Bone erosions in rheumatoid arthritis: ultrasound findings in the early stage of the disease

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Abstract

Objective. The objective of this study was to determine the prevalence and distribution of bone erosions detectable by US in patients with early RA (ERA) in comparison with long-standing RA (LSRA), other erosive diseases and healthy controls.

Methods. Thirty patients with ERA and 80 patients with LSRA were consecutively recruited. Thirty patients with PsA, 15 with primary OA, 10 with gout and 20 healthy subjects were included as controls. Bone erosions were investigated at the following anatomical sites: the second and fifth metacarpal heads, the ulnar head and the first and fifth metatarsal heads, bilaterally. Dorsal, volar and lateral aspects were explored on longitudinal and transverse views.

Results. At least one US bone erosion was found in 20 (66.7%) of 30 patients with ERA and in 10 (33%) of them it was found on the fifth metatarsal head. Bone erosions were most frequently found on the lateral quadrants of all scanned anatomical sites. If the second and fifth metacarpal heads and the fifth metatarsal head were scanned, an erosive disease could be found in 60% of ERA patients. The first metatarsal head was most frequently involved in the disease control group.

Conclusion. This study found a high percentage of ERA patients with US bone erosions, with the fifth metatarsal head and the lateral aspects the most frequently involved site and quadrants. US scanning for bone erosions on a few target joints was found feasible and provided information not obtainable with clinical examination.

Key words: early rheumatoid arthritis, rheumatoid arthritis, ultrasound, bone erosions, erosive diseases.

Introduction

Bone erosion marks the joint damage in RA, and its early detection is important not only for the diagnosis, but also for revealing more severe disease [1–3]. While conventional radiography is the standard imaging modality for joint damage assessment in daily clinical practice, its sensitivity is poor compared with that of CT, MRI and US [4–13]. Several studies have investigated the value of US in the assessment of bone erosions in specific anatomical sites chosen because they were frequently involved in RA and easily accessible by US [4–17].

Over the past few years, an increasing number of rheumatologists have started to use US in the clinical setting of the early arthritis clinic. While US allows for an accurate and non-invasive multisite assessment of joint involvement in patients with RA, time for US examination is not infinite. Thus the ideal approach is the one obtaining the information required in the shortest time. At present, patients presenting with clinical features of early arthritis undergo clinically driven US examination mainly for confirming or ruling out the presence of joint inflammation.

Knowledge of the most frequently involved sites, where erosions occur in the early stage of the disease, is essential for developing a target-oriented US examination.
Such an approach, aimed at revealing the erosive character of the disease at patient level, could save time and facilitate systematic US use in the busy setting of the early arthritis clinic.

This study was aimed at determining the prevalence and distribution of bone erosions detectable by US in patients with early RA (ERA) compared with established RA and other chronic arthritis.

Methods

Patients

Thirty patients with a diagnosis of ERA according to the new 2010 ACR/European League Against Rheumatism (EULAR) criteria [18] with <12 months disease duration and 80 patients with long-standing RA (LSRA) satisfying the 1987 ACR criteria [19] were consecutively recruited in the present study. Fifty-five patients (30 with PsA, 15 with OA and 10 with gout) diagnosed using international clinical criteria were recruited as disease controls [20–22]. Twenty healthy control subjects were recruited among the hospital staff without previous history of joint pathology.

Study design

The presence of bone erosions was investigated by US at the following anatomical sites: the second and fifth metacarpal heads of both hands, the ulnar head bilaterally and the first and fifth metatarsal heads of both feet. These anatomical sites were chosen because they represent frequent targets of the erosive process and large portions of these sites could be explored by US [4–7, 11, 23, 37]. The study was conducted according to the Declaration of Helsinki and local regulations. Approval from the institutional ethics committee (Comitato Etero ASUR Marche) was obtained and all recruited subjects gave their informed consent to participate in the study.

Clinical assessment and laboratory data

Twenty-eight joints were clinically assessed for tenderness and swelling. General health status reported by patients on a 100 mm visual analogue scale (VAS) was also recorded. CRP (normal <0.5 mg/l), ESR (normal <15 mm/first hour in men and <20 in women) as well as IgM RF (<40 UI/ml was considered negative) and anti-CCP antibodies (<10 UI/ml was considered negative) were determined. The 28-joint DAS (DAS28) was calculated [24].

US scanning technique

The US examinations were performed by the same experienced rheumatologist sonographer (>4 years experience) using a MyLabTwice (Esaote, Genoa, Italy) equipped with a broadband 6–18 MHz linear probe, according to the scanning technique described in the EULAR guidelines for musculoskeletal US in rheumatology [25]. The dorsal, volar and lateral aspects of all anatomical sites were explored on both longitudinal and transverse views. The ultrasonographer was blinded to the clinical diagnosis. Patients were asked not to talk about their clinical condition with the sonographer.

