

Original article

Disease activity and severity in early inflammatory arthritis predict hand cortical bone loss

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Abstract

Objectives. To determine the influence of disease-related variables on hand cortical bone loss in women with early inflammatory arthritis (IA), and whether hand cortical bone mass predicts subsequent joint damage.

Method. Adults aged ≥ 16 years with recent onset of IA were recruited to the Norfolk Arthritis Register between 1990 and 1998, and followed prospectively. At baseline, patients had their joints examined for swelling and tenderness and had CRP and disease activity 28-joint assessment score (DAS-28) measured. Radiographs of the hands were performed in a subgroup of patients at Year 1 and at follow-up, which were assessed using digital X-ray radiogrammetry (DXR). They were also evaluated for the presence of erosions using Larsen's method. Linear mixed models were used to investigate whether disease-related factors predicted change in DXR–areal bone mineral density (BMD_a). We also evaluated whether DXR–BMD_a predicted the subsequent occurrence of erosive disease.

Results. Two hundred and four women, mean (s.d.) age 55.1 (14.0) years, were included. Median follow-up between radiographs was 4 years. The mean within-subject change in BMD_a was 0.024 g/cm² equivalent to 1% decline per year. After adjustment for age, height and weight, compared with those within the lower tertile for CRP, those in the upper tertile had greater subsequent loss of bone. This was true also for DAS-28 and Larsen score. Among those without erosions on the initial radiograph (121), DXR–BMD_a at baseline did not predict the new occurrence of erosions.

Conclusion. Increased disease activity and severity are associated with accelerated bone loss. However, lower BMD_a did not predict the new occurrence of erosive disease.

Key words: Inflammatory arthritis, Digital X-ray radiogrammetry, Norfolk Arthritis Register, Radiological erosions.

Introduction

Individuals with inflammatory arthritis (IA) are at increased risk of bone loss and fracture. The level of disease activity is linked with greater bone loss, as measured at the spine,

hip or hand using dual energy X-ray absorptiometry (DXA) [1–4].

Radiogrammetry, developed in the 1960s, was based on morphometric measurements of cortical bone width (metacarpal bones) on hand radiographs to provide an estimate of bone mass [5]. The method was widely used and inexpensive; however, with manual use of callipers for the measurement precision was limited [coefficient of variation (CV)% = 8–11%] [6]. Other X-ray-based absorptiometry methods (DXA and QCT) for quantitative assessment of the skeleton subsequently replaced radiogrammetry. However, over the past decade computer vision techniques [active shape/appearance models (ASM/AAM)] have been applied to the measurements [digital X-ray radiogrammetry (DXR) Pronosco A/S, HERLEV, Region Hovedstaden, Denmark] resulting in improved precision

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(CV = 0.6–1.0%) [7–11]. Areal bone mineral density (BMD_a) assessed using DXR has been shown to correlate well with central and peripheral DXA [12].

Hand radiographs are part of routine management of RA and IA, and therefore DXR provides a method for quantifying BMD_a in these patients. Data from cross-sectional studies of RA patients suggest that a reduction in DXR–BMD_a is associated with markers of disease severity [13–20]. Less is known about the influence of disease activity and functional variables with data from both cross-sectional and prospective studies providing inconsistent results [18, 20–23]. If hand bone loss using DXR is to be considered as an outcome measure or prognostic indicator of IA, it should be associated with measures of disease activity and severity.

We studied women recruited to the Norfolk Arthritis Register (NOAR), a unique primary care-based cohort of adults with recent onset of IA, in which information about disease activity is recorded in a standardized fashion. The aim of this analysis was to assess the validity of DXR as a research tool in patients with IA by determining the influence of disease-related variables on hand cortical bone loss in early IA. We also examined whether hand cortical bone mass can predict the subsequent development of erosive disease.

Methods

Patients

Patients were recruited from the NOAR, a primary care-based inception cohort of adults aged ≥ 16 years with early IA based in Norfolk, UK. Patients are included in the register if they have two or more swollen joints for a period of at least 4 weeks, with a symptom onset since 1 January 1990. Detailed methods for the study have been published previously [24]. All aspects of the study were approved by the Norwich Research Ethics Committee. All patients gave written informed consent before entering into the study.

