The sonographic identification of cortical bone interruptions in rheumatoid arthritis: a morphological approach

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Abstract: Bone erosions are the hallmark of structural damage in rheumatoid arthritis (RA). Among imaging techniques, ultrasonography (US) has emerged as an accurate, reliable, repeatable, low-cost and non-invasive imaging modality to detect erosive changes in RA. However, small interruptions of the cortical bone detectable by last generation US equipment do not necessarily represent bone erosions. According to the available data, in addition to cortical bone interruption itself, only a few morphological US findings have been proposed to define RA bone erosions. However, other additional features may be considered to facilitate the interpretation of US cortical bone interruptions in RA. These could be summarised using the following four domains: size, site, shape and scenery. This hypothesis article provides a critical literature review of US features characteristic of RA bone erosions and pictorial evidence supporting the potential role of a morphological analysis in the US identification of bone erosions in RA patients.

Keywords: bone erosions, OMERACT, rheumatoid arthritis, structural damage, ultrasonography

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Plain language summary

The ultrasonographic morphology of cortical interruptions is helpful for the identification of bone erosions in rheumatoid arthritis: the “four Ss” approach

- Bone erosions are characteristic features of rheumatoid arthritis. They are associated with a more aggressive disease and with irreversible physical disability.
- In recent years, ultrasonography has emerged as an accurate and reliable technique for the detection of bone erosions, that appear as interruptions of the cortical bone with variable size. However, cortical bone interruptions do not necessarily represent bone erosions. Since bone erosions represent the earliest evidence of the destructive behaviour of RA, their identification is crucial.
- Besides the cortical interruption itself, only a few morphological ultrasonographic features were proposed to characterise bone erosions in rheumatoid arthritis.
- We believe that a morphological approach, including size, site, shape and scenery, may be considered to facilitate the interpretation of ultrasonographic cortical bone interruptions in rheumatoid arthritis.
- In this hypothesis article we carried out a critical review of the scientific literature and provided extensive pictorial evidence of the ultrasonographic spectrum of cortical interruptions supporting the potential role of considering the “four Ss” for the ultrasonographic identification of bone erosions in rheumatoid arthritis.
The relevance of bone erosions in rheumatoid arthritis

In patients with rheumatoid arthritis (RA), chronic synovitis leads to joint damage and irreversible physical disability. Structural joint damage in RA affects both bone and cartilage, resulting in bone erosions and cartilage thinning. Bone erosions are the hallmark of structural damage in RA and they can occur in the very early stage of the disease, affecting approximately half of untreated patients within 6 months after disease onset. Since their first description, more than 60 years ago, bone erosions have become a key feature in the diagnosis and prognosis of RA patients. In fact, the European League Against Rheumatism (EULAR) allows the diagnosis of RA (erosive criterion) when at least three separate joints show typical bone erosions on conventional radiography (CR) even without the fulfilment of the 2010 American College of Rheumatology (ACR)/EULAR classification criteria. Moreover, the updated 2019 EULAR recommendations for the management of RA suggest to add a biologic or a targeted-synthetic disease modifying anti-rheumatic drug (DMARD) when the treatment target is not achieved with the first-line conventional DMARD and in the presence of poor prognostic factors, such as bone erosions. Furthermore, preventing the development and progression of bone erosions is one of the most important endpoints in randomised clinical trials in RA.

Imaging techniques in the detection of bone erosions in RA

Currently, CR remains the reference imaging tool for the detection of joint damage in RA. In fact, according to the EULAR recommendations for the use of imaging of the joints in the clinical management of RA, CR should be used as the first-line imaging tool for the identification of joint damage (i.e. bone erosions and joint space narrowing). However, the sensitivity of CR in the identification of bone erosions is lower compared with other imaging techniques such as magnetic resonance imaging (MRI), ultrasonography (US) and computed tomography (CT), especially in the early phase of the disease. These techniques have generated new opportunities and challenges in the interpretation of cortical bone discontinuities. In particular, US has emerged as an accurate, reliable, repeatable and low-cost imaging modality to detect erosive changes in RA, widely accepted by patients due to its safety and non-invasive profile. The US identification of bone erosions is noteworthy. In fact, US-detected bone erosions predict the development of RA in both undifferentiated arthritis and anti-cyclic citrullinated peptide (CCP) positive at-risk individuals, and the radiographic progression of structural damage in RA patients. In contrast, a recent study has demonstrated that CR-detected bone erosions are uncommon and do not predict the development of RA in ‘at-risk’ individuals with positive anti-CCP antibodies. The results of these studies suggest that US may represent the optimal imaging technique in the assessment of bone erosions in RA.