US image interpretation

Bone erosion was interpreted according to the OMERACT preliminary definition as an IA discontinuity of the bone surface that is visible in two perpendicular planes [26]. Erosions >1 mm in both longitudinal and transverse scans were considered for the study. Bone erosions were classified according to the involved bones (metacarpus, metatarsus or ulna), their topography (dorsal, volar or lateral quadrants) and their extent (unifocal: no more than one erosion per quadrant; multifocal: more than one, but no more than three definite erosions per quadrant; massive: more than three erosions, confluent erosions or wide bone destruction per quadrant). The sonographer paid particular attention in assessing unifocal bony breaks of small size to avoid misinterpretation with anatomical necks [27] or vascular bone channels [15].

Statistical analysis

Baseline characteristics were reported as the mean (±S.D.) for normal distributed variables, median (25th–75th percentiles) for non-normal quantitative variables or number with corresponding percentage. Student’s t-test was used to compare means for normally distributed variables and the chi-square test was used to compare frequencies, and 95% CIs for proportions. Statistical analyses were performed using the software package MedCalc 12.0 (MedCalc Software, Mariakerke, Belgium) and Microsoft Excel.

Results

Patients

Table 1 summarizes patient demographic, clinical and laboratory data. Two of the 80 patients with LSRA did not agree to participate in the study.

Prevalence and distribution of bone erosions by groups

Table 2 illustrates the number of patients with erosive disease and the number of bone erosions detected by US in patients with ERA, LSRA and in disease and healthy controls. At least one bone erosion was found in a total of 20 (66.7%) of 30 patients with ERA and in 70 (89%) of 78 LSRA patients. A total of 65 bone erosions were found in 170 joints (510 quadrants) of 20 patients with ERA. A total of 556 bone erosions were found in the LSRA patients.

Prevalence and distribution of bone erosions by sites

Table 3 shows the numbers and percentages of RA patients and controls showing at least one bone erosion at the anatomical sites examined. The fifth metatarsal head was the most frequently involved site in terms of bone erosion occurrence in ERA patients: 10 (33.3%) of 30 ERA patients presented at least one bone erosion at this level. In Fig. 1 the arrows indicate focal bone erosions of
different sizes acquired in longitudinal lateral view at the fifth metatarsal head in a patient with ERA. The second metacarpal, the fifth metatarsal and the first metatarsal heads were shown to be involved in 23.3% of cases each; 16.6% of patients had bone erosions localized at the distal ulna in the ERA group.

Global differences in the presence of bone erosions between groups

Significantly more LSRA patients presented at least one bone erosion located at the investigated sites compared with ERA and the disease controls, with the exception of the first metatarsal head, which was equally involved in LSRA and disease controls. No significant differences were observed regarding the involvement of the targeted sites in ERA patients and disease controls, except that significantly more disease controls were shown to present at least one bone erosion at the first metatarsal head compared with ERA patients (Table 3).

A total of four focal bone erosions were found at the metatarsal head of three first toes and one at the fifth toe in two healthy controls, while no erosions were found at both the second and fifth metacarpal heads and the distal ulna. Significantly fewer healthy controls presented bone erosions compared with the disease groups for all the investigated sites, except for the first metatarsal head involvement in ERA patients, similarly to the healthy individuals (Table 3).

Site differences in the presence of bone erosions between groups

The highest number of bone erosions was found at the first metatarsal head in ERA patients and disease and healthy controls. The fifth metatarsal head occupies the second position in terms of the number of bone erosions in ERA patients (Fig. 2A–D). Significantly more bone erosions were found at the second metacarpal head in LSRA compared with ERA patients ($P = 0.01$) and disease controls ($P = 0.01$). More bone erosions were found at the fifth metatarsal head in LSRA than in disease controls, but without significance ($P = 0.06$). No significant difference in the number of bone erosions was detected between
ERA patients and disease or healthy controls. The majority of erosions at the target sites were distributed in the lateral quadrant in all groups of patients and controls (Fig. 2A/C150D).

**US features of bone erosions**

Almost all patients with ERA and erosive disease detected by US were shown to have unifocal bone erosions (18 of 20). Multifocal erosions were found in only five patients (16.7%), located on the fifth metatarsal head in two cases and on the first metatarsal head in three cases. No massive erosions were seen in ERA patients. In LSRA patients, >50% of patients had multifocal bone erosions, while they occurred in only 25% of disease controls.

