New applications of imaging techniques for monitoring progression of rheumatoid arthritis and predicting outcome

Imaging continues to assume an increasingly important role in the assessment of patients with rheumatoid arthritis. Application of MRI and Doppler ultrasound to this group of patients has revealed important insights into disease processes in rheumatoid arthritis, identifying previously concealed processes that cannot be viewed with conventional imaging. These processes include osteitis, synovitis and early bone erosion. Together, these imaging techniques provide methods for assessment of treatment response as well as short- and long-term outcome. This article examines the current state of imaging in rheumatoid arthritis, with an emphasis on assessment of treatment outcome.

KEYWORDS: bone erosion, Doppler ultrasound, MRI, osteitis, rheumatoid arthritis, synovitis

Rheumatoid arthritis (RA) is a chronic multisystem disorder that affects 1% of the adult population, causing considerable morbidity, a reduction in life expectancy and a significant burden to the community in terms of economic cost [1]. Untreated, patients with RA have a poor prognosis, with the major cause of death being cardiovascular disease [2,3].

The ultimate goals of therapy in RA are to prevent or control joint activity and damage, thereby preventing loss of function and disability [4], and reducing cardiovascular events [5,6]. With treatment options expanding and treatment regimens becoming more complex, the search for precise methods to measure treatment objectives is becoming more urgent. As new therapies emerge, rheumatologists must be able to assess rapidly whether the new treatment can achieve the target objectives better than an older, perhaps safer alternative, and thereby whether the risks of exposure to new or multiple medications justifies the risk to the patient and the cost to the community.

Medical imaging is becoming increasingly important in assessing outcome in patients with RA. Combined with clinical and laboratory techniques, imaging in RA represents a powerful tool for the assessment of outcome.

This article will examine the important role of imaging, incorporating radiographs, CT Doppler ultrasound and MRI, in the assessment of patients with RA.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic, systemic inflammatory disorder with unknown etiology. Joint manifestations are accompanied by elevation of the inflammatory parameters, such as the erythrocyte sedimentation rate and the C-reactive protein, as well as anemia of chronic disease. The disease predominantly involves joints in a symmetrical, polyarticular fashion and leads to joint pain and swelling. The clinical course is variable, but in many cases, the disease causes joint destruction, deformity and disability.

The diagnosis is based upon a total score of 6 or greater (of a possible 10) from the individual scores in four domains from the American College of Rheumatology (ACR)/ The European League Against Rheumatism (EULAR) Criteria [7], present for 6 or more weeks:

- Number and site of involved joints (range 0–5)
- Serological abnormality (range 0–3)
- Elevated acute-phase response (range 0–1)
- Symptom duration (two levels; range 0–1)

In addition to the joint manifestations, the systemic nature of the disease is reflected in constitutional features, such as fatigue, lethargy, weight loss and, occasionally, fevers. The prevalence of RA differs throughout the world, being less in developed rural areas. The most recent prevalence estimates from the Rochester study are 1.4% for women and 0.74% for men [8]. This finding is supported by other studies [9–12] of prevalence in developed populations, leading to the generally quoted figure of prevalence between 0.5 and 1% of the adult population [13].

The inflamed synovium is considered to be the central player in the pathogenesis of RA and although synovitis and bony damage seem to
be intertwined, more recent evidence suggests that additional factors may be important in bone destruction in RA [14,15].

Treatment
There has been a dramatic shift in the approach to treatment of RA in the past 10 years.

A major advance has been the introduction of biological agents, notably etanercept, adalimumab and infliximab, which have demonstrated efficacy in reducing disease activity and have the capacity to slow damage progression [16–19]. The chief advantage of these agents is their rapid onset of action compared with traditional disease-modifying antirheumatic drugs, providing symptom relief in weeks rather than months [20], and the capacity to slow damage progression alone or in combination with methotrexate [21,22]. Further agents targeting B-cell receptors [23], T-cell receptors [24] and IL-6 [25] are available, expanding the therapeutic armamentarium for treatment. Treatment has shifted dramatically, from an observational approach, to an aggressive multidrug intervention, treating patients to normalize inflammatory parameters and clinical indices [26].

