Ultrasound *versus* conventional radiography in the assessment of bone erosions in rheumatoid arthritis

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ABSTRACT

Bone erosions are the hallmark of joint damage in rheumatoid arthritis and both their detection and increase in number and/or in size are indicative of a poor outcome. To date, conventional radiography is still the most common imaging tool adopted for detecting and scoring joint damage in daily clinical practice, in spite of its low sensitivity with respect computerised tomography, magnetic resonance imaging or ultrasound.

Ultrasound is a rapidly evolving technique that is gaining an increasing success in the assessment of patients with rheumatoid arthritis. It permits an early detection and careful characterisation of bone erosions playing a key role in both diagnostic and therapeutic procedures. Ultrasound presents several advantages over other imaging techniques: it is patient-friendly, safe and non-invasive, free of ionising radiation, less expensive, and permit multiple target assessment in real time without the need for external referral.

The aim of this review is to compare conventional radiography and ultrasound in the assessment of bone erosions in RA in daily rheumatology practice and to provide insights into which modality can provide the optimal information for a desired outcome in a given clinical trial or practice situation.

Introduction

Rheumatoid arthritis (RA) is a chronic disease characterised by destructive, and progressive inflammatory polyarthritis. Its prevalence is approximately 1% of the world population and 0.5% in Italy (1). If not properly treated, RA leads to pain, swelling, and progressive destruction of joints, with resulting disability, and decrease in quality of life (2-5). Bone erosions are the hallmark of joint damage in RA and both their detection and increase in number and/or in size are indicative of a poor outcome (6-8). To date, conventional radiography (CR) is still the standard imaging technique used for detecting and scoring joint damage in daily clinical practice, in spite of its low sensitivity with respect to other imaging modalities such as computerised tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US). The advantages of CR are well known and include the low costs, the wide availability, the possibility to use validated scoring systems, and the good reproducibility. Currently it is widely accepted that early diagnosis and true remission are the most important factors to slow joint damage progression (9-11). Thus, the ideal imaging tool should be accurate and reliable for the detection of bone erosions, especially in the early phases of the disease. In this context, US offer characteristics as ideal tool to detect early anatomical damage, including erosions, and to establish its accurate follow-up. It is safe able to rapidly assess multiple joints with a multiplanar technique, provides accurate depiction of the minimal morphostructural changes at bone and soft tissues level in real time, the set of images can be achieved taken for comparison with images taken at later dates. Moreover, US is patient-friendly, free of ionising radiation and less expensive. For these peculiar characteristics a large number of rheumatologists are currently incorporating US into their clinical practice in patients with RA (Table I).

This review is designed to compare CR and US in the assessment of bone erosions in RA and to provide insights into which modality can provide the optimal information for a desired outcome in a given clinical trial or practice situation.

Detection and evaluation of bone erosions

The presence of bone erosions is an important criteria for both the American College of Rheumatology (ACR)

Table I. Advantages and disadvantages of US and CR.

Imaging modality	Advantages	Disadvantages
Conventional radiography	• Wide availability and easy access • Low cost • Images easily understood by clinicians • Standardisation available • Valid assessment methods • Good reproducibility • High specificity for bone changes (differential diagnostic work-up) • ACR classification criteria criteria of RA	• Ionising radiation • Non-sensitive to early changes • Insufficient to assess soft-tissue • Requires training (*e.g.* Sharp scoring) • Pitfall due to over-impression of three-dimensional structures on two-dimensional image
Ultrasonography	• Non-invasive method • Relatively low cost • Portable and immediately accessible • Real-time and dynamic imaging • No ionising radiation • Can assess synovitis, erosions, tendons, and vascular flow • More sensitive than radiography for erosion detection • Both grey-scale and power Doppler synovitis may predict erosion progression • Can be used to guide intra-articular injections/aspiration	• High degree of operator dependence • Specialist training not always available • Low reproducibility • Need to standardise which joints are evaluated • Certain joint regions not well visualised due to lack of good acoustic window (wrists) • Unable to visualise bone marrow abnormalities • Difficulties with temporal comparison • Scoring system developed but requiring further validation for trials • Well-tolerated by patients

1987 (12) and the ACR/EULAR 2010 classification criteria for RA (13). Erosive disease for use in the 2010 ACR/EULAR RA classification criteria is defined when an erosion (defined as a cortical break) is seen in at least three separate joints at any of the following sites: the proximal interphalangeal joints (PIPj), the metacarpophalangeal joints (MCPj), the wrist (counted as one joint) and the metatarsophalangeal joints (MTPj) (14).