Limits of the current sonographic definition of bone erosion

Small interruptions of the cortical bone detectable by last generation US equipment, which would fulfil the Outcome Measure in Rheumatology (OMERACT) definition (intra-articular discontinuity of the bone surface that is visible in two perpendicular planes), do not necessarily represent bone erosions. In fact, several imaging studies have documented different mimickers of bone erosions (pseudo-erosions) including physiological cortical vascular channels and cortical irregularities (osteophytes, cortical bone notches and subcortical bone cysts), particularly when cortical defects are smaller than 2 mm. In fact, the prevalence of the OMERACT-defined bone erosions at metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints ranges from 0% to 18% of healthy subjects and increases with age. Since bone erosions represent the earliest evidence of the destructive behaviour of RA, the differentiation between bone erosions and pseudo-erosions has relevant implications, because false-positive results would lead to an overestimation of structural damage in RA, whereas false-negative results to a delay in the identification of an aggressive disease. In a considerable number of RA patients, the US diagnosis of bone erosions is achievable using only the current OMERACT definition. However, in doubtful cases, other additional US features may be useful to distinguish between bone erosions and pseudo-erosions. In fact, the OMERACT US
definition of bone erosion may not encompass the entire morphological spectrum of erosive changes in RA, being anchored solely to the concept of cortical break.

**Morphological analysis of bone erosions in RA: current concepts**

According to literature data, only a few morphological US features have been proposed to define RA bone erosions: the irregular floor, the presence of an intense power Doppler signal inside the cortical break, the anatomical site and the size of the cortical defect greater than 1 or 2 mm.\textsuperscript{24,28,31,46–50} A recently published systematic literature review on US and bone erosions in RA was used as the starting point.\textsuperscript{47} Since the research question for the present article aimed to identify the morphological appearance of RA bone erosions, we extracted studies on this topic from the original systematic literature review,\textsuperscript{47} and using the same search strategy we added relevant articles from an updated search in PubMed (from May 2014 to May 2020). The references of the included studies were then screened for additional studies that may have been missed. Table 1 provides a schematic representation of the morphological US features adopted by previous studies in the identification of RA bone erosions.

**Table 1.** Morphological US features reported in previous studies for the identification of RA bone erosions.

| Authors        | Morphological domains                                                                 |
|----------------|----------------------------------------------------------------------------------------|
| **Size**       | **Site (at joint level)**                                                              | **Shape**     | **Scenery**                                       |
| Wakefield et al.\textsuperscript{24} | Any size                                                                             | Irregular floor | /                                               |
| Bajaj et al.\textsuperscript{46}   | BE with its largest diameter $\geq 2$ mm                                               | Irregular floor | /                                               |
| Finzel et al.\textsuperscript{28}  | Any size                                                                             | Palmar region of MHs and PBs are rich of cortical vascular channels | / | Osteophytes can mimic BE, especially when these lesions form forceps-like structures |
| Tamas et al.\textsuperscript{31}   | BE with its largest diameter $\geq 1$ mm                                               | /               | /                                               |
| Zayat et al.\textsuperscript{50}   | BE of any size in the MTP5 or a BE with its largest diameter $\geq 2.5$ mm in the DU, MCP2, MCP5 | BE were more frequent at the proximal dorso-radial quadrant of MCP2, proximal dorso-ulnar quadrant of MCP5 and dorso-ulnar side of the DU. In the MTP5, BE were more frequent in the proximal dorso-lateral and plantar-lateral quadrants | / | /                                               |
| Roux et al.\textsuperscript{49}    | Single BE with its largest diameter $\geq 2$ mm or multiple BE                          | /               | /                                               |
| Finzel et al.\textsuperscript{48}  | Cortical vascular channels were generally smaller than BE (e.g. mean width 0.68 versus 1.56 mm) | RA BE clearly predominated at the radial and to a lesser extent ulnar sites of the bare areas of MCP and PIP, whereas cortical vascular channels were found mainly in the palmar regions of these joints | / | In cortical vascular channels, the PD signal is rather low and may be synchronous with heart rhythm. In contrast, BE usually showed an overall more intensive PD signal than cortical vascular channels |

BE, bone erosion; DU, distal ulna; MCP, metacarpophalangeal joint; MH, metacarpal head; MT, metatarsal head; MTP, metatarsophalangeal joint; PB, phalangeal base; PD, power Doppler; PIP, proximal interphalangeal joint; RA, rheumatoid arthritis; US, ultrasonography.
in RA patients and may broaden the current OMERACT definition. In fact, our hypothesis is not in contrast with the OMERACT definition, which is the ‘conditio sine qua non’. In fact, it consists of an extension of the OMERACT definition to include further morphological features that may increase the ability of US in the identification of RA bone erosions.

