

Rheumatoid arthritis

MRI of the wrist in early rheumatoid arthritis

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Can it be used to predict long term functional outcome?

The past several years have witnessed unprecedented advances in rheumatology, with the introduction of several new compounds capable of halting the relentless progression of joint destruction and functional disability in patients with rheumatoid arthritis (RA). With these successes, however, have come new pressures for medical imaging to resolve even the slightest traces of erosive joint damage and to identify pre-erosive inflammatory features that can accurately predict which patients will go on to severe functional debility if they do not receive aggressive structure modifying treatment immediately.

PREVIOUS DEMAND FOR IMAGING JOINT STRUCTURE

Before the introduction of effective treatment, rheumatology's demand for imaging joint structure was modest, at best (fig 1). Although it was widely accepted that joint damage was a key driver of functional disability in RA, particularly in late disease,¹⁻³ without effective treatments to prevent erosive destruction, there was limited need for detailed information about the integrity of joint structure. Magnetic resonance imaging (MRI) promised to tell more about bone erosion, synovitis, and the integrity of cartilage, ligaments and other articular tissues than radiography ever could, but the additional cost and inconveniences associated with MRI were not felt to be worth the extra performance. The information simply did not impact on clinical management. Accordingly, most rheumatologists focused primarily on clinical and laboratory features of the disease, and used imaging only sparingly—if at all. Not surprisingly, the development of MRI for this purpose languished. However, the recent introduction of effective structure modifying treatments has changed the way that rheumatologists manage patients with RA, and this has created new demands on imaging both in clinical practice and in clinical research.

MONITORING TRIALS: MORE SENSITIVE METHODS NEEDED

One important change is that it is no longer ethical to withhold effective treatment from patients, and therefore to conduct placebo controlled clinical trials. This means that putative new agents must be tested against established treatments with known efficacy. Because such studies show much slower progression and smaller differences among treatment groups, they take substantially longer and require greater numbers of patients and clinical sites to achieve statistical significance. This increases the cost of clinical research and slows progress considerably. Unless more sensitive methods of predicting and monitoring treatment effect are developed the financial and practical ramifications of this problem will severely hinder further progress in therapeutic agents for RA.

“Sensitive methods of monitoring treatment effects are needed urgently”

TARGETING EARLY DISEASE

Additionally, the availability of effective structure modifying treatment has stimulated a trend towards early, aggressive treatment before the development of joint damage⁴⁻⁵ and associated irreversible functional disability.⁶⁻⁸ During the first few years of disease, inflammation rather than structural damage accounts for most functional disability in RA.¹⁻⁹ By eliminating inflammation at this stage, therefore, one can achieve full functional recovery. Indeed, inflammation is potentially reversible at any stage of the disease. However, as structural damage accumulates an increasing proportion of functional disability becomes irreversible. Accordingly, current treatment strategies target early disease to limit cumulative structural damage.⁵⁻⁶

However, 30%–40% of cohorts with early RA do not progress, and therefore may not require aggressive treatment. Some have advocated treating all patients aggressively anyway in order

to avoid missing those who might progress.¹⁰ However, such a catch-all strategy carries significant financial and toxicity implications, as well as potential production challenges in some cases. Moreover, including non-progressors in clinical trials dilutes statistical power and necessitates exposing larger numbers of patients to experimental treatments for longer periods of time in order to test therapeutic efficacy adequately. Clearly, there is a need for better ways of identifying the aggressive phenotype of RA in early disease.

DETECTION OF EROSIVE DAMAGE

Absence of erosive damage on radiographs accurately identifies non-progressors among patients with established disease (>18 months), but is only 41% accurate in patients with RA of less than 6 months' duration.¹⁰ Devauchelle Pensec *et al* found that radiographs acquired before 1 year of disease could not even reliably predict which patients would still have the diagnosis of RA 2 years later.¹¹ Positive radiographs in their study were highly specific (96%) but diagnostically insensitive (17%). Others have reported similar findings.¹²⁻¹⁴ Earlier reports by McQueen¹⁵⁻¹⁶ of the same cohort of patients described in Benton's article in this issue of the *Annals*²⁰ asserted that fewer than 20% of patients with RA of less than 6 months' duration show erosions on radiographs. In a different study by Machold *et al* fewer than 13% of patients with RA showed radiographic erosions before 3 months.¹⁷ Accordingly, technical sensitivity for bone erosion is a critical performance requirement for imaging in early RA.