Hand

In 2000, Wakefield *et al*. studied 100 RA patients and found that US, detected 6.5 times and 3.4 times more erosions in the MCPj of patients with early and established RA than those detected with CR. MRI was used to corroborate the US findings showing a good sensitivity, specificity, and accuracy of US for the detection of bone erosions (0.79, 0.97, and 0.96, respectively), while the corresponding values for CR were 0.32, 0.98, and 0.93. The study also reported a high level of inter and intra-observer reliability for the US findings (15). In 2006, Szkudlarek *et al* obtained good reliability for US in detecting bone erosions at the MCPj and PIPj. Using MRI as the reference method, the sensitivity, specificity and accuracy of US for the detection of bone erosions were 0.59, 0.98 and 0.96, respectively, whereas 0.42, 0.99 and 0.95 were the data for CR. Moreover, reasonable inter-observer reliability data have also been demonstrated in studies of expert sonographers in a wide variety of joints (16).

In the ESPOIR (Etude et Suivides Polyarthrites Indifferenciees Recentes) study that included a cohort with early arthritis US detected 6.8-fold more joints with erosion than CR (3.3-fold more than with usual reading) (17). Furthermore, Døhn *et al*. showed an overall moderate sensitivity (42-44%) and a very high specificity (95%) for US-detected erosions when using CT as the reference method (18). These authors discussed how the sensitivity of US improved considerably (71%) when only areas with good US accessibility were included. US performs at its best at sites where access is optimal and enables placement of the probe perpendicular to the structure in question. Thus, sites such as the 2nd and 5th MCPj and the 5th MTPj, which lend themselves to a near 360° assessment, are optimal (*e.g.* since 3rd and 4th MCPj do not permit an accurate assessment of the lateral aspect), whereas sites such as the intercarpal compartments of the wrist are more difficult to assess. Sensitivity may also be reduced in the presence of associated degenerative joint disease and in established and advanced RA; however, the same can also be said for plain radiography in this context.

Alarcon *et al*., Lopez-Ben *et al*. and Magnani *et al*. confirmed the previous data reporting a high accuracy of US, compared with MRI, in the detection of bone erosions when the examination is focused on the 2nd and 5th MCPj (19-21).

Wrist

The wrist is a difficult joint for US and CR. Difficulties for a detail evaluation of wrist are respectively due to its complex anatomy, the presence of multiple soft tissues around the joint, the lack of a reproducible window for visualising these structures, the anatomical irregularities of the bone margins (*e.g.* at level of ligaments attachment) and the presence of several nutritive foramina that can appear like erosions (22). In a longitudinal study of wrist involvement in RA patients, Leak *et al*. showed radiographic erosions of the styloid ulna were seen as a relatively early isolated finding in 25% of the patients (23). The presence of US erosions at the distal ulna was associated with joint damage, confirmed by longitudinal follow-up with CR and MRI. Most of the US erosions were found at the distal ulnar area (close to extensor carpi ulnaris). Thus, inflammation in the tendon sheath may cause bone erosions.

MRI studies have confirmed that the tenosynovitis of the extensor carpi ulnaris is frequently found in patients with bone erosions located at the distal ulnar bone. A large cohort study conducted by Leak *et al*. identified the radioulnar joint as a frequent site of erosions in establish RA which was involved in 78% of patients (23).

