EXTENDED REPORT

Assessing periarticular bone mineral density in patients with early psoriatic arthritis or rheumatoid arthritis

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Osteoporosis is an important feature of rheumatoid arthritis (RA), and may be generalised or localised around inflamed joints.^{1,2} Periarticular osteoporosis has been considered an important early radiological feature of RA.³ The mechanisms underlying periarticular bone loss are not fully understood, but include (a) release of bone resorbing cytokines from the inflamed synovium, (b) increased vascularity, and (c) immobility of affected joints.^{2,4} In clinical practice, rheumatologists and radiologists refer to periarticular osteoporosis that is visible on plain radiographs of the hands. However, this method is unreliable and insensitive, as over one third of bone needs to be lost before it can be detected on plain x ray film.⁵

Since its introduction in the late 1980s, dual energy x ray absorptiometry (DEXA) has emerged as the gold standard for assessment of bone mineral density (BMD). Some studies have used DEXA to record global measurements of hand BMD in patients with early RA.^{6–9} They confirmed that bone loss occurs early and is greater in patients with active disease.^{6,7} Only two studies used DEXA to make detailed measurements of periarticular BMD around the finger joints of patients with RA¹⁰ and inflammatory arthropathies.¹¹

Inflammation of the finger joints commonly occurs in patients with psoriatic arthritis (PsA). It might therefore be expected that patients with PsA would also exhibit periarticular bone loss. Interpreting the appearances on plain radiographs, previous authors have disagreed as to whether periarticular osteoporosis is a feature of PsA.^{12–15} Similar disagreement existed when more sensitive techniques were used to measure BMD.^{16–18} This may be due to the tendency towards

Background: Periarticular osteoporosis is an early finding in the hands of patients with rheumatoid arthritis (RA), due to release of bone resorbing cytokines from the inflamed synovium. There has been disagreement as to whether periarticular bone loss occurs in psoriatic arthritis (PsA). Bone mineral density (BMD) can now be measured accurately using dual energy x ray absorptiometry (DEXA). Recently, DEXA has been used to measure periarticular BMD at predefined regions of interest (ROIs) around the joints.

Objectives: Firstly, to compare periarticular BMD around the finger joints of patients with early RA or PsA. Secondly, to determine whether periarticular bone loss is related to joint inflammation and radiological erosions in RA and PsA.

Methods: Seventeen patients with RA and 15 with PsA were recruited, all with disease duration of less than five years. All finger joints were examined by one person for swelling, or tenderness, or both. Hand radiographs were scored for the presence of erosions. Periarticular BMD was measured at 10 predetermined ROIs using a Hologic QDA-4500A fan-beam densitometer.

Results: Patients with PsA were less likely to be positive for rheumatoid factor (RF) (13% v 94%) and more likely to be men (60% v 23%) than patients with RA. There were no other clinical differences between patients with RA or PsA. Patients with RA had significantly lower BMD at each of the ROIs than those with PsA ($p < 0.05$). However, these differences disappeared after adjusting for age and sex. Among patients with RA, those with a higher total number of swollen and/or tender hand joints had significantly lower periarticular BMD at the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. No such association was found for patients with PsA.

Conclusions: In early disease, periarticular bone loss occurred both in patients with RA and those with PsA. Among patients with RA, periarticular osteoporosis was related to measures of joint inflammation. There was no association between joint inflammation and periarticular bone loss in patients with PsA, which lends support to the hypothesis that the primary site of inflammation in PsA is extrasynovial.

proliferative new bone formation which occurs in patients with established PsA. No previous studies have recorded detailed measurements of periarticular BMD using DEXA in patients with early PsA.

In this study we compared periarticular BMD in patients with early (<five years) PsA or RA using detailed DEXA measurements of BMD around the finger joints. We have also explored the association of periarticular bone loss with local joint inflammation and erosion in the two patient groups.