Assessment

At baseline, patients were assessed by a research nurse using a structured questionnaire and completed the British version of the HAQ [25]. The nurse-administered questionnaire covered smoking, previous hormone therapy use and menopausal status. The nurse also examined the joints for swelling, tenderness and deformity. A blood sample was taken for the measurement of CRP and RF. Patients were followed prospectively including assessment at 5 years. Height and weight were measured in a standardized manner at 5 years.

Radiographs

The 1987 ACR classification criteria for RA were applied at the baseline and first-year visits [26]. Radiographs of the hands and feet were performed 1 year after the baseline assessment if patients satisfied the ACR criteria for RA or if the presence of erosions would enable them to satisfy these criteria [26]. Radiographs were performed at Year 5

on all subjects who consented, and then again at Year 10 if erosive change was present on the 5-year radiograph. Radiographs were independently scored by two observers using Larsen's method [27]. In 2005, hand radiographs from participants who had at least two sets of radiographs were analysed using DXR (Sectra Pronosco X-Posure system; Sectra Imtec AB, Linköping, Sweden). After digitization of the X-ray the narrowest parts of the shafts of the second, third and fourth metacarpals were identified and, for set lengths of these metacarpals (second = 2 cm; third = 1.8 cm and fourth = 1.6 cm), the cortical width, bone width, metacarpal index (MCI) and BMD (BMD_a g/cm²) were calculated automatically. Further details have been described previously [11]. The precision (hand analysis only) in this cohort ($n = 30$) with duplicate digitization and analysis was CV = 0.19% and standardized coefficient of variation (SCV) = 0.35%.

Analysis

The analysis was restricted to women with an onset of symptoms before 2000, an initial radiograph performed within 2 years of the baseline assessment and at least one follow-up radiograph. The relatively small number of men fulfilling these criteria precluded meaningful analysis. Using baseline joint counts, we calculated a (CRP-derived) disease activity 28-joint assessment score (DAS-28) [29]. Linear regression was used to determine the association between DXR and BMD_a assessed on the initial radiograph and the various arthritis and non-arthritis-related risk factors assessed at baseline, with DXR–BMD_a as the dependent variable and adjustments made for age, height and weight. Results are expressed as β -coefficients (g/cm²) and 95% CI. Linear mixed models were used to determine the impact of baseline arthritis and non-arthritis-related variables on the within-subject change in DXR–BMD_a (using serial radiographs) with the results expressed as mean change in DXR–BMD_a with time (g/cm²/year). Among patients, who were free from erosions on their initial radiograph, we used logistic regression to determine whether DXR–BMD_a predicted the occurrence of new erosions in the subsequent radiographs.

We explored (also using linear regression) whether DXR–BMD_a based on assessment of the initial radiograph predicted change in disease-related variables between Years 1 and 5. The changes in disease-related variables were logarithmically transformed if their distribution was skewed. Finally, we used Spearman's rank correlation coefficient to examine the correlation between change in DXR–BMD_a and change in disease-related factors between Years 1 and 5. Statistical analysis was performed using STATA v9.2 (Stata Corp, College Station, TX, USA, 2008).

Results

Subject characteristics

Two hundred and four women, mean (s.d.) age 55.1 (14.0) years, were included in the analysis. Mean

height was 1.6 m and weight 69.4 kg; 17.7% were current smokers; 45% were post-menopausal and of these, 13.0% reported taking HRT (Table 1). The median swollen joint count was 8 and tender joint count 8; 37% of patients had a positive RF and 81% satisfied the ACR criteria for RA at baseline (Table 2). With respect to the radiographs at Year 1, the mean (s.d.) Larsen score at Year 1 was 8.8 (11.8) and 39% of patients had radiological erosions.

DXR-BMD_a

One hundred and twenty-two had two films and 82 had three or more. The median time between first and follow-up radiographs was 4 years (interquartile range 3.8–4.4). Mean BMD_a on the initial radiograph was 0.527 and 0.499 g/cm² on the subsequent film. The mean within-subject change in BMD_a was -0.024 g/cm², an ~1% decline per year.