In a longitudinal study conducted by Hammer *et al*. (24) was explored the presence, localisation and development of erosions at the distal ulna by US in patients with recent onset RA. They have tested additionally whether erosions at this localisation were associated with joint damage in hands assessed by CR and MRI. Seventy patients were examined by US of the distal ulna, in

addition to hand radiography (assessed by van der Heijde-modified Sharp score (vdHSS), and MRI of the wrist (assessed by RA MRI scoring (RAMRIS) erosion score). Twelve months later, 58 patients were re-assessed. US showed a superior sensitivity with respect CR in the detection of bone erosions at the dorsal part of the distal ulna. It detected erosions at the distal ulna in 11% of the patients at baseline and 24% at follow-up. Logistic regression analysis showed that the presence of erosions at baseline was associated with baseline RA MRI scoring system (RAMRIS) ($p<0.001$), and at follow-up to RAMRIS erosion score ($p=0.02$). The study detected a significant number of patients showing US erosions at the distal ulna at baseline, with increased prevalence after 1 year. Moreover, the US-detected erosions were associated with structural joint damage in hands assessed by both MRI and CR.

Although the detection of bone erosions plays a key role in the outcome of RA, it is important taking into account that those could also be present under no pathological conditions. Døhn *et al*. proposed an interesting paper aimed to demonstrated whether bone erosions in RA MCPj detected with MRI and US, but not with radiography, represent true erosive changes (25). They included 17 RA patients with at least one, previously detected, radiographically invisible MCPj MRI erosion, and four healthy controls. They all underwent CT, MRI, US and radiography of the 2nd to 5th MCPj of one hand on the same day. Each imaging modality was evaluated for the presence of bone erosions in each MCPj quadrant. In total, 336 quadrants were examined. The sensitivity, specificity and accuracy, respectively, for detecting bone erosions (with CT as the reference method) were 19%, 100% and 81% for radiography; 68%, 96% and 89% for MRI; and 42%, 91% and 80% for US. When the 16 quadrants with radiographic erosions were excluded from the analysis, similar values for MRI (65%, 96% and 90%) and US (30%, 92% and 80%) were obtained. CT and MRI detected at least one erosion in all patients but none in healthy controls. US detected at least one erosion in 15 patients, however, erosion-like changes were seen on US in all control individuals. Nine patients had no erosions on radiography. The authors concluded that MRI and US exhibited high specificities (96% and 91%, respectively) in detecting bone erosions in RA MCPj, even in the radiographically non-erosive joints (96% and 92%). This study indicates that bone erosions, detected with MRI and US in RA patients can be considered true bone erosions.

In another similar study conducted by Skudlarek *et al*., when compared to MRI as the reference method, US showed even higher values of sensitivity and specificity; MRI-detected erosions were also detected in 7 of the 20 healthy controls (16).

Foot

Skudlarek *et al*. (26) concentrated their attention on comparing US with MRI, CR, and clinical examination in the evaluation of bone erosions at MTPj level in patients with RA.

Two hundred MTPj of 40 patients RA patients and 100 MTPj of 20 healthy control subjects were assessed in this study. With MRI considered the reference method, the sensitivity, specificity, and accuracy of US for the detection of bone erosions were 0.79, 0.97, and 0.96, respectively, while the corresponding values for radiography were 0.32, 0.98, and 0.93. Erosive disease was identified in 26 patients by US, compared with 20 patients by MRI and 11 patients by radiography. The MRI and CR visualisations of US-detected bone changes were closely related to their size-based gradings on US. The study demonstrated that US enables detection and grading of bone erosions at MTPj of patients with RA. Additionally showed by comparison with MRI, US was found to be markedly more sensitive and accurate than clinical examination and CR.

Shoulder

The value of US, MRI and CR in detecting bone erosions at humeral head was tested in a study conducted by Alasaarela *et al*. (27), in 26 RA patients. MRI depicted humeral erosions in 25 (96%), US in 24 (92%), CT in 20 (77%) and CR in 19 (73%) of 26 shoulders. MRI and US were superior to CT in detecting small erosions. US was the most sensitive method to show erosions at the great tuberosity. US, CT and MRI depicted large erosions quite similarly whereas CR was less sensitive to detect small erosions at humeral head level.

Hermann *et al*. proposed (28) a study focused on determining the role of US and MRI compared with CR in the detection of bone erosions at shoulder level in RA patients. Forty-three consecutive patients with known RA prospectively underwent clinical examination, CR, US and MRI of the shoulder. Erosions were assessed using all 3 imaging techniques on a 4-point scale. The results in the study group were compared with those obtained in a control group of 10 patients with shoulder pain. In the study group, erosions of the humeroscapular joint were detected by CR in 26 patients, by US in 30 patients, and by MRI in 39 patients. The differences were statistically significant for the comparisons of CR with MRI and for US *versus* MRI ($p<0.0001$). CR detected 12 erosions of the scapula and MRI detected 15. The study proposed US as supplement to CR in assessing the anatomical damage at shoulder joint.