METHODS

Patients

The study population was recruited from three teaching hospitals around Manchester, UK. All patients had a clinical diagnosis of RA or PsA made by a consultant rheumatologist and a disease duration (from first onset of symptoms) of less than five years. Patients were included if they had current or previous soft tissue swelling of at least one of the hand distal interphalangeal joints (DIPs), proximal interphalangeal joints (PIPs), or metacarpophalangeal joints (MCPs). Informed consent was obtained. The final study population comprised 15

Abbreviations: ANOVA, analysis of variance; BMD, bone mineral density; CV, coefficient of variation; DEXA, dual energy x ray absorptiometry; DIPs, distal interphalangeal joints; MCPs, metacarpophalangeal joints; PIPs, proximal interphalangeal joints; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; ROIs, regions of interest; SPA, single photon absorptiometry; TNF, tumour necrosis factor

Figure 1 Hand DEXA measurements using the Hologic QDA-4500A densitometer.

patients with PsA and 17 patients with RA. Sample size was calculated with reference to recent data for periarticular BMD in patients with early RA.¹⁰ Our sample size provided 80% power ($\alpha=0.05$) to detect a minimum mean BMD difference of 0.05 g/cm^2 between patients with RA or PsA.

Clinical assessment

All patients were examined by one of us (BJH). The diagnosis was confirmed by clinical assessment and by reference to the

case notes. Eight DIPs, 10 PIPs, and 10 MCPs were examined for tenderness, soft tissue swelling, or both (ascertained by direct palpation around the joint line). Rheumatoid factor (RF) was classified as being positive if the patient had an RF titre of 1/40 or more at any time since the onset of disease.

Radiological assessment

Plain radiographs of the hands were taken within four weeks of the clinical assessment. Eight DIPs, 10 PIPs, and 10 MCPs were scored for the presence of erosions. The films were scored by three of us (BJH, CEH, and ALH) working independently. In cases of disagreement as to whether a joint was eroded or not, a consensus decision was made.

Measurements of DEXA

The BMD was measured using a Hologic QDA-4500A bone densitometer (fig 1). The software for analysis was modified to record hand BMD according to the method of Pye and Law using the RAT protocol developed for small animal work.¹⁹ One person (JA) measured BMD (g/cm^2) at 10 predetermined regions of interest (ROIs) from the second, third, and fourth fingers of the non-dominant hand. Figure 2 illustrates these 10 ROIs only for the third finger.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (release 9.0.1) and STATA for Windows 95 (version 4.0).

Reproducibility of the BMD measurements

The reproducibility (precision) of the technique was assessed by taking four repeat measurements at each ROI for a subset of 10 patients. Reproducibility was assessed using the coefficient of variation (CV), where $\text{CV}(\%) = (\text{standard deviation}/\text{mean}) \times 100$. The CV was calculated from repeated measurements using a one way analysis of variance (ANOVA).

Figure 2 Predetermined regions of interest (ROIs) for BMD measurements taken from the non-dominant hand. Only regions from the third finger are shown.

Table 1 Clinical and demographic characteristics of patients with RA or PsA

	RA (n=17)	PsA (n=15)	Difference, % (95% CI)
Age (years), median (range)	51 (21–73)	53 (27–71)	p=0.53*
Males, n (%)	4 (23)	9 (60)	–37 (–70 to –5)
Disease duration (months), median (range)	31 (7–60)	27 (1–59)	p=0.82*
Ever RF positive, n (%)	16 (94)	2 (13)	81 (62 to 100)
No of swollen hand joints, median (range)	2 (0–8)	1 (0–6)	p=0.07*
No of tender hand joints, median (range)	0 (0–9)	1 (0–14)	p=0.43*
Erosions in hand joints, n (%)	6 (35)	7 (47)	–12 (–47 to 23)
No of eroded hand joints, median (range)	0 (0–4)	0 (0–13)	p=0.74*

*Mann-Whitney U test.