Determinants of BMD_a and change in BMD_a

Age at baseline was associated with a lower BMD_a at baseline (β -coefficient per 10 years = -0.035 ; 95% CI -0.041 , -0.029), see Fig. 1. Ever use of the oral contraceptive pill (OCP) was significantly associated with higher

BMD_a (β -coefficient = 0.024; 95% CI 0.004, 0.045) as was HRT use (β -coefficient = 0.020) although the CIs around the parameter estimates embraced unity. Parity and smoking were not linked with BMD_a. A higher swollen joint count was associated with lower BMD_a (upper vs lower tertile, β -coefficient = -0.028) (Table 3). Individuals satisfying the ACR criteria had a lower BMD_a than those who did not (β -coefficient = -0.028 ; 95% CI -0.050 , -0.007). BMD_a was lower in those with higher CRP, Larsen score, HAQ score and DAS-28 although the CIs around the parameter estimates embraced unity.

Those in the highest tertile of CRP had a greater rate of subsequent bone loss than those in the lowest tertile group (-0.007 vs -0.003 g/cm²/year) (Table 4). This was true also for DAS-28 (-0.005 vs -0.001 g/cm²/year) and Larsen score (-0.007 vs -0.004 g/cm²/year). None of the other arthritis-related variables predicted accelerated bone loss.

We then examined whether change in disease-related variables between Years 1 and 5 was associated with baseline DXR-BMD_a and also change in DXR-BMD_a between Years 1 and 5. Change in disease-related variables was not associated with either baseline DXR-BMD_a or change in DXR-BMD_a between Years 1 and 5. Change in DXR-BMD_a was similar in those taking steroids at Year 1 and/or Year 5 compared with those not taking steroids at either time point.

TABLE 1 Baseline demographic characteristics

Variable	n = 204
Age at interview, mean (s.d.), years	55.1 (14.0)
Height ^a , mean (s.d.), m	1.6 (0.1)
Weight ^a , mean (s.d.), kg	69.4 (13.2)
Age at natural menopause ^b , mean (s.d.), years	49.3 (4.5)
Post-menopausal, %	45.1
Current smoker, %	17.7
Ever taken OCP, %	43.6
Ever taken HRT ^b , %	13.0

^aHeight and weight were measured at the fifth anniversary visit. ^bOf the 45.1% women who were post-menopausal.

TABLE 2 Disease-related characteristics measured at baseline

Variable	n = 204
CRP, mean (s.d.), mg/l	19.7 (38.6)
DAS-28, mean (s.d.)	4.6 (1.3)
HAQ score (0–3), mean (s.d.)	1.1 (0.7)
Number of swollen joints (0–28), median (IQR)	8 (4–14)
Number of tender joints (0–28), median (IQR)	8 (3–15)
Number of both swollen and tender joints (0–28), median (IQR)	5 (1–9)
RF positive (titre $\geq 1/40$), %	36.9
Satisfied ACR RA criteria (4/7 definition), %	80.9
Currently taking steroids, %	8.9

DXR-BMD_a and joint damage

Among those without erosions on the initial radiograph ($n=121$), after adjusting for age at onset, height and weight, DXR-BMD_a did not predict the development of erosions (odds ratio/per s.d. change in DXR-BMD_a = 0.72; 95% CI = 0.4, 1.2). Mean (s.d.) Larsen score was 8.8 (11.8) on the first radiograph and 19.2 (22.2) at follow-up. DXR-BMD_a at baseline (expressed as a Z-score, with adjustments for age at onset, height, weight and baseline Larsen score) did not predict a change in Larsen score (after log transformation) during follow-up (β -coefficient = -0.18 ; 95% CI = -0.46 , 0.1).

Fig. 1 DXR-BMD_a at Year 1 by age.