In our opinion, when assessing an US picture showing an interruption of the cortical bone visible in at least two perpendicular planes the following additional US features, which we call the ‘four Ss’, should be considered:

- Size (measured in the largest diameter of the cortical bone interruption after a multi-planar assessment)
- Site (in the dorsal, volar or lateral aspect of the joint; in the bare area or in the subchondral bone)
- Shape (linear or irregular delineation of the cortical bone interruption)
- Scenery (presence or absence of surrounding soft tissues abnormalities such as synovial hypertrophy and/or power Doppler signal and/or osteophytes).

To support our hypotheses, we provided pictorial evidence and a literature review describing how
morphological analysis of the US images could facilitate the interpretation of cortical bone interruptions. To do that, we selected representative US images of normal bone surface (Figure 1) and of pseudo-erosions (Figure 2) in healthy subjects and in patients with osteoarthritis. Moreover, we selected US images showing examples of bone erosions and pre-erosive changes in RA patients (Figures 3–6).

**Size**
The size of an US bone erosion is one of the key features determining its specificity. In fact, Roux et al. reported that the US detection of a single bone erosion >2 mm or of multiple bone erosions <2 mm was accurate in the discrimination between RA and other disease controls with a sensitivity of 72.1% and a specificity of 89.1%. Similar results were obtained by Zayat et al., who reported that the identification of a bone erosion with its maximum diameter ≥2.5 mm yielded to a sensitivity of 58.6% and a specificity of 90.0%. In both these studies, the inclusion of small (<1 mm) bone erosions in the analysis led to a higher sensitivity and a lower specificity.

The size of the cortical break can also discriminate between a RA bone erosion and a physiological vascular channel, the former being significantly larger and deeper than the latter (cf. Figures 2 and 3). In fact, several authors defined RA bone erosion as an interruption of the bony cortex >1 mm or >2 mm in its largest diameter.

Nevertheless, we think that the adoption of a cut-off value could strongly impair the diagnostic potential of US in the early identification of a bone erosion in RA patients. In fact, as shown in Figures 4 and 6, definite microerosive changes and Ω-shaped bone erosions may appear as interruptions of the cortical bone <1 mm.

However, an association between bone erosions and age was reported in both healthy subjects and RA patients, with a progressive increase in the number of bone erosions above the age of 50 years. This suggests that the threshold between normality and pathology changes with increasing age.

To summarise, the size of a cortical break is an important issue to consider in its interpretation: the greater the size, the higher the chance that a cortical break is a bone erosion. However, to maximise the sensitivity of US, the definition of US bone erosion should not include any size threshold.

**Site**
Although US allows for a multi-site and multi-tissue assessment, the ideal scanning protocol for the detection of bone erosions in RA should include all the relevant anatomical areas without being time-consuming. According to current evidence, the most specific sites for the detection of bone erosions in RA are MCP joints (especially the second and the fifth), fifth MTP joints and ulnar styloids. Zayat et al. found that the identification of bone erosions of any size in the fifth MTP joint was accurate for RA (sensitivity 68.6% and specificity 85.4%). Conversely, the first MTP joint and the humeral head are not
**Figure 4.** (a–d) Site. Metacarpophalangeal joint. Longitudinal [a, a’, c, c’] and transverse [b, d] scans obtained at the dorsal side of the metacarpal head using a 22 MHz probe with [a’, c’] and without [a, b, c, d] power Doppler, revealing active submillimetric [0.4 mm (a, b); 1.1 mm (c, d)] subchondral cortical breaks (arrowheads), indicative of bone erosions. mc, metacarpal bone; pp, proximal phalanx.

**Figure 5.** Scenery. (a, b) Metacarpophalangeal joint. Longitudinal [a, a’] and transverse [b, b’] scans obtained at the dorsal aspect using a 18 MHz probe with [a’, b’] and without [a, b] power Doppler. Note a cortical break (arrowheads) in the area of the metacarpal depression, which is a common site for pseudo-erosions. The surrounding scenery, characterised by florid synovial hypertrophy (+) showing power Doppler signal in contact with, and invading into, the cortical break [open arrows], provides additional information supporting the diagnosis of bone erosion. The deep echoes (curved arrows) in b and b’ suggest the presence of bone erosions despite submillimetric small cortical interruptions [0.2 and 0.6 mm] [arrowheads]. mc, metacarpal bone; pp, proximal phalanx.
specific targets due to the high prevalence of bone erosions in patients with other rheumatic diseases and healthy controls.\textsuperscript{31,47,59–61}