Table 2 Comparison of periarticular BMD in patients with RA or PsA

	RA (n=17) BMD (g/cm ²): mean (SD)	PsA (n=15) BMD (g/cm ²): mean (SD)	Difference p value* (unadjusted)	Difference p value† (adjusted for age and sex)
ROI 1	0.173 (0.05)	0.222 (0.05)	0.01	0.02
ROI 2	0.317 (0.07)	0.379 (0.07)	0.02	0.11
ROI 3	0.272 (0.07)	0.341 (0.06)	0.01	0.06
ROI 4	0.399 (0.10)	0.463 (0.08)	0.04	0.42
ROI 5	0.284 (0.07)	0.352 (0.06)	0.01	0.04
ROI 6	0.263 (0.08)	0.343 (0.09)	0.01	0.07
ROI 7	0.227 (0.04)	0.266 (0.04)	0.01	0.09
ROI 8	0.292 (0.06)	0.339 (0.05)	0.03	0.26
ROI 9	0.255 (0.06)	0.315 (0.06)	0.01	0.05
ROI 10	0.417 (0.09)	0.474 (0.06)	0.04	0.27
Ratio of BMD in ROI 10 to ROI 7	1.626 (0.26)	1.515 (0.19)	0.18	0.13

*Student's *t* test for independent samples; †adjusted for age and sex using multiple linear regression.

Comparison of periarticular BMD in patients with RA or PsA

The mean BMD at each of the 10 ROIs was compared in patients with RA or PsA using Student's *t* test for independent samples. To determine whether differences in BMD between patients with RA or PsA were due to differences in age and sex between the two groups of patients we used multiple linear regression techniques. The dependent variable was periarticular BMD, with age, sex, and disease status (RA or PsA) added as independent (predictor) variables. For simplicity, the results were expressed as *p* values which relate to the independent association of disease subtype with periarticular BMD, after adjusting for age and sex.

Association of BMD with disease activity/severity

Multiple linear regression was also used to examine the association of periarticular BMD with the following disease activity/severity measures: (a) total number of swollen hand joints; (b) total number of tender hand joints; (c) erosive status; and (d) total number of eroded joints. For this analysis we used BMD measured around the MCPs PIPs, and DIPs (fig 2, ROIs 7–9). Age and sex were entered into the regression model as covariates. Separate analyses were conducted for patients with RA and those with PsA. The results were expressed as the regression coefficients (B) with their associated *p* values.

RESULTS

Clinical and demographic data

Table 1 illustrates the clinical and demographic characteristics of the study population. The median age of the patients was 52 years, and median disease duration 31 months, with no differences between patients with RA and those with PsA. As expected, patients with PsA were more likely to be men, and less likely to be RF positive. However, the two groups of patients had similar joint inflammation and erosion. Of the 17 patients with RA, five (29%) had ever taken oral corticosteroids for more than three months, compared with two of the 15 (13%) patients with PsA. Only two of the patients with

RA and one of the patients with PsA had ever had steroid injections into the small finger joints.

As reported in the methods, periarticular BMD was measured at 10 ROIs for the second, third, and fourth fingers of the non-dominant hand. The results obtained from the middle finger were no different from those at the second and fourth fingers. Therefore, for simplicity, only the results from the third (middle) finger are reported in this paper.

Reproducibility of the BMD measurements

The reproducibility (CV) at ROIs 1 to 6 was as follows: ROI 6 (3.4%), ROI 5 (3.9%), ROI 4 (3.9%), ROI 3 (3.5%), ROI 2 (4.5%), ROI 1 (6.6%). Reproducibility was better at ROIs 7–9, where BMD measurements incorporating the whole joint were taken: ROI 9 (1.2%), ROI 8 (1.6%), and ROI 7 (0.9%).

Comparison of periarticular BMD in patients with RA or PsA

Table 2 gives the mean BMD measurements at each of the ROIs for patients with RA or PsA. Patients with RA had significantly lower BMD at each of the ROIs than the patients with PsA. Given that patients with PsA were more likely to be men and that men had higher overall BMD, we adjusted the results for age and sex using multiple linear regression. After adjustment, most of these differences were no longer significant. We then explored whether the degree of periarticular bone loss differed between patients with RA and those with PsA. The degree of periarticular bone loss was assessed as the ratio of BMD measured at the diaphysis of the proximal phalanx (fig 2, ROI 10) to BMD measured at the MCP (fig 2, ROI 9). We found no difference between the degree of periarticular bone between RA and PsA, either unadjusted (*p*=0.18) or adjusted for age and sex (*p*=0.13).