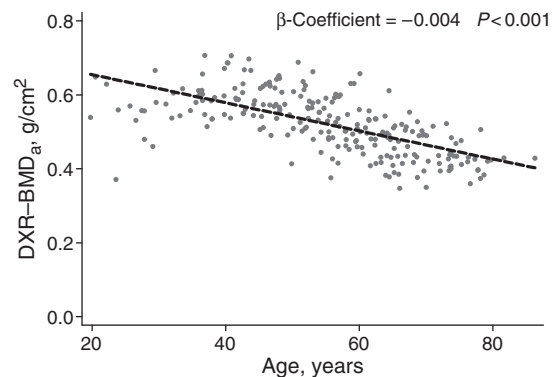


TABLE 3 Influence of disease-related factors on DXR-BMD_a at Year 1 in women

	DXR-BMD _a , g/cm ² β-coefficient ^a (95% CI)
Swollen joint count tertiles	
Lower	Referent
Mid	-0.022 (-0.042, -0.001)*
Upper	-0.028 (-0.047, -0.008)*
Tender joint count tertiles	
Lower	Referent
Mid	0.003 (-0.017, 0.023)
Upper	0.005 (-0.016, 0.026)
Both S + T joint count tertiles	
Lower	Referent
Mid	0.006 (-0.014, 0.026)
Upper	-0.010 (-0.031, 0.011)
CRP tertiles	
Lower	Referent
Mid	-0.003 (-0.028, 0.022)
Upper	-0.008 (-0.032, 0.017)
DAS-28	
<3.2	Referent
3.2–5.1	-0.007 (-0.038, 0.024)
>5.1	-0.004 (-0.037, 0.028)
HAQ score tertiles	
Lower	Referent
Mid	-0.018 (-0.039, 0.002)
Upper	-0.010 (-0.030, 0.010)
Larsen score at Year 1 tertiles	
Lower	Referent
Mid	-0.012 (-0.033, 0.010)
Upper	-0.018 (-0.038, 0.002)
Erosions at Year 1 (yes vs no)	-0.017 (-0.034, 0.001)
RF positive (yes vs no)	-0.004 (-0.024, 0.015)
Satisfy ACR criteria (yes vs no)	-0.028 (-0.050, -0.007)*
Current steroid use (yes vs no)	-0.006 (-0.037, 0.026)

^aAdjusted for age, height and weight. **P* < 0.05. S + T: swollen and tender.

Discussion

In this population-based inception cohort of women with IA, BMD_a assessed by DXR declined by 1% per year. Measures of disease activity including CRP and DAS-28, and disease severity predicted subsequent cortical bone loss in the hand. However, bone mass did not predict the development of erosive disease.

Our study used standard methods of clinical assessment. The patients were deliberately selected to include all cases of IA and not just those with RA. Indeed, we have shown that assigning criteria for RA is unstable in this setting during the first 5 years of disease [24]. Clinical assessment of disease activity is subject to measurement error; in an attempt to minimize this, all of the assessments were undertaken by trained research nurses, and formal assessment of inter- and intra-observer variation in assessment of joint counts was good. Any misclassification related to measurement error would tend to reduce the likelihood of finding significant associations. The hand

TABLE 4 Influence of disease-related factors on change in DXR-BMD_a in women

	Mean change _a (95% CI) in DXR-BMD _a , g/cm ² /year
Swollen joint count tertiles	
Lower	Ref: -0.005 (-0.007, -0.003)
Mid	-0.006 (-0.008, -0.004)
Upper	-0.004 (-0.006, -0.002)
Tender joint count tertiles	
Lower	Ref: -0.006 (-0.008, -0.004)
Mid	-0.004 (-0.006, -0.003)
Upper	-0.005 (-0.007, -0.003)
Both S + T joint count tertiles	
Lower	Ref: -0.005 (-0.007, -0.003)
Mid	-0.005 (-0.007, -0.003)
Upper	-0.005 (-0.007, -0.003)
CRP tertiles	
Lower	Ref: -0.003 (-0.005, -0.001)
Mid	-0.004 (-0.007, -0.002)
Upper	-0.007 (-0.010, -0.005)*
DAS-28	
<3.2	Ref: -0.001 (-0.004, 0.004)
3.2–5.1	-0.005 (-0.007, -0.003)*
>5.1	-0.005 (-0.008, -0.003)*
HAQ score tertiles	
Lower	Ref: -0.004 (-0.006, -0.003)
Mid	-0.004 (-0.006, -0.002)
Upper	-0.007 (-0.008, -0.005)
Larsen score at Year 1 tertiles	
Lower	Ref: -0.004 (-0.006, -0.002)
Mid	-0.003 (-0.005, -0.001)
Upper	-0.007 (-0.009, -0.005)*
Erosions at Year 1	
No	Ref: -0.004 (-0.006, -0.003)
Yes	-0.006 (-0.007, -0.004)
RF positive	
No	Ref: -0.004 (-0.006, -0.003)
Yes	-0.006 (-0.008, -0.004)
Satisfy ACR criteria	
No	Ref: -0.004 (-0.007, -0.001)
Yes	-0.005 (-0.006, -0.004)
Current steroid use	
No	Ref: -0.005 (-0.006, -0.004)
Yes	-0.006 (-0.010, -0.002)

