A comparative analysis of magnetic resonance imaging and high-resolution peripheral quantitative computed tomography of the hand for the detection of erosion repair in rheumatoid arthritis

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Abstract

Objectives. To investigate whether MRI allows the detection of osteosclerosis as a sign of repair of bone erosions compared with high-resolution peripheral quantitative computed tomography (HR-pQCT) as a reference and whether the presence of osteosclerosis on HR-pQCT is linked to synovitis and osteitis on MRI.

Methods. A total of 103 RA patients underwent HR-pQCT and MRI of the dominant hand. The presence and size of erosions and the presence and extent (grades 0–2) of osteosclerosis were assessed by both imaging modalities, focusing on MCP 2 and 3 and wrist joints. By MRI, the presence and grading of osteitis and synovitis were assessed according to the Rheumatoid Arthritis MRI Score (RAMRIS).

Results. Parallel evaluation was feasible by both modalities on 126 bone erosions. Signs of osteosclerosis were found on 87 erosions by HR-pQCT and on 22 by MRI. False-positive results (MRI + CT) accounted for 3%, while false-negative results (MRI C150 CT+) accounted for 76%. MRI sensitivity for the detection of osteosclerosis was 24% and specificity was 97%. The semi-quantitative scoring of osteosclerosis was reliable between MRI and HR-pQCT [intraclass correlation coefficient 0.917 (95% CI 0.884, 0.941), P < 0.001]. The presence of osteosclerosis on HR-pQCT showed a trend towards an inverse relationship to the occurrence and extent of osteitis on MRI [X^2(1) = 3.285; coefficient = 0.124; P = 0.070] but not to synovitis [X^2(1) = 0.039; coefficient = 0.14; P = 0.844].

Conclusion. MRI can only rarely detect osteosclerosis associated with bone erosions in RA. Indeed, the sensitivity compared with HR-pQCT is limited, while the specificity is high. The presence of osteitis makes osteosclerosis more unlikely, whereas the presence of synovitis is not related to osteosclerosis.

Key words: rheumatoid arthritis, magnetic resonance imaging, high-resolution peripheral computed tomography, erosion repair, inflammation.

Rheumatology key messages

- Sclerosis characterizes erosion repair, which can be detected by HR-pQCT.
- Osteosclerosis appears as hypointense lining at the bottom of the erosion in coronal T1-weighted MRI sections.
- Specificity of MRI in detecting osteosclerosis is high, whereas its sensitivity is low with current standard MRI protocols.

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Introduction

Bone erosion represents the main feature of anatomical damage in RA and results from an altered balance between local bone resorption and bone formation [1]. The pathophysiological processes underlying bone erosion are intimately linked to inflammation and autoimmunity in RA [1]. Experimental work has demonstrated that inflammation leads to an enhanced generation of bone-resorbing osteoclasts, while osteoblast maturation is impaired and insufficient to counteract bone resorption [2]. The suppression of inflammation and reversal of the periartricular bone microenvironment towards bone anabolism has been shown to be central for the induction of erosion repair in experimental models of arthritis [3].

In the clinical setting, detection of erosions and quantification of their extent are important for both diagnosis and clinical management of RA. Current anti-rheumatic therapy is aimed at retarding or even arresting the progression of bone erosions in patients with RA in order to prevent further damage and functional decline. In RA patients, it has been shown that erosion repair can occur under certain circumstances, as in the case of sustained TNF inhibition [4]. This evidence was obtained through detailed bone analysis by high-resolution peripheral quantitative CT (HR-pQCT), showing bone apposition at the bottom of the erosions (osteosclerosis) that is associated with the formation of a new cortical lining and a decrease in erosion depth. HR-pQCT allows detailed visualization of bone structure and its pathological changes (such as erosions); however, it is not widely available in clinical practice and, to date, is mostly confined to the research environment. In addition, HR-pQCT does not allow for the visualization of inflammatory signs such as synovitis and bone marrow oedema (osteitis) and therefore it is not possible to clarify under which condition repair occurs, i.e. whether it occurs in the absence of inflammation or despite it. On the other hand, MRI is more widespread for analysing the joints of RA patients and has been shown to reliably detect and quantify bone erosions as well as synovitis and osteitis, the latter being further predictive of erosion appearance [5–7].

The MRI appearance of sclerosis is the same as the cortical bone (hypointensity) due to the virtually absent water content in the bone. It has been observed that this imaging appearance could either lead to over- or underestimation of erosion size, but no systematic errors have been found in compared evaluations with CT [8].

