Concise report

Striking difference of periarticular bone density change in early psoriatic arthritis and rheumatoid arthritis following anti-rheumatic treatment as measured by digital X-ray radiogrammetry

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Abstract

Objectives. To examine changes in hand BMD as measured by digital X-ray radiogrammetry (DXR-BMD) in early PsA compared with RA patients prior to and 3 and 12 months after introducing an antirheumatic treatment. Further, to identify predictors for hand bone loss at the time of disease presentation.

Methods. Recent-onset, active, treatment-naıve patients were recruited. Clinical assessment, hand X-rays and DXR were obtained at 0, 3 and 12 months. Mean DXR-BMD for both hands and changes in DXR-BMD (mg/cm²/month) were compared between the two groups. We compared baseline disease characteristics of patients with normal hand DXR-BMD with those with bone loss. Logistic regression analyses were performed to identify predictors of hand BMD loss.

Results. A total of 64 patients were included. Hand DXR-BMD decreased in RA throughout the study (P = 0.043). Changes in periarticular bone density over 12 months differed between PsA and RA (P = 0.001). Hand bone loss at 3 months was associated with elevated BMI [odds ratio (OR) = 3.59, P = 0.041] and heavier alcohol intake (OR = 1.13, P = 0.035). Diagnosis of RA (OR = 57.48, P = 0.008), heavier alcohol intake (OR = 1.27, P = 0.012) and higher swollen joint count (SJC28) (OR = 1.5, P = 0.036) were independent predictors for hand bone loss in the first year.

Conclusion. Following treatment, we found ongoing hand bone loss in RA and unchanged periarticular bone density in PsA, supporting the hypothesis that different pathomechanisms are involved in hand bone remodelling in PsA. Presence of RA, heavier alcohol intake and higher SJC were identified as independent predictors for hand bone loss over 1 year.

Key words: psoriatic arthritis, rheumatoid arthritis, periarticular bone, alcohol, digital X-ray radiogrammetry

Rheumatology key messages

- There is periarticular bone loss in early RA but not in PsA.
- Presence of RA, heavier alcohol intake and higher SJC are predictors for early hand bone loss.
- Alcohol may have a negative effect on periarticular bone in inflammatory arthritis.

Introduction

PsA and RA are chronic inflammatory arthropathies characterized by bone destruction. Inflammation is the key trigger for local bone erosions affecting the juxta-articular cortical bone, which is in direct contact with the inflamed synovium, and it induces resorption of periarticular bone close to affected joints. PsA is also characterized by
inflammation at enthesial sites, where bone is directly exposed to inflammatory tissue [1]. Despite PsA and RA sharing similar pathophysiological concepts, there are important differences in the anatomical localization of inflammatory lesions and in periarticular bone changes [2]. While RA is considered the prototype of a destructive arthritis with only few signs of repair, PsA combines features of bone erosions and new bone formation [3]. High-resolution peripheral QCT (HR-pQCT) imaging showed that, in RA, erosions are dominantly at the radial sites of the joints and are U-shaped. In PsA, erosions are more evenly distributed, smaller and \( \Omega \) or tubule-shaped. Osteophytes are increased in number and extent in PsA compared with RA, suggesting that bone-repairing mechanisms may be more active in PsA [2].

Periarticular bone loss may precede the development of erosions; therefore, its recognition at an early stage is essential [4]. It has been suggested that digital X-ray radiography (DXR) is a sensitive method for detecting and monitoring cortical osteoporosis in both early and late stages of RA and that it is superior to DXA as an outcome measure [5–7]. Another advantage of this technique is that the analysis of cortical bone loss is based on hand radiographs, which are routinely obtained in clinical practice. Previous research in early RA has shown that metacarpal BMD loss as measured by DXR is associated with disease activity, and BMD loss in the first year after diagnosis is predictive of radiologic progression up to 20 years later [8–11].