What is clear from the preceding discussion is that treatment for RA is more complex than it has ever been. The obligation of the rheumatologist is to decide which therapy will produce the most beneficial effect for the least toxicity. To perform this function, the rheumatologist and the researcher need a sensitive instrument to document synovitis and detect joint damage progression early, with recordable change in weeks or months, to allow informed decisions regarding changes in therapy.

Imaging provides an opportunity to assist in fulfilling this important objective. The next part of this article will examine the three main methods utilized for assessment of patients with RA – radiographs, ultrasound and MRI – and their respective roles in the assessment of patients with RA.

Methods of imaging assessment in RA

- Radiographs
Radiographic imaging is widely accepted as the gold standard for the assessment of disease progression in RA. The major radiographic indicators of damage in the hands and feet of patients with early RA are joint space narrowing, periarticular osteoporosis and bony erosions [27]. Radiographic scores, such as the Larsen and Sharp scores [28,29], and their modifications [30–32], are the standard methods to determine joint damage and its progression. The Sharp score evaluates joint erosion with a score between 0 and 5 for each joint, with a separate score for joint space narrowing on a scale of 0–4 per joint. The Larsen score assesses the degree of joint destruction with a single score from 0 to 5 – the score is mainly determined by erosive changes [33]. The original scoring methods included only the hands, but later modifications of the Sharp score have included the feet as part of the scoring method (Figure 1).

The advantages of radiographs are that they provide an easily accessible, low-cost, permanent record of joint damage in patients with RA [34]. Reproducibility of the scoring methods has been demonstrated over a broad spectrum of severity (intra-reader and inter-reader) [35,36] as well as sensitivity to change in longitudinal studies [37], particularly for the Sharp method [38].

Despite these documented benefits, radiographs have significant limitations. In RA, these limitations relate primarily to sensitivity, especially in early disease, and responsiveness, both in clinical practice and in drug trials. These factors in turn are affected by image acquisition specifications, by reader variability, and also by the phenomenon of ceiling effects, especially in patients with more advanced disease [39].

The issue of sensitivity is an understandable one. Radiographs are a 1D method of representing complex 3D structures and whilst providing excellent spatial resolution, impart poor contrast resolution when compared with techniques such as CT or MRI. The result is that pathology is sometimes difficult to distinguish from normal anatomy, especially in early disease, with the consequence that there is a well-documented lag time of up to 12 months after diagnosis before definite abnormalities become apparent [40,41]. This has implications not only for clinical practice but also for drug trials in patients with newly diagnosed RA.

The issue of contrast resolution also has an impact on the responsiveness of the radiographs – the fundamental property of providing an adequate representation of damage progression. Radiographs have an impressive track record in documenting damage progression in clinical trials of new therapeutic agents and remain the gold standard in this respect [42], but the framework is shifting rapidly.

This is reflected in the lack of correlation between radiographic findings and measures of disability in patients with RA in clinical trials [43]. With respect to longer term cohorts,
Scott et al. have demonstrated that there is a poor correlation between radiographic damage and loss of physical function until disease has reached 8–15 years [44]. This lack of correlation confounds attempts to determine a meaning for the important minimal difference in radiographic progression and raises concerns that radiographs may represent only the tip of the joint damage iceberg.

The other major drawback of radiographs is that they provide only a qualitative, rather than a quantitative, expression of joint damage and joint damage progression. To circumvent these problems, quantitative radiographic analysis has been examined by a number of groups. Inexpensive methods have included erosion volume and joint space measurement using plastic template overlays [45]. This technique demonstrated good correlation with standard Sharp scores but reader reliability was not assessed. More recently, computerized image analysis of joint space and erosion volumes in the hands have been trialed by several groups. The computerized system has proved to be reproducible on each occasion, but showed poor correlation with standard joint space scoring in the study by Angwin et al. [46], and poor correlation between erosion volume and the standard erosion score in the study by Sharp et al. [47]. Therefore, radiographs remain the gold standard for assessing outcome and damage progression in clinical trials [48], but this is rapidly altering, with MRI and ultrasound providing viable, sensitive and responsive alternatives.