The present study was conducted to test whether MRI allows the detection of signs of repair, as indicated by the presence of osteosclerosis at the bottom of the erosion, compared with HR-pQCT as a reference method, and to unravel the actual relationship between repair, as represented by osteosclerosis at the base of the erosion on HR-pQCT, and the presence and extent of signs of inflammation such as synovitis and osteitis on MRI.

Patients and methods

Study population

Patients diagnosed with RA (n = 103, 70 females) according to the 1987 ACR criteria [9] and also fulfilling the 2010 ACR/EULAR classification criteria for RA [10] were enrolled into the study and underwent 1.5T MRI and HR-pQCT imaging of the clinically dominant hand. Data collection included demographic and clinical features such as age, sex, BMI and smoking habit as well as disease-specific characteristics such as disease duration, 28-joint DAS (DAS28), autoantibody status (RF and ACPA) and current anti-rheumatic treatment. The study was performed in accordance with the Declaration of Helsinki. Approval from the local ethics committee and the national radiation safety agency (Bundesamt für Strahlenschutz) and informed consent were obtained.

Description of the HR-pQCT procedure

MCP joints 2 and 3 and the wrist (distal radius and ulna) were imaged through an XtremeCT scanner (SCANCO Medical, Brütisellen, Switzerland). This system uses a two-dimensional (2D) detector array in combination with a 0.08 mm point-focus X-ray tube, enabling the simultaneous acquisition of a stack of parallel CT slices with an isotropic voxel size of 82 μm and a spatial resolution of about 105 μm [10% modulation transfer function (MTF)]. Correct positioning of the imaged hand was assured by the use of a custom holder that allowed reduction of movement artefacts. The radiation dose was 6 μSv for the wrist examination and 9 μSv for the MCP examination. Scanning (effective energy 60 kVp, X-ray tube current 95 mA) of the MCP region extended between 80 slices distal to the edge of the third metacarpal head and 242 slices proximal to it, with a scanning time of 8.4 min. For the wrist, the region of interest was between the edge of the ulnar styloid and 210 slices proximal to it (time of scanning ~6 min) [11]. For each patient, six compartments were examined: the head of metacarpal bones 2 and 3 and their corresponding phalangeal bases, the distal surface of the radius and the ulna. As previously reported, erosion was defined as a clear juxta-articular bone lesion with a cortical break that can be seen in two consecutive images in two perpendicular planes [11]. The biggest visible erosion in each compartment was assessed for maximal width and depth: measurements were performed using the open-source digital imaging and communications in medicine (DICOM) viewer Osirix V3.2 (NEMA, Rosslyn, VA, USA) investigating a total of 532 2D slices per patient [11]. Erosion volume was calculated according to the half ellipsoid formula described elsewhere [12]. The presence of osteosclerosis was defined as bone apposition at the bottom of the erosion [4]. Semi-quantitative scoring (0–2 scale) of osteosclerosis was performed on the biggest visible erosion in each compartment using coronal reconstructions as follows: 0 = 0%, 1 = 1–75%, 2 = 75–100% bone apposition along the surrounding bone. Images were evaluated by two independent readers (A.R. and...
S.K.) blinded to identity, clinical characteristics and treatment of the patients.

**Description of the MRI procedure**

MRI scans were performed with a 1.5T Magnetom Avanto system (Siemens, Erlangen, Germany). Patients were examined in a prone position with the hand to be imaged stretched and overhead. According to the OMERACT definition, erosion was defined as a sharply marginated bone lesion with correct juxta-articular localization and typical signal characteristics that is visible in two planes with a cortical break visible in at least one plane [13]. Coronal T1-weighted images (voxel size 0.4 × 0.4 × 2.5 mm, field of view (FOV) 220 mm, echo time (TE) 12 ms, repetition time (TR) 485 ms, slice thickness 2.5 mm) were used for erosion scoring as previously described [12]. T1-weighted axial images (voxel size 0.5 × 0.5 × 3 mm, FOV 150 mm, TE 13 ms, TR 766 ms, slice thickness 3 mm) after i.v. gadolinium injection (0.2 ml/kg) were used to assess synovitis, which was defined as an area in the synovial compartment that shows above-normal gadolinium enhancement of a thickness greater than the width of the normal synovium [13]. T2-weighted coronal fat saturated (TIRM) sequences (voxel size 0.5 × 0.5 × 2.5 mm, FOV 220 mm, TE 60 ms, TR 3500 ms, slice thickness 2.5 mm) were used to assess osteitis, which was defined as a lesion within the trabecular bone, with ill-defined margins and signal characteristics consistent with increased water content [13].