At joint level, the site of a cortical break might be specific enough to define it as a bone erosion. In fact, given a clinical suspicion of RA, a subchondral cortical break of any size is highly indicative of a bone erosion (Figure 4). However, subchondral bone erosions are a late and relatively infrequent US finding in RA. Thus, a careful evaluation of the whole joint should always be performed. Among the other areas of the MCP and MTP joints, the lateral aspect was found to be the most specific site to be assessed,\textsuperscript{24,26,28,31,48} whereas, in the proximal interphalangeal (PIP) joints, the dorsal side was the most frequently affected.\textsuperscript{48} In fact, in both MCP and PIP joints of RA patients, physiological vascular channels predominated in the palmar aspect (78.8\% of MCP joints and 100\% of PIP joints).\textsuperscript{48} As documented by Finzel \textit{et al.} in a comparative study with high-resolution peripheral quantitative CT,\textsuperscript{28} false-positive results in the identification of US bone erosions were related mainly to the misinterpretation of vascular channels in the volar side of the MCP joint. On the other hand, false-negative results were linked mainly to the underestimation of US bone erosions in the dorsal metacarpal depression.\textsuperscript{28} At that level, pseudo-erosions correspond to the physiological depression of the dorsal aspect of the metacarpal bone, located just proximal to the hyaline cartilage. Using US, Falkowski \textit{et al.} evaluated the MCP joints of 100 healthy subjects.\textsuperscript{39} The authors found that every subject had pseudo-erosions in at least one MCP joint, 99\% of them had a bilateral involvement and 81.5\% had at least three or more MCP joints with pseudo-erosions on the metacarpal depression. The shape and the size of the cortical break and the surrounding scenery may provide further evidence to distinguish pseudo-erosions from RA bone erosions at that level (cf. Figures 2 and 5).

To summarise, the site of the cortical break has a relevant impact on its interpretation, both with regard to which joint (e.g. fifth \textit{versus} first MTP joints) or which area of a joint (e.g. subchondral \textit{versus} palmar aspect of a MCP joint) is under examination.

\textbf{Shape}

The shape is not included in the OMERACT US definition of bone erosion. Conversely, the high-resolution peripheral quantitative CT definition of bone erosion includes the nonlinear shape of the cortical break to differentiate it from vascular channels penetrating the cortex.\textsuperscript{62} Accordingly, the irregular floor and the ill-defined borders of the erosive crater have been reported as US features of RA bone erosions.\textsuperscript{46,63}

In our experience, as shown in Figures 3–6, the
irregular lining of the cortical breaks is a distinctive US feature of RA bone erosions. In addition, the identification of other US abnormalities, such as the focal loss of sharpness of the bony cortex under orthogonal insonation and/or atypical deep echoes under the cortical surface may help in the detection of Ω-shaped bone erosions characterised by a very small interruption of the cortical bone and a larger defect of the trabecular bone as documented by high resolution CT studies (Figure 6).²⁶,²⁸

Scenery
Unlike CR and CT, US is able not only to assess cortical bone interruptions but also to reveal even minimal morpho-structural and vascular changes of the surrounding soft tissues. Thus, the presence of an inflamed synovial tissue in or around an interruption of the cortical bone can help to discriminate between bone erosions and physiological vascular channels.¹⁹,⁴⁸,⁶⁴ In fact, nonlinear or multifocal power Doppler signal within the cortical defect is highly indicative of active bone erosion regardless of its size, whereas a single and thin linear vessel crossing the cortical line is indicative of a feeding vessel. Moreover, pathological Doppler signal is usually wider and more intense than the physiological vascular signal.⁴⁸ In addition, the identification of synovial hypertrophy in close contact with a cortical defect is highly suggestive of a bone erosion rather than pseudo-erosion as shown in Figures 5 and 6.

Conclusions
The representative images presented in this report provide pictorial evidence supporting the hypothesis that inclusion of the ‘four S’ domains (size, site, shape and scenery) to the simple assessment of a cortical discontinuity may improve the interpretation of US cortical bone interruptions. Besides the cortical break itself, other additional features may be considered to facilitate the interpretation of US cortical bone interruptions in RA patients, especially in the early phases of the erosive disease. However, given the high variability of scenarios that may be encountered in daily practice, we decided not to adopt a hierarchical approach with regard to the ‘four Ss’. In fact, one single morphological characteristic (e.g. a very large cortical break or a subchondral cortical interruption) may be sufficient in some cases to define a cortical break as a bone erosion; on the other hand, a combination of suggestive features may be needed, especially in the early phases of disease.

This hypothesis needs to be further corroborated through the application of the OMERACT methodology in order to develop, test and validate an updated definition of US bone erosion.

Conflict of interest statement
E.F. has received speaking fees from AbbVie, Bristol-Myers Squibb, Celgene, Janssen-Cilag, Novartis, Pfizer, Roche and Union Chimique Belge Pharma. M.D.C. has received speaking fees from AbbVie, Novartis, Pfizer and Sanofi Aventis. W.G. has received speaking fees from AbbVie, Celgene, Grünenthal, Pfizer and Union Chimique Belge Pharma. All other authors have declared no conflict of interest.

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Data availability statement
The data underlying this article will be shared on reasonable request to the corresponding author.

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