Ultrasound
Ultrasound features that are evaluated in RA for determining disease activity include evaluation of synovitis and tendon inflammation, and in terms of damage, bone erosions. The validity of ultrasound is established through comparison to other methods of imaging (construct validity), as well as to histology (criterion validity). Importantly for the evaluation of synovitis there are also data to support responsiveness to change after the treatment of RA.

Bone erosion
Ultrasound provides information on the bone surface, allowing the evaluation of cortical defects in RA. Bony erosions are an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes [49]. This appears as hypoechoic areas along the surface of hyperechoic bone (Figure 2A & 2B).

The difficulties in ultrasound evaluation of erosions are in two areas. First, the reliability of acquisition of the ultrasound image, and second...
the inability to insonate past other bony surfaces precludes total evaluation of the 3D structure of the bony surface.

Therefore, in comparison to other imaging techniques the greater definition of the bony surface on ultrasound in comparison to plain radiograph provides advantages, whilst CT and MRI will provide more information given the greater joint coverage. Certainly, in areas where there is good access to the joint, for example at the radial aspect of metacarpophalangeal (MCP)-2, ultrasound is equivalent to MRI in evaluating erosions [50].

The ability of ultrasound to evaluate bone erosions superiorly to plain radiographs but inferiorly to MRI and CT are well described by cross-sectional studies in the metacarpophalangeal joints and metatarsophalangeal joints [51,52]. Longitudinal studies at the MCP joints and wrist have further confirmed that ultrasound-detected erosions are seen on plain radiographs at 7 years [53]. Importantly, ultrasound-detected erosion are shown to reflect erosions seen on CT and MRI, confirming the validity of ultrasound erosion evaluation [54]. Further ultrasound is more responsive to erosions progression over 12 months in early disease when compared with conventional radiology [55,56].

**Cartilage**

Cartilage can be seen as a hypoechoic layer above the hyperechoic bone on ultrasound. It has not been well studied in RA and further work is progressing to try to establish whether ultrasound evaluation is both valid and practical.

There are increasing data regarding the use of ultrasound in the evaluation of cartilage in disorders such as osteoarthritis and crystal arthropathies, but discussion of these entities is beyond the scope of this article.

**Tendon pathology**

The available data for tendon evaluation in RA are somewhat heterogeneous in terms of results, and this section therefore reflects the available data.

Tenosynovitis in RA can be depicted on ultrasound as thickening of the tendon with a hypoechoic layer surrounding the tendon. There is often Doppler flow in the tendon sheath in association with the hypoechoic fluid (Figure 3). Ultrasound in comparison to MRI in evaluation of tenosynovitis in limited studies suggests similar to slightly better results with MRI [57,58].

Tendon tears appear as a hypoechoic defect in the fibrillar pattern of the tendon on ultrasound. Similar results to the limited tenosynovitis studies comparing ultrasound to MRI were seen in the detection of tendon tears in RA [59].

**Synovitis**

This is the most studied area with ultrasound in RA. It is seen on B-mode ultrasound as a hypoechoic area, which is often hyperemic with Doppler sonography (Figure 4). Technically, power Doppler is the best method of detecting hyperemia of synovium in comparison with color Doppler, as it has in general a higher sensitivity in low blood flow tissues. It is also a more accurate depiction of the number of red blood cells in comparison with the speed and direction of blood flow that is shown with color Doppler sonography [60,61].

Validation of ultrasound-detected synovitis has been performed against histology in the knee and hip and, importantly, in these studies the Doppler signal was shown to correlate with histological vessel numbers [62]. Ultrasound detection of synovitis has also been evaluated against MRI in the knee, wrist, metacarpophalangeal, metatarsophalangeal
joints, ankle and shoulder, all showing the superiority for the detection of synovitis with MRI in comparison with ultrasound related to the better total joint capture of MRI [63–65].

There are multiple studies showing that synovitis on ultrasound reduces in size and vascularity with treatment [66–68]. Importantly, the presence of vascular synovium seen on ultrasound has been shown to predict erosive change [69]. This relationship has been seen in other studies confirming the predictive validity of ultrasound [70,71]. The work by Brown et al., in particular, has shown that the presence of ultrasound-detected synovitis predicts erosive change in RA patients thought to be in clinical remission [71].