The images were scored in a semi-quantitative manner in accordance with the RAMRIS system [14–18]: for erosion, the score ranged from 0 to 10, while for synovitis and osteitis the score ranged from 0 to 3. The examined joint regions corresponded to those assessed by HR-pQCT (MCP 2 and 3, distal radius and ulna and their articular surfaces). Analogous to the definition provided for the HR-pQCT imaging [4], MRI appearance of osteosclerosis was defined as the presence of a hypointense contour (isointense with respect to the cortical bone signal) at the bottom of the erosion, visible on post-gadolinium injection coronal T1-weighted images [8]. The extent of osteosclerosis was graded semi-quantitatively on a 0–2 scale (0 = 0%, 1 = 1–75%, 2 = 75–100%), similar to the above-mentioned scoring performed on HR-pQCT, focusing on the largest detectable erosion in each evaluated compartment. A visual example of the basic definition of MRI and HR-pQCT is shown in Fig. 1. The reading process was performed by two independent readers (A.R. and F.F.) in a blinded manner, as for HR-pQCT.

**Statistical analysis**

Data were analysed using SPSS 21.0 software (IBM, Armonk, NY, USA). Continuous variables are described as mean (s.d.) and categorical variables are provided as numbers and percentages. Cohen’s $\kappa$ coefficient was calculated to assess the agreement between the readers in detecting the presence/absence of erosions, osteosclerosis, synovitis and osteitis on MRI and the presence/absence of erosions and osteosclerosis on HR-pQCT. The concordance between the readers in grading erosions, counting erosions and grading osteosclerosis, osteitis and synovitis on MRI and erosion volume, erosion count and grading of osteosclerosis on HR-pQCT was assessed by calculation of intraclass correlation coefficients (ICCs).

Regarding the detection of erosions and osteosclerosis, MRI was compared with HR-pQCT as a reference in view of sensitivities, specificity, negative predictive value (NPV) and positive predictive value (PPV). In order to unravel any possible association of osteosclerosis with the presence of MRI signs of inflammation (osteitis and synovitis), Pearson’s correlation analysis was performed. In addition, a logistic regression analysis was set up that considered osteosclerosis in relation to demographic and disease-specific variables. The presence or absence of osteosclerosis was set as the dependent variable in the model and tested against several independent variables. A $P$-value $\leq 0.05$ was regarded as statistically significant.

**Results**

**Patient characteristics**

Demographic and clinical characteristics of the 103 RA patients are shown in Table 1. Briefly, RA patients had a mean age of 53.9 years (s.d. 14.4), were mostly female ($n = 70$ (68.0%)), with a majority of patients positive for either RF ($n = 56$ (54.4%)) and/or ACPA ($n = 56$ (54.4%)). Mean disease duration was 63.6 months (s.d. 92.4), resembling an established RA population, and mean disease activity was 3.3 units (s.d. 1.7) on the DAS28. Thirty-nine (37.9%) of the patients were in remission (DAS28 $\leq 2.6$), 15 (14.6%) in low disease activity (DAS28 $> 2.6$ but $\leq 3.2$), whereas the rest of the patients showed moderate [DAS28 $> 3.2$ but $\leq 5.1$; 33 patients (32%)] or high [DAS28 $> 5.1$; 16 patients (15.5%)] disease activity. The majority of the patients were treated with conventional DMARDs, predominantly MTX ($n = 55$ (53.4%)), whereas biologics were used by 39 (37.9%) patients.

**Detection of erosions by both modalities**

Images from 618 joint compartments were acquired. Quality was sufficient in 581 joint compartments to perform parallel evaluation by HR-pQCT and MRI. Images from 37 compartments had to be excluded because of poor quality in either HR-pQCT or MRI scanning. Erosions were found in 211 compartments on HR-pQCT (total counted erosions = 360) and in 136 compartments on MRI (total counted erosions = 159) (Fig. 2a). Compared with HR-pQCT, MRI showed a sensitivity of 60% in reading the presence of erosions and a specificity of 97%.