**Feasibility of US examination focused on detecting bone erosions in ERA patients**

When the second metacarpal, fifth metacarpal and fifth metatarsal heads were examined, 60% of ERA patients were identified as having at least one bone erosion. When only the lateral quadrants of these three joints were examined, US detected 53% of patients with an early erosive RA. Each US examination lasted a mean of 25 min (5 min/joint, bilaterally). US examination of the dorsal and lateral quadrants lasted longer (a mean of 2 min each) compared with the volar quadrant (a mean of 1 min). These observations suggest that in 15 min there is a 60% probability and in only 6 min a 53% probability of finding at least one bone erosion in patients with ERA.

**Discussion**

Several studies have shown US to be a sensitive and accurate imaging tool for detecting bone erosions [28–30]. Therefore, the use of US in the clinical setting of an early arthritis clinic may help rheumatologists reveal a greater number of patients with erosive disease. Unfortunately many rheumatologists still do not use US in their daily clinical practice because of their heavy workload. The early detection of bone erosions is of major importance because they represent a marker for both the persistence and severity of the disease [31]. There is substantial evidence that early, aggressive treatment in ERA can prevent further structural damage [32, 33]. Therefore, losing the opportunity to use US because it can be time consuming may lead to a delay in appropriate management in the early stages of RA. Although US is considered the most operator-dependent imaging modality, there is literature supporting the fact that it is easy to learn US for specific targets, such as detecting bone erosions using dedicated scanning protocols [16].

High-frequency transducers allow the detection of very small bone erosions, and recent studies have revealed that bone erosions detected by US are indeed erosion lesions as indicated by micro-CT analysis [15, 34].

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**Table 3** Number and percentage of RA patients and controls showing at least one bone erosion at the target sites

<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>ERA (30 patients), n (%), (95% CI)</th>
<th>LSRA (78 patients), n (%), (95% CI)</th>
<th>Disease controls (55 patients), n (%), (95% CI)</th>
<th>Healthy controls (20 patients), n (%), (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second MC head</td>
<td>7 (23.3), (0.117, 0.409)</td>
<td>50 (64.1), (0.530, 0.738)</td>
<td>17 (30.9), (0.202, 0.440)</td>
<td>0 (0), (0, 0.161)</td>
</tr>
<tr>
<td>Fifth MC head</td>
<td>7 (23.3), (0.117, 0.409)</td>
<td>35 (44.8), (0.343, 0.558)</td>
<td>13 (23.6), (0.143, 0.363)</td>
<td>0 (0), (0, 0.161)</td>
</tr>
<tr>
<td>Distal ulna</td>
<td>5 (16.6), (0.073, 0.335)</td>
<td>29 (35.9), (0.261, 0.469)</td>
<td>10 (18.1), (0.101, 0.303)</td>
<td>0 (0), (0, 0.161)</td>
</tr>
<tr>
<td>First MT head</td>
<td>7 (23.3), (0.117, 0.409)</td>
<td>37 (47.4), (0.367, 0.583)</td>
<td>29 (52.7), (0.390, 0.636)</td>
<td>2 (10), (0.027, 0.301)</td>
</tr>
<tr>
<td>Fifth MT head</td>
<td>10 (33.3), (0.192, 0.512)</td>
<td>45 (57.7), (0.466, 0.680)</td>
<td>16 (29), (0.187, 0.421)</td>
<td>1 (5), (0.008, 0.236)</td>
</tr>
</tbody>
</table>

* P < 0.05 LSRA vs ERA; †P < 0.05 LSRA vs disease controls; ‡P < 0.05 disease controls vs ERA; §P < 0.05 healthy subjects vs ERA; ¶P < 0.05 healthy subjects vs disease controls. MC: metacarpal; MT: metatarsal.
However, small changes might be overinterpreted. Particular attention must be paid by the sonographer in order to distinguish true bone erosions from the bone channels and to avoid misinterpretation due to the presence of osteophytes.

The present study was aimed at identifying the anatomical sites where US can find erosions even in the early stages of RA. The results of this study will help to refine the priority list of target areas to scan to reveal patients with erosive disease, shortening the US examination time. In 66.7% of ERA patients US revealed the presence of bone erosions, with the fifth metatarsal head the most frequently affected site and its lateral quadrant the one where the greatest number of bone erosions was found. Bone erosions were also frequently detected on other examined sites in early disease. In LSRA patients, the second metacarpal was the most frequently involved site in terms of bone erosion occurrence.