Scoring the degree of synovitis and vascularity has not been standardized, although there are a number of semiquantitative scoring systems, usually grading from 0 to 3, or none, mild, moderate and severe [72–74]. Quantitative scoring systems use the amount of synovium on grayscale through measurement in a single axis, but this has been difficult due to reliability issues. The quantification of Doppler results has been performed through outlining a region of interest and either measuring the number of color pixels or the color pixel intensity [75,76]. The OMERACT ultrasound group is moving towards a global scoring system that is still in development but has undergone the initial stages of reliability testing [77].

MRI

Several MRI outcome features have emerged as most frequently utilized for the assessment of RA. These were measures of activity (e.g., synovial assessment, bone edema [osteitis] and tendon inflammation) and measures of damage (e.g., bone erosions and cartilage loss) [78]. First, a brief discussion of each MRI abnormality will be presented. It is important to recognize that the criterion validity of the MRI lesions has not been completely established; therefore, the appearance of each abnormality is discussed with the relevant information regarding validity for each finding.

Bone erosion

MRI provides 3D representation of bony structures, and therefore provides better definition of bony abnormalities when compared with plain radiography, especially in complex regions, such as the wrist. Bone lesions regarded as bony erosions on MRI appear as focal areas of reduced signal [79] intensity on T1-weighted images (Figure 5).

The advantages of MRI of the wrist and MCP joints when compared with radiographs are well documented in cross-sectional studies of patients with early disease (disease duration less than 12 months) [80–85]. MRI provides earlier identification of erosions, with MRI abnormalities appearing well before radiographic change. Importantly, longitudinal studies of unilateral-dominant wrist MRI, compared with standard radiographs in early disease, have shown that MRI is more responsive to erosion progression over a 12-month period [86] and that early MRI erosions correspond to radiographic erosions appearing at 2 and 6 years (Figure 6) [87,88].

The issue of joint capture was an early barrier for MRI. While radiographs are not responsive in the short term to joint damage progression, they do provide capture of more joints than MRI (both hands and feet). However, rigorous examination of this issue demonstrated that MRI of the MCP joints and wrist of the dominant hand is equivalent to radiographs of the hands and feet in documenting RA progression [89,90]. What MRI loses...
in joint capture, it gains in responsiveness and, therefore, MRI of the dominant wrist and MCP joints can be viewed as an adequate representation of global joint damage progression.

**Osteitis (bone edema)**
Areas of bone abnormality, termed bone edema, appear as areas of low signal intensity on T1-weighted images, with high signal intensity apparent on corresponding T2-weighted images. The lesion is often described as ‘feathery’ in appearance, with ill-defined margins (Figure 7). In practice, fat-suppressed T2-weighted images are employed to identify areas of bone marrow edema, providing a more distinct delineation of the bone marrow pathology [91]. There is strong evidence to suggest that bone marrow edema precedes the development of subsequent MRI and.

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**Figure 5. Bony erosion third proximal metacarpophalangeal joint – low signal on T1-weighted image.**
Reproduced with permission from [134].

**Figure 6. MRI and radiograph of the wrist at 12 months of erosion progression (A) and baseline (B).** Bone lesions on MRI (arrowed) not shown on radiograph; progressive enlargement of the MRI bone lesion at 12 months of erosion progression with corresponding abnormalities on x-ray. Reproduced with permission from [135].
radiographic erosion [92,93], and therefore the finding has been proposed as a predictor for erosion in patients with early RA (Figure 8) [94,95]. The finding has been demonstrated in surgical specimens of patients with RA [96] undergoing joint replacement, and increased numbers of osteoclasts and RANK-ligand have been demonstrated on pathological specimens. Osteoclast numbers and expression of RANK-ligand, two important factors in bone erosion, have been noted in higher concentration in the areas on MRI osteitis [97].