**Detection of osteosclerosis by both modalities**

In each of the 211 compartments showing erosions on HR-pQCT, the largest visible erosion (target erosion) was assessed for osteosclerosis. The corresponding lesions on MRI could be evaluated for osteosclerosis in 126
Fig. 1 Grading of the extent of erosion-associated osteosclerosis

(A–C) T1-weighted pre-gadolinium injection MR images; (D–F) coronal reconstruction of HR-pQCT images. Examples of each degree of osteosclerosis are provided for both imaging modalities. Grading was carried out in a semi-quantitative manner as follows: 0–2 scale (0, 0%; 1, 1–75%; 2, 75–100%) of osteosclerosis in the bone surrounding the erosion. (A and D) Osteosclerosis score 0; (B and E) osteosclerosis score 1; (C and F) osteosclerosis score 2. Arrows highlight osteosclerosis on MRI and HR-pQCT. HR-pQCT: high-resolution peripheral quantitative computed tomography.
compartments. Thus a total of 126 bone erosions could be assessed for osteosclerosis in both imaging modalities. Of these 126 bone erosions, 87 showed osteosclerosis on HR-pQCT. Osteosclerosis on MRI was found in 22 erosions. The rate of false-positive sclerotic erosions (osteosclerosis on MRI but not on HR-pQCT) was 3%, while the rate of false-negative sclerotic lesions (negative on MRI and positive on HR-pQCT) was 76% (Fig. 2b). Hence MRI showed a sensitivity of 24% and a specificity of 97% for detecting osteosclerosis. The PPV of MRI for osteosclerosis was 95% and the NPV was 37%.

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean (s.d.)</th>
<th>Range</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>53.9 (14.4)</td>
<td>19–83</td>
<td>52.12, 56.74</td>
</tr>
<tr>
<td>BMI, kg/m² (n = 101)</td>
<td>26.5 (5.3)</td>
<td>16–42</td>
<td>25.46, 27.56</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>63.6 (92.4)</td>
<td>0–519</td>
<td>45.49, 81.61</td>
</tr>
<tr>
<td>DAS28 score</td>
<td>3.3 (1.7)</td>
<td>0–7.7</td>
<td>2.97, 3.62</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>70 (68.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serological status (positive), n (%)</td>
<td>62 (60.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission (DAS28 &lt; 2.6), n (%)</td>
<td>39 (37.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low disease activity (DAS28 2.6–≤3.2), n (%)</td>
<td>15 (14.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate disease activity (DAS28 &gt;3.2–≤5.1), n (%)</td>
<td>33 (32.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High disease activity (DAS28 &gt;5.1), n (%)</td>
<td>16 (15.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF positive, n (%)</td>
<td>56 (54.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACPA positive, n (%)</td>
<td>56 (54.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active smokers (n = 100), n (%)</td>
<td>27 (27.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-dose (&lt;5 mg/day) glucocorticoids, n (%)</td>
<td>33 (32.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular use of NSAIDs, n (%)</td>
<td>41 (39.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX treatment, n (%)</td>
<td>55 (53.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other conventional DMARDs, n (%)</td>
<td>10 (9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologic DMARDs, n (%)</td>
<td>39 (37.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF inhibitor, n (%)</td>
<td>27 (26.2)</td>
<td></td>
<td></td>
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</tbody>
</table>

There were a total of 103 patients. DAS28: 28-joint DAS.

Fig. 2 Comparison between MRI and HR-pQCT

Comparison between MRI and HR-pQCT as the reference method for the assessment of (A) erosions (n = 581 compartments) and (B) osteosclerosis (n = 126 compartments). Thus a total of 126 bone erosions could be assessed for osteosclerosis in both imaging modalities. Of these 126 bone erosions, 87 showed osteosclerosis on HR-pQCT. Osteosclerosis on MRI was found in 22 erosions. The rate of false-positive sclerotic erosions (osteosclerosis on MRI but not on HR-pQCT) was 3%, while the rate of false-negative sclerotic lesions (negative on MRI and positive on HR-pQCT) was 76% (Fig. 2b). Hence MRI showed a sensitivity of 24% and a specificity of 97% for detecting osteosclerosis. The PPV of MRI for osteosclerosis was 95% and the NPV was 37%. Interreader reliability in detecting erosions and the presence of osteosclerosis was also assessed for both imaging modalities. The degree of concordance between the readers was found to be high for both MRI and HR-pQCT changes (Table 2).