Amin *et al*. (29) recently published a prospective study determining the accuracy of US in early detection of shoulder bone erosions and monitoring disease activity in RA patients using MRI as a gold standard. Fifty patients with known RA and 15 healthy controls were involved. Erosions of the humeroscapular joint were detected by CR in 15 (30%), by US in 41 (82%), and by MRI in 46 (92%) of the shoulders examined. No statistically significant difference was noted between US and MRI in overall detection of erosion. The study proposed US as a helpful imaging method to assess shoulder anatomical damage in the initial diagnostic evaluation when CR is negative.

Prognostic role of US

The presence of bone erosions at the time of diagnosis has been shown to be related to a poor long-term clinical

outcome, therefore, identifying persistent and erosive arthritis appears to be a crucial step. With the increasing use of disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents, early diagnosis is now of paramount importance and disease progression is assessed regularly to monitor efficacy of the treatment. The introduction of these new therapies has placed increased importance on imaging, particularly on the identification of early changes, with the emphasis now on early diagnosis and treatment of RA before irreversible joint damage occurs. On the other hand, there is an increasing body of evidence supporting power Doppler (PD) US as a sensitive imaging technique for the assessment of disease activity and therapy monitoring in patients with RA. Moreover, the recent availability of probes with Doppler frequency higher than 10 MHz, allows for the detection of even minimal blood flow changes at different tissue.

Fukae *et al*. showed in a longitudinal US study, how the improvement of vascularity (reduction of the PD signal) by DMARDs was correlated with suppression of radiographic progression (30). Brown et al, in a cohort of patients with RA under clinical remission, reported as the persistence of residual intra-articular PD could be considered a risk factor for bone erosions (31).

The correlation between US abnormalities and the development of radiological damage has also been object of the study conducted by Taylor *et al*. The study was carried out in a cohort of early RA treated with conventional therapy or biological agents. The results showed a significant positive correlation between synovial thickening and PD signal and the development of radiological damage at the hands and feet level in the group of conventional treatment, after 54 weeks of follow-up (32). Another multicentre longitudinal trial of 367 RA patients treated with anti-tumour necrosis factor found that the time-integrated US joint count for PD signal had predictive value for the development of radiographic erosions and the progression of the total radiographic score (33). Backhaus *et al*. performed a prospective two year follow-up US study comparing US and CR in patients with arthritic finger joints. A total of 49 RA patients were included; US at baseline detected 5 of the 12 newly appeared erosions seen on radiography after 2 years (34).

