoid arthritis by human leukocyte antigen genotyping. Rheum Dis Clin North Am 1992;18:785–92.
24 **Good P**. *Permutation tests*. New York: Springer, 2000.
25 **SBU**. Mätning av bentäthet; Blomberg and Janson Offsettryck, 1995.
26 **Ahmed AI**, Blake GM, Rymer JM, Fogelman I. Screening for osteopenia and osteoporosis: do the accepted normal ranges lead to overdiagnosis? Osteoporos Int 1997;7:432–8.
27 **Faulkner KG**, Roberts LA, McClung MR. Discrepancies in normative data between Lunar and Hologic DXA systems. Osteoporos Int 1996;6:432–6.
28 **Welsing PM**, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44:2009–17.
29 **Kroger H**, Tuppurainen M, Honkanen R, Alhava E, Saarikoski S. Bone mineral density and risk factors for osteoporosis—a population-based study of 1600 perimenopausal women. Calcif Tissue Int 1994;55:1–7.
30 **Landin-Wilhelmsen K**, Wilhelmsen L, Bengtsson BA. Postmenopausal osteoporosis is more related to hormonal aberrations than to lifestyle factors. Clin Endocrinol (Oxf) 1999;51:387–94.
31 **Michel BA**, Bloch DA, Wolfe F, Fries JF. Fractures in rheumatoid arthritis: an evaluation of associated risk factors. J Rheumatol 1993;20:1666–9.
32 **Dykman TR**, Gluck OS, Murphy WA, Hahn TJ, Hahn BH. Evaluation of factors associated with glucocorticoid-induced osteopenia in patients with rheumatic diseases. Arthritis Rheum 1985;28:361–8.
33 **Laan RF**, van Riel PL, van Erning LJ, Lemmens JA, Ruijs SH, van de Putte LB. Vertebral osteoporosis in rheumatoid arthritis patients: effect of low dose prednisone therapy. Br J Rheumatol 1992;31:91–6.
34 **Laan RF**, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. Ann Intern Med 1993;119:963–8.
35 **Sambrook PN**, Cohen ML, Eisman JA, Pocock NA, Champion GD, Yeates MG. Effects of low dose corticosteroids on bone mass in rheumatoid arthritis: a longitudinal study. Ann Rheum Dis 1989;48:535–8.
36 **Kirwan JR**. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med 1995;333:142–6.
37 **van Everdingen AA**, Jacobs JW, Siewertsz Van Reesema DR, Bijlsma JW. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002;136:1–12.
38 **Wolfe F**, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. Arthritis Rheum 1998;41:1571–82.
39 **Arend WP**, Gabay C. Physiologic role of interleukin-1 receptor antagonist. Arthritis Res 2000;2:245–8.
40 **Roux S**, Orcel P. Bone loss. Factors that regulate osteoclast differentiation: an update. Arthritis Res 2000;2:451–6.
41 **Goldring SR**, Gravallese EM. Pathogenesis of bone erosions in rheumatoid arthritis. Curr Opin Rheumatol 2000;12:195–9.
42 **Cortet B**, Flipo RM, Pigny P, Duquesnoy B, Boersma A, Marchandise X, *et al*. Is bone turnover a determinant of bone mass in rheumatoid arthritis? J Rheumatol 1998;25:2339–44.
43 **Gough A**, Sambrook P, Devlin J, Huissoon A, Njeh C, Robbins S, *et al*. Osteoclastic activation is the principal mechanism leading to secondary osteoporosis in rheumatoid arthritis. J Rheumatol 1998;25:1282–9.
44 **Gough AK**, Peel NF, Eastell R, Holder RL, Lilley J, Emery P. Excretion of pyridinium crosslinks correlates with disease activity and appendicular bone loss in early rheumatoid arthritis. Ann Rheum Dis 1994;53:14–17.
45 **Saxne T**, Heinegard D. Cartilage oligomeric matrix protein: a novel marker of cartilage turnover detectable in synovial fluid and blood. Br J Rheumatol 1992;31:583–91.
46 **Forslind K**, Eberhardt K, Jonsson A, Saxne T. Increased serum concentrations of cartilage oligomeric matrix protein. A prognostic marker in early rheumatoid arthritis. Br J Rheumatol 1992;31:593–8.
47 **Fex E**, Eberhardt K, Saxne T. Tissue-derived macromolecules and markers of inflammation in serum in early rheumatoid arthritis: relationship to development of joint destruction in hands and feet. Br J Rheumatol 1997;36:1161–5.