Far less is known about periarticular bone changes in early PsA. Hand bone loss in PsA as measured by DXR was studied in only one clinical trial, and no study to date has compared changes in cortical bone mineral density of RA and PsA using DXR [12]. Therefore, our primary objective was to assess changes in hand BMD as measured by DXR (DXR-BMD) in early, treatment-naïve PsA patients compared with RA prior to and 3 and 12 months after introducing an antirheumatic drug. Our secondary objective was to identify predictors for early hand bone loss at the time of disease presentation in PsA and RA.

Methods

Patients and study design

Recent-onset (<12 months), treatment naïve PsA and RA patients with active joint inflammation, aged 18–80 years were enrolled consecutively. PsA patients fulfilled the CASPAR criteria and patients with RA met the 2010 ACR/EULAR classification criteria for RA [1]. The use of a stable dose of steroids <10 mg/day was permitted. Informed, written consent was obtained according to the Declaration of Helsinki. The study was approved by the St. Vincent’s Healthcare Group Ethics and Medical Research Committee.

Demographic and clinical variables

Clinical assessments were performed at baseline and at 3 (n = 60) and 12 (n = 58) months. Demographic parameters, physicians-assessed and patients’ self-reported clinical data were collected at each visit. BMI was calculated and was further divided into normal (<25 kg/m\(^2\)) and overweight/obese (\( \geq 25 \) kg/m\(^2\)) categories. Laboratory assessments included a recording of antibodies against CCPs (aCCPs), RF positivity, ESR and CRP.

Radiological scoring

X-rays of hands and feet obtained at 0, 3 and 12 months were read by a radiologist blinded to the patients’ characteristics. For all patients, the Sharp–van der Heijde Modified Scoring Method for PsA was used. Erosion and joint space narrowing scores were calculated and added up for the total score (mSHS). X-rays from PsA patients were also scored for proliferation according to the PsA Ratingen Score [13].

Hand DXR measurements

DXR was used to measure hand BMD by analysing the cortical thickness of the second, third and fourth metacarpals on the same digital hand X-rays scored for radiographic joint damage. The DXR-BMD technique (Sectra, Sweden) has been described in detail previously [10]. To achieve better precision, mean DXR-BMD (mg/cm\(^2\)) values of both hands were analysed. Changes in DXR-BMD (mg/cm\(^2\)/month) were compared between the two groups at the three time points and were stratified into three subgroups based on previously established cut-offs by the manufacturer (dxr-online.com/ReportsWebTool/ManualChange.aspx): normal, moderately and highly elevated BMD loss (<0.25, \( \geq 0.25 \) and >2.5 mg/cm\(^2\)/month, respectively) [6].

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 20.0. Differences between PsA and RA in response of clinical measures to treatment were compared using the Mann–Whitney U test. Qualitative variables were compared by chi-square test, and the independent sample t test and the Mann–Whitney U test were used to compare quantitative variables. Logistic regression analyses were used to identify demographic and disease-related factors associated with hand BMD loss. P < 0.05 was considered as statistically significant.

Results

Demographic and clinical characteristics of PsA and RA patients

Results are summarized in Table 1. We recruited 64 patients: 32 PsA and 32 RA. The clinical subtypes of the PsA patients were symmetrical polyarthritis (n = 17) and asymmetrical oligoarthritis (n = 15); two patients had axial involvement. ESR, CRP, TJC, SJC and DAS28-CRP were significantly higher in RA compared with in PsA (Table 1).

Sixty-one patients (29 PsA and 32 RA) were commenced on a synthetic (s)DMARD therapy at baseline, the majority (29 PsA and 30 RA) starting MTX. Three PsA patients with fertility concerns were commenced on TNF inhibitor (TNFi) monotherapy. In each group, 4
patients commenced on TNFi in combination with MTX. Eleven patients were on oral glucocorticoids (6 PsA and 5 RA) at <10 mg/day. At 12 months, 55 patients were on a sDMARD (25 PsA and 30 RA), 2 patients remained on TNfi monotherapy, 20 (10 PsA and 10 RA) received a TNfi in combination with MTX, and no patients were on glucocorticoids.