Association of periarticular BMD with disease activity/severity

Table 3 illustrates the association between periarticular BMD (measured around the joints at ROIs 7–9) and overall

Table 3 Association of periarticular BMD with disease activity/severity

	Periarticular BMD in patients with RA			Periarticular BMD in patients with PsA		
	MCP joint (ROI 9)	PIP joint (ROI 8)	DIP joint (ROI 7)	MCP joint (ROI 9)	PIP joint (ROI 8)	DIP joint (ROI 7)
Total number of swollen hand joints	B=-0.01 p=0.01	B=-0.01 p=0.03	B=-0.01 p=0.33	B=-0.01 p=0.61	B=0.01 p=0.45	B=0.01 p=0.85
Total number of tender hand joints	B=-0.01 p=0.03	B=-0.01 p=0.04	B=-0.01 p=0.11	B=-0.01 p=0.33	B=-0.01 p=0.50	B=-0.01 p=0.42
Hand erosions (yes/no)	B=-0.04 p=0.26	B=-0.05 p=0.11	B=-0.03 p=0.21	B=0.03 p=0.61	B=0.01 p=0.75	B=0.02 p=0.59
Total number of eroded hand joints	B<0.01 p=0.85	B<-0.01 p=0.59	B<-0.01 p=0.71	B<0.01 p=0.58	B<0.01 p=0.09	B<0.01 p=0.01

B=regression coefficients obtained using multiple linear regression, adjusting for age and sex.

measures of hand joint inflammation and erosion. Among patients with RA, those with higher numbers of swollen or tender hand joints had significantly lower levels of periarticular BMD at the MCP and PIP. However, there was no such association for patients with PsA. There was no association between BMD measured at the diaphysis (ROI 10) and disease activity/severity (data not shown). There was no consistent association between periarticular BMD and erosive status in patients with RA or PsA. There were insufficient numbers to permit meaningful analyses of the association between periarticular BMD and joint swelling/tenderness/erosion within individual joints.

DISCUSSION

In this study, we have shown that DEXA can be used to measure periarticular BMD at specified ROIs around the joints of patients with early inflammatory arthritis. We found that periarticular BMD was significantly lower among patients with RA compared with those with PsA. However, when we examined the degree of periarticular bone osteoporosis (defined as the ratio diaphyseal BMD:MCP BMD) then patients with RA and those with PsA had similar levels of periarticular bone loss. One possible explanation for these findings is that patients with RA are more likely to have generalised osteoporosis, which will be reflected in lower absolute (but not relative) periarticular BMD measurements. In addition, patients with PsA are more likely to be men, which will raise overall BMD values. This may explain the fact that there was little difference in periarticular BMD measurements after adjusting for age and sex.

This is the first study to assess periarticular BMD using detailed DEXA measurements in patients with early PsA. One previous study, as yet only reported in abstract form, assessed periarticular BMD in patients with various inflammatory arthropathies, whose disease duration was not specified.¹¹ These authors also found that periarticular bone loss occurred in patients with PsA. That study had the advantage of including a control group of normal patients. We did not include a control group in our study, which would have been helpful to strengthen our suggestion that periarticular bone loss also occurs in PsA. Interpreting plain radiographs, Wright noted that periarticular osteoporosis occurred commonly in patients with PsA¹³ whereas Avila *et al* concluded that it was uncommon.¹² Resnick stated that "periarticular... osteoporosis is not a feature..."¹⁴ and later Resnick and Niwayama reported that "Osteoporosis is not a prominent feature of PsA, although it may be demonstrated in early phases of the disease."¹⁵ Similar disagreements exist when more sensitive techniques are employed. For example, Reid *et al* reported that BMD in 12 patients with PsA (assessed by metacarpal index) was not different from controls.¹⁶ Whereas Cooper *et al*, using single photon absorptiometry (SPA) measurements of the distal

forearm, noted bone loss in both RA and PsA, suggesting their patients had more active disease than those of Reid *et al*.¹⁷

By contrast with RA, few studies have investigated generalised osteoporosis in PsA. Recently, Frediani *et al* found that patients with PsA (n=186) had lower BMD than healthy subjects.¹⁸ Hein *et al* reported high bone turnover as judged by excretion of collagen cross links in 99 patients with PsA compared with controls.²⁰ However, Nolla *et al* found no difference in BMD measured at the spine and femoral neck in 52 patients with active peripheral PsA compared with controls.²¹