The lateral quadrant was more frequently affected by the erosive process in all joints examined and in all patients with RA. Several studies based on X-ray findings demonstrated the occurrence of bone erosions early in the course of RA and identified bone erosions as a marker for the persistence and severity of the disease [31, 35–37]. Many published papers have addressed the issue of US and bone erosions in RA [4–17, 28–30, 42], but this is the first study aimed at investigating the ability of US to detect bone erosions in ERA using a comprehensive multisite approach. By using this approach, we demonstrated that a large number of ERA patients already have bone erosions in different areas at the time of diagnosis.

Studies based on X-ray findings have indicated that the foot is one of the earliest targets of the erosive process [38, 39]. Previous US studies also identified the fifth MTP joint as a site of early joint inflammation [5, 16, 17]. In the study of Sheane et al. [13], 57% of RA patients with a mean disease duration of 15.2 months had bone erosions located at the fifth MTP joint. Our results also indicate that the fifth metatarsal head might be the first site involved in ERA patients in terms of bone erosion occurrence.

Hammer et al. [12] found 11% of patients presenting bone erosions at the distal ulna in early arthritis at baseline. The results of the present study are similar in terms of bone erosions detected by US at the distal ulna in ERA patients. There is literature supporting the fact that bone erosions occur mainly on the radial side of the second metacarpal, third metacarpal and fourth metacarpal heads, but not the fifth metacarpal head, due to the involvement of the radial collateral ligament [40]. Lateral scans may be important...
for showing bone erosions since indications of an erosive process may be absent on a standard dorsal view [6]. Our results show that the lateral quadrant was the most affected of all targeted sites in RA patients and controls.

In patients with gout, bone erosions occur mostly on the first metatarsal head, especially on the medial aspect, being more frequently multifocal [41]. In the present study >50% of the disease controls showed at least one bone erosion at this level. Moreover, a similar percentage of LSRA patients were found to be positive for bone erosions at the first metatarsal head, suggesting that bone erosions at this site are not specific for RA. In ERA the majority of bone erosions were unifocal, while in LSRA we found >50% and in disease controls >25% of patients with multifocal bone erosions. The lower frequency of multifocal bone erosions in ERA is probably explained by the short duration of the disease as well as the high percentage of patients treated with DMARDs.

A study from the ESPOIR cohort showed that bone erosions were detected in 14 (11%) of 127 healthy subjects when the second and fifth metacarpal head and the fifth metatarsal heads of both hands and feet were examined [42]. Moreover, Wright et al. [41] found erosive changes of the first metatarsal head in healthy controls. Our results showed only 10% of healthy controls presenting bone erosions, all in the lower limbs, with the first metatarsal head being the most frequent affected site. This figure could be the expression of a pre-clinical stage of OA or it could be explained by the presence of a previous trauma. However, given the lack of comparison with other imaging techniques, it is not possible to state whether the erosions identified with the US examinations in this study are real bone erosions.

There are some limitations in our study. First, the small number of ERA patients did not permit accurate evaluation in terms of prevalence sensitivity and specificity that could better support these data. The study was conducted over 2.5 months, thus explaining the number of ERA patients included in the study. Second, a test for intraobserver agreement to support our reliability data more consistently was not performed. Although the anatomical sites that we examined may be considered as target areas in RA, we consider the limited number of US-examined sites as another limitation of the study. Finally, the study is limited by the absence of the use of other imaging modalities as reference methods in detecting bone erosions. Several published studies have shown a high correlation between US-detected bone erosions and CT or MRI [9–11, 15, 17]. In a recent study, Dohn et al. [34] demonstrated that US was able to diagnose bone erosions with a high specificity and, in areas with good accessibility for the assessment, a sensitivity comparable to that of MRI or CT. Even though US findings were not part of the ACR 1987 classification criteria for RA and are not part of the new ACR/EULAR 2010 criteria, the value offered by this imaging method in showing early inflammation and bone destruction should be considered [43].

This study found a high number of ERA patients with US bone erosions, with the lateral aspect of the fifth metatarsal head being the most frequently involved site. Due to the relatively high prevalence of US bone erosions in disease controls, the first metatarsal head is probably not a target site to be examined by US in patients with ERA. In only 6 min a sonographer might detect up to 53% of patients with erosive ERA. We believe that the results of this study contribute to improvement in the feasibility and efficiency of the US examination aimed at revealing bone erosions in patients with ERA. However, further clinical studies in a larger cohort of patients are warranted to confirm these findings.

### Rheumatology key messages

- A high percentage of early RA patients present with US bone erosions.
- US bone erosions are most frequently found at the fifth metatarsal head in early RA patients.
- US scanning for bone erosions on few target joints is feasible in early RA patients.

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### References