Osteitis represents a special issue. In RA, some areas of osteitis progress to erosion, but the association is not absolute, and there is evidence that areas of osteitis can regress, being ephemeral in nature, and not leading to erosion. For example, the study by McQueen et al. demonstrated a positive relationship between osteitis and erosion, but the relationship was modest, indicating that whilst it is a reasonable predictor of subsequent damage, not all osteitis leads to erosion [98]. The sensitivity and specificity of osteitis in RA has not been established, and this remains an ongoing research issue. The challenge for researchers is to identify what MRI features are candidates to allow discrimination between nonthreatening and threatening areas of osteitis.

**Synovitis**

Normal synovial tissue does not enhance postgadolinium – synovitis appears as an area of increased signal intensity greater than the width of normal synovium, on T₁-weighted postgadolinium images (Figure 9) [99]. Synovitis can be detected by static or dynamic methods. Obviously, the synovial tissue cannot be visualized by radiographs and study of the appearance on imaging of the synovial membrane in patients with RA is restricted to MRI and ultrasound.

Synovitis has been correlated with subsequent erosive disease on MRI [100,101] and has been used as an indicator of treatment efficacy (Figure 10) [102–104].

Validation of the MRI abnormality identified as synovitis has been more rigorously evaluated for the knee and MCP joints.

**Tendon pathology**

Tendonitis, tendon sheath inflammation and tendon rupture are all depicted by MRI [105]. While MRI findings correlate with clinical and ultrasound findings [106,107], the significance of tendon pathology in predicting erosive disease is uncertain, as only one group [108] have incorporated tendon abnormalities as part of a global scoring system. Therefore, the significance of tendon abnormalities in RA remains an ongoing research issue.

**Cartilage defects/cartilage loss**

A standard T₁ axial and coronal sequence is accepted widely as providing adequate resolution for the detection of erosions, but this does not provide adequate visualization of cartilage. In larger joints, such as the knee, 3D gradient...
echo has been recommended as the most effective sequence for estimating cartilage defects and cartilage volume in osteoarthritis [109]. Unfortunately, studies examining the role of MRI in detecting cartilage defects in the knee in RA are small in number [110–114] without clear validation, and this remains an area where there is a lack of information regarding one of the important processes in RA. The visualization of cartilage in the MCP joints and wrist is an even more difficult problem – whilst 3D gradient echo sequences provide some detail in this region, there are still problems related to the size of the joints in the hand, leading to problems differentiating articular cartilage from underlying bone. The use of thin partition 3D MRI combined with T₁-weighted images and specialized surface coils has been shown to be advantageous in delineating cartilage in the MCP joints [115], but studies examining the reproducibility of this method in large numbers of patients with RA are lacking. The OMERACT group is pursuing a cartilage score, but at the time of writing, the score has not been published.

MRI measurement technique

OMERACT MRI score

In 2003, the OMERACT [116] group published an international scoring system – a system with documented inter- and intrareader reliability with a semiquantitative approach to scoring erosions [117]. Through rigorous evaluation, reproducibility of the score for synovitis, osteitis and bone erosion has been established for both cross-sectional and longitudinal studies [118,119].

In 2004 an atlas was published, providing reference images and score rationalization [120,121]. This scoring system has become the standard method for scoring MRI in clinical trials, replacing previous scoring systems.

Quantitative measurement

Erosion volume and synovial volume measurement has been undertaken by several groups [122–124], with the aim of providing a more accurate representation of joint damage and inflammatory activity. Semiautomated and automated computer programs have been utilized, with correlation demonstrated between erosion volumes and the OMERACT erosion...
score (Figure 11). Barriers to widespread use largely relate to the time required for segmentation, and the lack of available software to provide a truly automated volume in joints. The recent development of software designed to display dynamic 3D images [125] will assist in the pursuit of automated volumes, and this remains an important goal for researchers.

Figure 11. Erosion volume manual (semiautomated) method triquetrum erosion. Reproduced with permission from [139].