^aAdjusted for age, height and weight. **P* < 0.05 compared with referent category. S + T: swollen and tender.

radiographs were assessed on the same radiogrammetry device and precision was good (standardized CV 0.35%). The procedure for taking hand radiographs was, however, not standardized. It is possible that differences between machines used may have contributed to some imprecision; however, the effect of any such imprecision would be to tend to reduce the chance of finding significant associations. Subjects who had undergone hand radiographs had more severe disease as determined by higher joint counts and CRP. Such selection factors are, however, unlikely to have influenced the strength of the

observed biological associations, which are based on an internal comparison of those who contributed data. DXR provides an estimate of cortical bone, which is less metabolically active than trabecular bone, and therefore potentially less responsive to change or metabolic effects. Bone loss using radiogrammetry has, however, been shown to be associated with clinically relevant outcomes, including fracture, in patients with RA and elderly women [13, 30]. Finally, our data were related to a cohort of Caucasian women living in the Norfolk (UK) area and so may not be applicable beyond this group.

Quantitative measurements by DXR from hand radiographs have been proposed as outcome measures and prognostic indicators of disease course in RA [17, 18, 22]. However, there are few data from prospective studies that examine the influence of disease-related factors, including disease activity and function on subsequent bone loss assessed using DXR. If bone loss is to be a valid outcome measure in IA, it should reflect changes in both disease severity and disease activity. Data from cross-sectional studies suggest an association between DXR-BMD_a and markers of disease severity including Larsen score [13–15, 17–19], Sharp scores [15, 20] and Steinbrocker scores [14, 15, 17]. Jensen (2004) in a 2-year prospective study reported accelerated bone loss in patients with erosive disease [21], whereas Guler-Yuksel (2009) reported no link with erosive disease at baseline, but change in erosive status from baseline to 1 year did predict subsequent bone loss [23]. Our data are broadly consistent with these findings.

In relation to disease activity, data from prospective studies provide discrepant results: with disease activity as assessed using DAS-28 linked with bone loss in one, but not another, study [22, 23]. Our data, which are based on a cohort of patients with relatively early disease confirm that active disease assessed using the DAS-28 and CRP is associated with accelerated bone loss. Change in disease activity was not correlated with change in DXR-BMD_a suggesting that radiogrammetry is not a marker of persistent disease activity. As with disease activity there are few prospective data examining the impact of function and the data are conflicting [22,23].

As expected, DXR-BMD_a decreased with age. DXR-BMD_a was associated with increased past use of OCP and HRT, though the latter failed to attain statistical significance, probably due to small numbers.

In a small pilot study of 24 RA patients, change in DXR-BMD_a between baseline and Year 1 predicted erosive disease at 4 years [31]. In a larger study, based on the European Research on Incapacitating Disease and Social Support (EURIDISS) cohort, bone loss in the first year was associated with progressive joint damage assessed by the Sharp score at 5 and 10 years [32]. In contrast to these observations, our study suggests that bone mass assessed at a single time point is unrelated to progressive joint damage. It may be that serial radiographs are required to provide an estimation of change in bone mass to predict worsening joint damage, and measurement at a single time point is not predictive of joint

damage. Alternatively, differences in the study design/populations sampled may partly explain these negative findings. We also found no evidence that bone mass as assessed by DXR-BMD_a assessed at a single time point was associated with the subsequent increase in disease activity or impaired function suggesting that it is not a marker of disease evolution.

In conclusion, DXR-BMD_a is a simple, sensitive and precise method of detecting change in hand cortical bone mass in women with early IA. Increased disease activity and severity are associated with accelerated bone loss, supporting the role of DXR as a research tool, not only in new studies but also retrospectively as hand radiographs are an integral part of disease management in patients with IA.

Rheumatology key messages

- DXR is a sensitive method of detecting change in hand cortical BMD_a.
- Increased disease activity and severity are associated with bone loss.
- Reduced BMD_a did not predict the new occurrence of erosive disease.

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