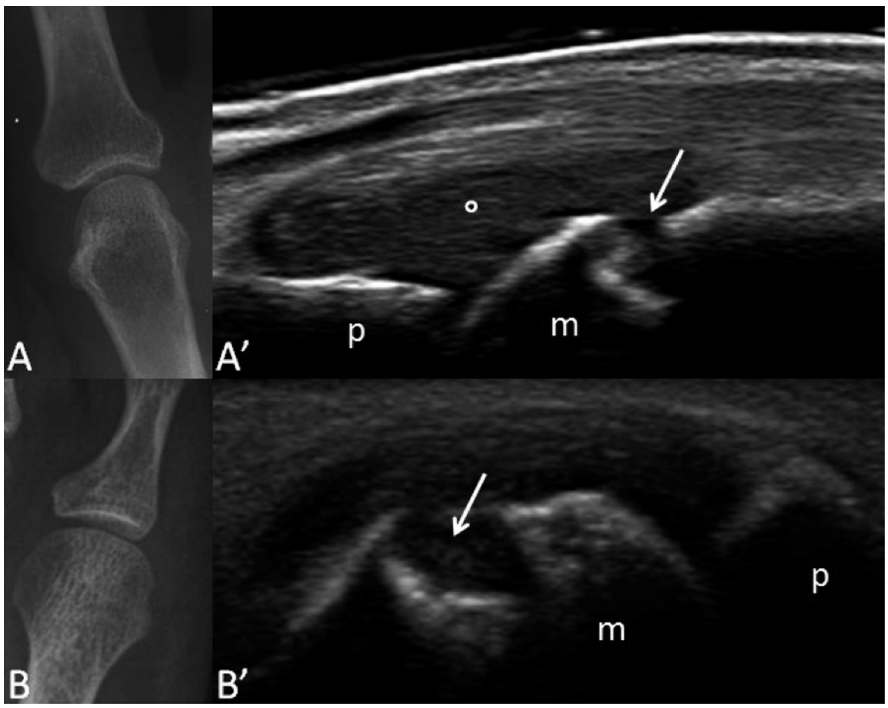

Fig. 1. A. Conventional radiography in postero-anterior view showing the second metacarpophalangeal joint. No alterations indicative of bone erosions are appreciable. The respective ultrasound examination shows a clear erosion (**arrow**) at the metacarpal head level. Moreover, it is possible to observe a proliferative joint cavity widening (**circle**) (**A'**).
B. A similar example is represented at metatarsophalangeal joint level among conventional radiography negative for clear erosion and ultrasound (**B'**) showing a large erosion (**arrow**), **m** = metacarpal head, **p** = basis of the proximal phalanx.

Brown *et al*. adopted PDUS and contrast enhanced high-field MRI of the hand in a study involving 102 RA subjects in clinical remission with a follow-up period of 1 year (35). The US score for synovial hypertrophy, PD, bone marrow oedema, and erosion was performed semi-quantitatively and then summed individually. MRI synovitis and bone erosions were scored adopting the RAMRIS. The presence of PD signal and MRI bone marrow oedema and synovitis were predictive of radiographic progression with odds ratio of 2.31, 4.00, 12.21 and 2.98, respectively. Similarly, Boyesen *et al*., using multivariate logistic regression analysis, identified both US inflammation and MRI bone marrow oedema as independent predictors of erosion progression with odds ratios of 2.01 and 1.28, respectively (36).

More recently, in a longitudinal study, Macchioni *et al*. demonstrated a positive correlation between baseline presence of PD signal and the development of structural damage in RA. In this study the presence of intra-articular PD signal in a single joint at baseline and its persistence over time showed a relevant prognostic value for the development of articular damage in the same joint (37). Sheane *et al*. indicate that a routine US examination of the 5th MTPj looking for erosions in early arthritis can help in the identification of those with a poor prognosis. The authors in the study detected superior sensitivity of US with respect the CR in the assessment of bone erosions at this level. In a single-centre study, Salaffi *et al*. developed a predictive rule combining clinical variables, serological biomarkers and PDUS for the progression from an early-onset undifferentiated arthritis (UA) to RA. A prediction rule was developed after a 12 months study of 149 adult patients with a recent-onset UA. Sixty-two patients (41.6%) developed a RA. The rule demonstrated excellent discriminative

ability. With the optimal cut-off point of 5, sensitivity was 89.9%, specificity was 88.6% and positive likelihood ratio was 7.89. If a threshold of 6.5 was applied, a higher value of specificity (97.7%) was obtained, but sensitivity (47.6%) decreased (38).

Conclusions

Although, there are no established studies comparing US and CR in the diagnostic evaluation of RA with relatively few looking at their comparative prognostic and monitoring role, the published evidence reaffirms the insensitivity of CR and supports a range of feasible and effective uses for US in the assessment of the erosions in RA. Particularly supported so far are the rapid and useful detection of erosive disease in early inflammatory arthritis. It gives a better indication of disease severity and prognosis compared with routinely available laboratory tests, even in the absence of a definite diagnosis. Despite this, US cannot replace radiography for detection of erosion, and both techniques combined show complementary efficiency and displayed the best results, especially at disease onset. The specificity of US for erosion detection and the clinical significance of US erosion should be studied in further prospective trials to determine whether US is a surrogate tool for early RA diagnosis. Future studies with increased patient numbers will be necessary if one of these two modalities is to emerge as a clear winner as the imaging modality of choice (39-42). Clearly defined quantitative measures will provide increased accuracy in monitoring disease change in patients and will also provide a reference standard for clinical trials to compare results in a formal reproducible manner.

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