Figure 12. Bony erosion in the third metacarpophalangeal joint, proximal portion. Coronal and axial views demonstrate the erosion. No statistical difference was demonstrated between the volumes on MRI and those for CT. Ax: Axial; Cor: Coronal. Reproduced with permission from [140].
Computerized tomography

Computerized tomography is arguably the best method to demonstrate bony pathology, and entails use of ionizing radiation. This is not ideal, especially in situations where repeat examinations are required in a short period of time. The main utility of CT is related to erosion detection, but the technique does not provide information regarding synovitis and osteitis. Comparison studies of CT and MRI [126–128] in the assessment of bone erosion in patients with RA have shown no significant difference for detection of erosions or measurement of erosion size (Figure 12). Therefore, while CT remains a possible technique for assessment of RA patients, limitations of information gained with each examination, as well as concerns regarding ionizing radiation, have limited its widespread application.

Low-field versus high-field MRI comparison

Extremity MRI is an attractive alternative to conventional MRI; the main advantages of this method over conventional MRI include lower cost, enhanced patient comfort and reduced imaging time. The main perceived disadvantage of the low-field method is lower signal-to-noise ratio, which may affect image quality, and therefore erosion, osteitis and synovitis scoring.

Initial unireader studies comparing low-field and high-field MRI [129,130] in RA demonstrated an advantage of high-field over low-field MRI. More recent multireader studies have demonstrated excellent inter-reader agreement for erosions, with the apparent lower image quality of extremity imaging not affecting erosion scoring (Figure 13) [131]. Osteitis and synovitis agreement...
was, however, less robust in these studies, but still demonstrated acceptable inter-reader reliability. Whilst this is not a barrier to the use of low-field extremity imaging in the assessment of synovitis and osteitis, caution needs to be exercised when comparing low- and high-field measures of activity, particularly if readers are not familiar with the appearance of synovitis and osteitis on low-field imaging [132].

**Executive summary**

- Rheumatoid arthritis (RA) is a severe, multisystem disorder that results in considerable morbidity and early mortality due to accelerated cardiovascular disease.

**Methods of joint imaging in RA**

- Radiographs:
  - 1D representation of damage.
  - No information on soft tissue structures.
  - Slow to detect change.
- Ultrasound
  - Easily accessible, widely used imaging method in rheumatology.
  - Provides useful and easy-to-access information on synovitis, tenosynovitis and bone erosions in RA.
  - Provides diagnostic information as well as assessment of treatment efficacy.
  - The use of grayscale and Doppler assessment of synovitis is an important method of determining disease activity.
- MRI
  - Provides information regarding the three key processes in RA – synovitis, osteitis and bone erosion.
  - More sensitive and responsive than radiographs and allows visualization of soft tissue structures.
  - Scoring systems, such as the OMERACT EULAR scoring system, provide standardization of scoring, and quantitative assessment of erosions and synovitis is increasing.
  - Osteitis appears to be a good predictor of subsequent bony erosion.
  - A cartilage narrowing score is currently being developed.
- CT
  - Excellent anatomic detail for erosions, but does not provide information on soft tissue processes.
  - Lack of soft tissue detail and radiation exposure reduces utility in RA.

**Future perspective**

MRI and ultrasound will continue to complement radiographs in the assessment of RA. In view of the sensitivity and responsiveness of ultrasound and MRI, it is anticipated that these methods will increasingly be utilized in the assessment of patients with RA.

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Papers of special note have been highlighted as:

- of interest
- of considerable interest


Monitoring progression of rheumatoid arthritis & predicting outcome


56 Hammer HB, Haavardsholm EA, Bøyesen P, Kviin TK: Bone erosions at the distal ulna detected by ultrasonography are associated with structural damage assessed by conventional radiography and MRI: a study of patients with recent onset rheumatoid arthritis. Rheumatology (Oxf) 48(12), 1530–1532 (2009).


** Good paper comparing MRI and ultrasonound.


** Very useful study, summarizing key issues related to sensitivity, specificity and responsiveness.


Excellent summary of techniques of Doppler ultrasound.

**Excellent summary of MRI quantification methods.**


Hertl MA, Ejbjerg B, Harløve-Petersen K et al.: CIMESTRA study group: MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). 68(3), 384–390 (2009).

**Examine the issue of osteitis as a predictor of erosive change.**


Excellent summary of current metacarpophalangeal joint MRI scoring methods.