Grading of osteosclerosis by both modalities

Semi-quantitative scoring of osteosclerosis was carried out on both HR-pQCT and MR images. On HR-pQCT, out of the 126 erosions, 39 (31.0%) showed no sign of osteosclerosis (grade 0), 71 (56.3%) showed sclerosis of grade 1 and 16 (12.7%) showed grade 2. On MRI, 104 erosions (82.5%) did not show any signs of osteosclerosis (score 0), while 18 (14.3%) showed osteosclerosis of grade 1 and 4 (3.2%) of grade 2. The grading of osteosclerosis on MRI showed a rather good correlation with...
Relationship between osteosclerosis on HR-pQCT and MRI inflammatory activity

The presence of osteosclerosis on HR-pQCT was subsequently examined with regard to MRI signs of inflammation, such as osteitis and synovitis, in order to investigate whether repair occurs in the absence of inflammation or regardless of it. Erosions with detectable osteosclerosis on HR-pQCT showed a trend towards a lower rate of occurrence of associated osteitis on MRI compared with those where osteosclerosis was not detected [osteitis score 0.18 (s.d. 0.52) vs 0.26 (s.d. 0.51); $U=4524$, $Z=-1.723$, $P=0.085$, respectively]. In contrast, the extent of synovitis showed no difference between erosions showing osteosclerosis and those without [synovitis score 0.87 (s.d. 0.83) vs 1.04 (s.d. 1.01); $U=4386$, $Z=0.899$, $P=0.369$, respectively].

Correlation between the presence of osteosclerosis and demographic and disease-specific variables

In order to find out whether demographic and disease-specific characteristics are associated with the presence or absence of osteosclerosis, a regression model was set up in which the dependent variable was the presence of osteosclerosis and the independent variables were age, disease duration, DAS28, sex, autoantibody status, smoking habit and BMI. The analysis was performed using logistic regression, and the results are presented in Table 3.

Table 3 shows the results of the logistic regression analysis. The model was statistically significant ($P=0.001$), and the Hosmer-Lemeshow test was not significant ($P=0.587$). The correct classification rate was 92.1%. The odds ratio (Exp(B)) of each variable is presented in the table, along with the 95% confidence interval (CI). The variable with the highest odds ratio is smoking status (RF), with an odds ratio of 5.265 (95% CI: 0.536, 51.763).

The results of the regression analysis suggest that smoking status (RF) and BMI are significantly associated with the presence of osteosclerosis. In contrast, age, disease duration, sex, ACPA status, and autoantibody status were not significantly associated with the presence of osteosclerosis.

Table 2 shows the interreader reliability for MRI and HR-pQCT findings. The Cohen's $\kappa$ values range from 0.917 to 0.981, indicating excellent agreement between readers. The ICC values range from 0.862 to 0.981, with 95% CI values ranging from 0.819 to 0.970, indicating high reliability of the measurements. The $P$-values are all less than 0.001, indicating statistical significance.

Table 3 Analysis of the correlation between osteosclerosis$^a$ and clinical characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>$B$</th>
<th>Wald</th>
<th>$P$-value</th>
<th>Exp(B) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at imaging</td>
<td>−0.049</td>
<td>1.907</td>
<td>0.167</td>
<td>0.953 (0.889, 1.021)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.008</td>
<td>0.030</td>
<td>0.810</td>
<td>1.008 (0.993, 1.023)</td>
</tr>
<tr>
<td>DAS28</td>
<td>0.191</td>
<td>0.440</td>
<td>0.440</td>
<td>1.510 (0.745, 2.918)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.778</td>
<td>0.409</td>
<td>0.409</td>
<td>1.210 (0.702, 2.116)</td>
</tr>
<tr>
<td>RF</td>
<td>1.661</td>
<td>2.029</td>
<td>0.154</td>
<td>5.265 (0.536, 51.763)</td>
</tr>
<tr>
<td>ACPA</td>
<td>−1.191</td>
<td>0.322</td>
<td>0.322</td>
<td>0.304 (0.029, 3.216)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>−0.651</td>
<td>0.445</td>
<td>0.445</td>
<td>0.521 (0.098, 2.775)</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.020</td>
<td>0.810</td>
<td>0.810</td>
<td>0.980 (0.833, 1.154)</td>
</tr>
<tr>
<td>Intercept</td>
<td>5.159</td>
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</tbody>
</table>