Response of clinical measures to anti-rheumatic treatment
Sixty patients (28 PsA and 32 RA) attended their 3 months visit and 58 patients completed the study (28 PsA and 30 RA). Significant improvements in disease activity scores were noted throughout the study in both groups. ESR, CRP and DAS28-CRP were lower in PsA than in RA at 3 months (P = 0.034, 0.021 and 0.005, respectively), with DAS28-CRP remaining lower at 12 months (P = 0.025). According to the EULAR response criteria [14], 68% of the patients (19 PsA and 22 RA) were responders at 3 months and 81% (23 PsA and 24 RA) were responders at 12 months.

Change in hand DXR-BMD
Mean hand DXR-BMD significantly decreased in RA and was 578 (66), 574(71) and 573 (72) mg/cm² at baseline, 3 and 12 months, respectively (0 vs 3 months P = 0.062; 3 vs 12 months P = 0.018; 0 vs 12 months P = 0.043). In contrast, hand DXR-BMD increased in PsA and was higher than in RA throughout the study at 584 (55), 585 (54) and 586 (56) mg/cm² at baseline, 3 and 12 months. Patients on a TNfi in combination with a sDMARD had higher hand DXR-BMD at 3 and 12 months compared with those on sDMARD monotherapy (P = 0.015; P = 0.021).

There was no significant bone loss in the PsA group throughout the study: mean ΔDXR-BMD from 0–3, 3–12 and 0–12 months were −0.1, 0.16 and 0.08 mg/cm²/month, respectively. In contrast, mean ΔDXR-BMD showed elevated bone loss in RA (−0.58, −0.62 and −0.6 mg/cm²/month, respectively). Changes in hand

### Table 1: Descriptive statistics at baseline

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Total (n = 64)</th>
<th>PsA (n = 32)</th>
<th>RA (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>44 (13.2)</td>
<td>40 (11.1)*</td>
<td>48 (14.1)</td>
</tr>
<tr>
<td>Female/male, n (%)</td>
<td>37 (58)/27 (42)</td>
<td>15 (47)/17 (53)</td>
<td>22 (69)/10 (31)</td>
</tr>
<tr>
<td>Menopausal, n (%)</td>
<td>5 (8)</td>
<td>2 (6)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Post-menopausal, n(%)</td>
<td>17 (27)</td>
<td>6 (19)</td>
<td>11 (34)</td>
</tr>
<tr>
<td><strong>Ever taken OCP of the female patients, n (%)</strong></td>
<td>26 (41)</td>
<td>11 (34)</td>
<td>15 (47)</td>
</tr>
<tr>
<td><strong>Ever taken HRT of the female patients, n (%)</strong></td>
<td>2 (3)</td>
<td>2 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Currently taking corticosteroids, n (%)</td>
<td>11 (17)</td>
<td>6 (19)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Currently taking calcium/vitamin D supplement, n (%)</td>
<td>2 (3)</td>
<td>2 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>42 (66)</td>
<td>21 (66)</td>
<td>21 (66)</td>
</tr>
<tr>
<td>Alcohol intake, mean (s.d.), units/week</td>
<td>7.1 (7.4)</td>
<td>8.6 (7.6)</td>
<td>5.6 (7)</td>
</tr>
</tbody>
</table>