The pathogenesis of periarticular osteopenia is not fully understood. Most authors suggest that it is due to the release of bone resorbing cytokines from the inflamed synovium, including prostaglandin E₂, osteoclast activating factor, tumour necrosis factor (TNF), and interleukin 1.²²⁻²⁶ Bone resorbing cytokines (including TNF α) are also released in patients with PsA. Therefore our finding of periarticular bone loss in patients with early PsA is not surprising. However, among patients with established disease there is a tendency to increased bony proliferation. This is reflected radiologically by bony sclerosis (including "ivory phalanx"), periostitis, and "whiskering" around bony erosions. This contrasts with the marked bone loss which occurs in patients with established RA. Therefore the presence of periarticular osteoporosis may distinguish patients with established (but not early) RA or PsA. In addition, the disease course may be milder in PsA with less synovitis and consequent bone loss.

Increased vascularity around the joints has been suggested as an additional contributor to periarticular bone loss.²² Jevtic *et al* examined the prevalence of bone marrow oedema on NMR scans (reflecting hyperaemia) in 16 patients with RA and 16 with seronegative arthropathies.²⁷ However, only two patients had bone marrow oedema (one with reactive arthritis and one with RA), neither of whom had periarticular osteopenia on radiography. Recently, Backhaus *et al* found no correlation between periarticular osteoporosis on radiography and enhancement on NMR in 60 patients with various types of inflammatory arthritis.²⁸ These findings lend doubt to the contribution of local hyperaemia to periarticular osteoporosis.

Our results are in agreement with others who also found that patients with early RA with more active disease had more marked periarticular bone loss.^{6-7, 29} By contrast, there are no data for patients with PsA. In our study, we found no association between the number of swollen/tender hand joints and periarticular BMD. This may lend support to the recently proposed hypothesis that the primary site of inflammation in PsA is extrasynovial.³⁰ We found no important association between periarticular BMD and radiological damage in RA or PsA.

Although we carefully collected a large amount of data on individual cases, we only examined a relatively few patients. This was partly due to the difficulty in recruiting patients with

recent onset PsA. The incidence of PsA in Norfolk, UK is between 3.4–3.6 cases/100 000/year.³¹ Given that these figures relate to patients with coexistent inflammatory arthritis and psoriasis presenting to primary care, the incidence of patients with a clinical diagnosis of PsA in a rheumatology clinic is likely to be much lower than this. However, despite this, we had at least 80% power to answer our primary question of whether there is a difference in periarticular bone loss between patients with early RA and PsA. In this study, for practical reasons, we included patients with a disease duration of up to five years. Ideally, we would like to have studied patients as closely as possible to disease onset. At this very early stage of disease, we hypothesise that patients with RA and those with PsA would be even more similar with respect to hand BMD. However, this would need to be confirmed in a separate study. Our findings with respect to the association between measures of disease activity and periarticular BMD are interesting, but need to be confirmed in a larger patient sample.

The precision estimates (CV) are naturally less than would be obtained by measuring BMD in a larger area such as the whole hand. At ROIs 1–6, the CV ranged from 3.4% to 6.6%. However, when measurements of BMD were taken that included the whole joint (ROIs 6–9), we obtained better estimates of precision (0.9% to 1.6%). Interestingly, our precision estimates are very similar to those reported by Alenfeld *et al.*¹⁰ Given the recent interest in early suppression of disease before erosive damage has occurred, this technique may prove useful for assessing treatment efficacy in clinical trials. However, the relative lack of precision in comparison with global measures of hand BMD may hamper this. Other techniques for measuring periarticular BMD are being evaluated, including quantitative ultrasound³² and radiogrammetry.³³

In summary, this is the first study to perform detailed measurements of periarticular BMD in patients with early inflammatory arthritis. We have suggested that periarticular bone loss occurs in patients with PsA, but that overall BMD values are higher than in patients with RA. By contrast with RA, there was no association between the number of swollen/tender joints and periarticular bone loss in patients with PsA. These findings raise interesting questions in relation to the similarities and differences in disease pathogenesis.

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