$^a$Patients without any signs of osteosclerosis vs patients with osteosclerosis in at least one compartment; $n=84$. Correct classified cases in the regression model = 90.5%. DAS28: 28-joint DAS.
shifts, which can hamper the exact codification of signals possibility of detecting osteosclerosis due to chemical position of these juxtaposed tissues likely influences the different resonance properties. Hence the chemical com-

localization at the interface between the fat-rich sclerosis by MRI are likely based on its anatomical reference method. The challenges in detecting osteo-

found to have a low sensitivity (24%) compared with the actual presence of bone apposition. However, MRI was that the detection of such an MRI sign corresponds to the formerly HR-pQCT-

imaging feature corresponded to the formerly HR-pQCT-lesion in T1-weighted images, we tested whether such an
to test the capability of MRI to detect osteosclerosis at the endosteal base of the erosion and to investigate whether osteosclerosis occurred in the presence or absence of inflammation. The overall performance of MRI in erosion detection was found to be in line with previous reports, as shown by a sensitivity of 60% [8]. The difference between MRI and HR-pQCT in detecting erosions is based on the very high resolution of this particular CT device, which enables visualization of even very small cortical breaks. Based on the definition of osteosclerosis on MRI as the presence of hypointense contour surrounding the lesion in T1-weighted images, we tested whether such an imaging feature corresponded to the formerly HR-pQCT-documented apposition of bone at the endosteal face of bone erosions. Comparison with HR-pQCT demonstrated that the detection of such an MRI sign corresponds to the actual presence of bone apposition. However, MRI was found to have a low sensitivity (24%) compared with the reference method. The challenges in detecting osteosclerosis by MRI are likely based on its anatomical localization at the interface between the fat-rich (or oedematous) bone marrow and synovial tissue with different resonance properties. Hence the chemical composition of these juxtaposed tissues likely influences the possibility of detecting osteosclerosis due to chemical shifts, which can hamper the exact codification of signals originating from different tissues. It remains to be determined whether advanced MRI techniques such as ultra-short echo time (UTE) and zero echo time (ZTE) can overcome this limitation. Nonetheless, the specificity of MRI in detecting bone apposition was high (97%), which, along with the rate of false-positive findings (3%) and the PPV (95%), indicates that even though less frequently detected, once identified, these MRI changes correspond to true osteosclerosis. Second, the attempt to assign a score of osteosclerosis on MR images gave reliable results, since the scores showed good correlation with the reference method.

We also addressed whether osteosclerosis occurs in the absence of inflammatory activity or independently of it. Previous observations from radiography suggested that repair occurs in the absence of clinical swelling [22, 30]. It was interesting to observe that the presence of osteosclerosis was generally associated with a lower frequency of osteitis, suggesting that active inflammation in the bone marrow inhibits bone apposition and repair of erosions. Similarly, a tendency to a lower extent of osteitis was observed in the compartments holding erosions with associated osteosclerosis compared with those where erosions did not show osteosclerosis. It has been speculated that the apposition of new bone at the endosteal part of the erosions (osteosclerosis) implies active participation of the bone marrow in the repair process [4]. On the other hand, osteitis is predictive of the development of erosions, supporting the concept that this phenomenon, which represents the presence of inflammatory lesions in the periarticular bone marrow, has a negative effect on the periarticular bone structure [6, 7, 31–33].

Some limitations of the study should be discussed. The study has a cross-sectional design, which gives only limited insight into the interdependence of repair and active inflammation. In this respect, the addition of longitudinal data would help to clarify how disease duration, longitudinal disease activity and treatment impact on repair and the detection of repair by MRI. Our study population had long-standing disease and was not large enough to allow stratification of the patients into subgroups according to different ranges of disease duration, which would probably allow us to better address the question of how the duration of local inflammation influences the development of repair phenomena.

In summary, our findings seem to preclude the role of MRI as a potential tool to detect signs of erosion repair, given the lower performance compared with HR-pQCT. The currently utilized MRI technology does not allow a systematic evaluation of erosion repair, which could possibly be improved by further development of MRI procedures and by the utilization of techniques and MRI settings with higher resolutions more suitable for the evaluation of bone structures [34, 35]. However, the study provides further insight into the pathological mechanisms that are linked to erosion formation and its reversal thanks to the possibility to combine information provided by MRI on the inflammatory aspects of the disease with the detailed structural analysis provided by HR-pQCT. Future research agenda should aim to establish the actual occurrence of erosion repair, better characterizing how it is related to
synovial and bone inflammation and how it can be influenced by different treatments. These efforts are seminal for a better understanding not only of the natural evolution of erosive lesions, but also to define the therapeutic pathways that can prevent and reverse bone damage in RA. Also, from a clinical perspective, it is essential to understand how repair is linked to function of the joint and whether therapies that foster the repair of bone lesions indeed improve the functional status of the joint.

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