Clinical parameters - physician's assessment

### Table 1: Descriptive statistics at baseline

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Total (n = 64)</th>
<th>PsA (n = 32)</th>
<th>RA (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AaCCP (normal 0–6.9), n (%)</strong></td>
<td>26 (41)</td>
<td>0</td>
<td>26 (81)</td>
</tr>
<tr>
<td><strong>RF [+] (normal 0–25), n (%)</strong></td>
<td>25 (39)</td>
<td>0</td>
<td>25 (78)</td>
</tr>
<tr>
<td><strong>ESR, mean (s.d.), mm/h</strong></td>
<td>19.4 ± 16.8</td>
<td>12 ± 8.1**</td>
<td>26.7 ± 20</td>
</tr>
<tr>
<td><strong>CRP, mean (s.d.), mg/L (normal &lt;5)</strong></td>
<td>14.4 ± 19.8</td>
<td>6.6 ± 8.3**</td>
<td>22.2 ± 24.6</td>
</tr>
<tr>
<td><strong>DAS28-CRP, median (IQR)</strong></td>
<td>4.2 (1.7–6.9)</td>
<td>3.7 (2.1–5.8)**</td>
<td>4.9 (1.7–6.9)</td>
</tr>
<tr>
<td><strong>TJC (0–28 joints), median (IQR)</strong></td>
<td>6 (0–23)</td>
<td>4 (0–20)**</td>
<td>8.5 (0–23)</td>
</tr>
<tr>
<td><strong>SJC (0–28 joints), median (IQR)</strong></td>
<td>2 (0–12)</td>
<td>1 (0–5)**</td>
<td>3.5 (0–12)</td>
</tr>
<tr>
<td><strong>Dactylitis, n (%)</strong></td>
<td>10 (31)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>BMI, men (S.D.), kg/cm²</strong></td>
<td>28.1 (6.3)</td>
<td>28 (6.3)</td>
<td>28.2 (6.3)</td>
</tr>
<tr>
<td><strong>PASI, median (IQR)</strong></td>
<td>3.3 (0–27.7)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Clinical parameters - self-reported

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Total (n = 64)</th>
<th>PsA (n = 32)</th>
<th>RA (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMS (min), median (IQR)</strong></td>
<td>35 (0–300)</td>
<td>30 (0–300)</td>
<td>60 (0–240)</td>
</tr>
<tr>
<td><strong>Pain (0–10 scale), median (IQR)</strong></td>
<td>6.5 (1–10)</td>
<td>6.5 (1–10)</td>
<td>6.5 (1–10)</td>
</tr>
<tr>
<td><strong>GVAS (0–100 mm VAS), median (IQR)</strong></td>
<td>54 (3–100)</td>
<td>51.5 (3–100)</td>
<td>57 (3–100)</td>
</tr>
<tr>
<td><strong>Fatigue (0–10 scale), median (IQR)</strong></td>
<td>6 (1–10)</td>
<td>5.5 (1–10)</td>
<td>6 (1–10)</td>
</tr>
<tr>
<td><strong>HAQ (0–3 scale), median (IQR)</strong></td>
<td>0.7 (0–2.4)</td>
<td>0.6 (0–2)</td>
<td>0.9 (0–2.4)</td>
</tr>
</tbody>
</table>

Differences between PsA and RA: *P < 0.05. **P < 0.01. ***P < 0.001. Alcohol intake (unit/week; the standard value of a unit of alcohol in Ireland is 10 g). DAS28-CRP is based on a 28 joint assessment for pain or swelling using the CRP-based formula (www.das-score.nl). Pain scale ranges from 0 = no pain to 10 = pain as bad as it could be. GVAS, visual analogue scale for global health ranges from 0 = worst imaginable health state to 100 = best imaginable health state. Fatigue scale ranges from 0 = no fatigue to 10 = fatigue as bad as it could be. Health Assessment Questionnaire scale ranges from 0 = no difficulty to 3 = unable to perform activity. OCP: oral contraceptive; aCCP: antibodies against CCPs; TJC: tender joint count; SJC: swollen joint count; PASI: Psoriasis Area and Severity Index; EMS: early morning stiffness.
DXR-BMD from 0–12 to 3–12 months in PsA were significantly different compared with RA patients (P = 0.001, respectively), reflecting unchanged cortical BMD in PsA and bone loss in RA.

Radiographic progression

There was no significant change in mean erosion, joint space narrowing scores, mSHS and proliferation score in either group over 1 year. Mean mSHS were 1.1 (3.2), 1.3 (3.6) and 1.4 (3.7) in PsA, and 1.9 (4.3), 2.4 (3.3) and 1.4 (3.1) in RA at 0, 3 and 12 months, respectively. Baseline mSHS did not correlate with mean DXR-BMD scores at any time points, whereas there were significant inverse correlations between mSHS prior to treatment and changes in DXR-BMD from 3 to 12 months in both groups.

Comparison of patients with bone loss with those with normal hand DXR-BMD

On univariate analysis, bone loss at 3 months was significantly associated with elevated BMI and higher alcohol consumption and at 12 months with diagnosis of RA, older age, higher aCCP and RF levels, higher TJC, SJC and DAS28-CRP, and lower PASI. No significant differences were found between the groups in terms of gender, smoking history, presence of erosions or treatment (Table 2).

Logistic regression analyses

Using multivariate forward stepwise logistic regression analysis and including variables demonstrating significant association on univariate analyses, BMI > 25 kg/cm², RA/
PsA, age, alcohol, aCCP, RF and SJC28 were entered into the model. Elevated BMI [odds ratio (OR) = 3.59, \( P = 0.041 \)] and heavier alcohol intake (OR = 1.13, \( P = 0.035 \)) were associated with early hand bone loss. Patients with RA (OR = 57.48, \( P = 0.008 \)), heavier alcohol intake (OR = 1.27, \( P = 0.012 \)) and higher SJC28 (OR = 1.5, \( P = 0.036 \)) at baseline had significantly increased risk for hand bone loss over 12 months.

Discussion

In this study we found hand BMD loss in both diseases in the first 3 months, possibly due to the modest structuresparing effect of the MTX on periarticular bone. It has been shown that MTX inhibits osteoclast formation in co-cultures of RA fibroblast-like synoviocytes and peripheral blood mononuclear cells by reducing rank ligand expression and increasing osteoprotegerin secretion [15]. In contrast, patients started on a TNFi in combination with a sDMARD had higher hand DXR-BMD at 3 and 12 months compared with those treated with sDMARD monotherapy. This reflects the known beneficial effects of TNFi on bone, because TNF is a key inducer of osteoclast formation and contributes to the imbalance between bone resorption and formation in arthritis. Interestingly, despite improvement in disease activity measures in both diseases, the observed change in hand DXR-BMD over 12 months was significantly different between PsA and RA, with unchanged hand BMD in PsA, but further bone loss in RA. Our observation may indicate that repair mechanisms in periarticular bone are different in early PsA with associated increased cortical bone formation compared with RA. This has been suggested previously, but observations were based on patients with established disease. A recent study showed that regardless of treatment with MTX or TNFi, osteophytes at the MCP joints progress in size in PsA [2, 16].

Hand bone loss in arthritis is associated with high inflammatory activity, longer disease duration, age, female gender and presence of autoantibodies [1, 3, 17]. In our study, elevated BMI and heavier alcohol intake were associated with hand bone loss in the first 3 months. This former finding was rather unexpected because increased adiposity has been shown to be protective against radiological progression in RA [18]. Diagnosis of RA, heavier alcohol intake and higher SJc28 were independent predictors for hand bone loss over 12 months. Presence of RA and SJc have been shown to be predictive of radiological damage in both RA and PsA [4, 5, 19]. One of the most interesting findings of our study is that heavier alcohol intake predicts hand bone loss by as early as 3 months and at 1 year. The effect of alcohol on the metacarpal bones has not been previously investigated in the early phase of inflammatory arthritis. While chronic heavy alcohol abuse is established as a risk factor for secondary osteoporosis, very little is known about its influence on periarticular bone. Chronic ethanol consumption in rats increased cortical bone damage in a dose-dependent manner. Reduction in bone mass is due to bone remodeling imbalance, with decrease in bone formation as a result of osteocyte apoptosis, suppression of the Wnt signaling pathway and the stimulation of oxidative stress [20].

Our work is limited by the small number of patients and the inhomogeneous treatment. A more standardized treatment may have given additional insight into changes in periarticular BMD.

Conclusion

This is the first prospective study comparing hand BMD changes in PsA with RA using DXR. We found unchanged hand BMD in PsA but bone loss in RA in the first year of the disease, supporting the hypothesis that different pathomechanisms are involved in hand bone remodelling in PsA. Presence of RA, heavier alcohol intake and SJc were identified as independent predictors for early hand bone loss. Since alcohol is widely consumed and may induce cortical bone loss, further studies are required to address the influence on periarticular bone.

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References