“Unlike MRI, radiography cannot detect all erosions or pre-erosive inflammation”

Unfortunately, radiography's capacity for increased sensitivity is limited. Erosions that are not aligned tangentially to the x ray beam (typically, erosions of dorsal and volar bone surfaces) are projected en face and can be obscured by superimposed bone. Penetrating erosions that are predominantly intramedullary and therefore surrounded by bone are also often obscured and difficult, if not impossible, to see. Additionally, joint flexion/contracture, subluxation or changes in x ray beam centring can simulate joint space narrowing on radiographs. Radiography also cannot detect pre-erosive inflammation or directly visualise non-osseous components of the joint, such as articular cartilage, synovium, joint effusion, ligaments, tendons, discs, labra, menisci, or muscles.

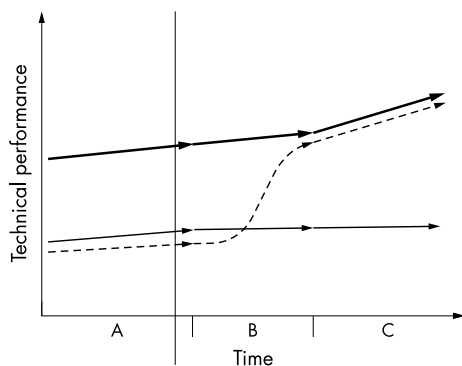


Figure 1 Technical demand-performance relationships for radiography and MRI in RA. (A) Before the availability of effective structure modifying treatment, clinical rheumatology's demand for technical performance in imaging (broken line) was modest and flat, increasing only slightly over time. Radiography (thin line) met these technical demands, and was the dominant imaging method used. MRI (thick line) was technically better than radiography, but rheumatologists were satisfied with radiography's performance, and therefore not willing to pay more for MRI. MRI exhibited a performance surplus, and was not used. (B) With the introduction of effective treatments for RA, rheumatology's technical requirements for imaging have increased beyond the delivery ability of radiography, creating a new demand for MRI's added performance. (C) Rheumatology's technical demands for imaging will continue to increase over time, and this will drive further technical development in MRI to keep pace.

MRI, on the other hand, is unparalleled in its ability to image arthritic joints. Because it generates tomographic rather than projectional images, MRI can delineate erosions along all surfaces of bones, including the dorsal and volar surfaces, as well as the intramedullary component of penetrating erosions (fig 2). Dozens of studies have shown that MRI is several times more sensitive than radiography¹⁶⁻¹⁸⁻²⁷ or ultrasound²⁷ for detecting bone erosions. This advantage of MRI has been demonstrated not only with conventional 1.5 T MRI but also with small, low field (0.2 T) MRI systems,²⁷⁻²⁸ which can image joints at a fraction of the cost of conventional MRI.²⁹

Baseline MRI showed bone erosions in 42% of the patients with early RA in Benton's study,⁷⁰ whereas radiography detected erosions in only 15% of these patients. Within 1 year, MRI was able to show the emergence of 134 new erosions. Moreover, the baseline erosion score was predictive of radiographic erosion score at 2 years ($p = 0.004$).¹⁶ Sixty one per cent of patients with erosions on MRI at baseline showed erosions on radiographs after 2 years, whereas only 18% of patients without baseline MRI erosions showed radiographic erosions in the same time interval. When bone marrow oedema, synovitis, and tendonitis/tenosynovitis were also taken into account, MRI was even more predictive of subsequent radiographic erosion, offering optimised sensitivity and specificity values of 80% and 76%, respectively, and a negative predictive value of 86%.¹⁶ Accordingly, in contrast with radiography, MRI can identify patients with early RA who are unlikely to express an aggressively erosive phenotype and therefore less in

need of aggressive, costly, structure modifying treatment. Excluding these people from clinical trials of putative new treatments can reduce the number of patients, study sites, and study duration required to test treatment efficacy.

BONE MARROW OEDEMA

One of the most intriguing MRI features of active RA is what many have called bone marrow oedema. This feature presents as free water signal in otherwise fatty marrow of articular bones, and is most conspicuous on fat suppressed, T₂ weighted images (fig 3). In contrast with bone erosions, which have sharply defined margins and contain only synovial fluid or synovial tissue, areas of marrow oedema typically have poorly defined, feathery margins and contain residual trabeculae and marrow tissue, which are identified by the presence of magnetic susceptibility effects and T₁ contrast, respectively. Additionally, these areas are enhanced after intravenous injection of contrast material containing gadolinium (Gd) (fig 3),³⁰ and correlate with clinical markers of inflammation, including C reactive protein (CRP) and disease activity score (DAS).⁷⁰ Accordingly, "osteitis" may be a more appropriate term for this inflammatory feature.³⁰

OSTEITIS

Several investigators have reported a high prevalence of osteitis in the hands and wrists of patients with RA, and presented evidence that osteitis can progress to bone erosions.¹⁵⁻¹⁹⁻²⁴⁻³¹⁻³³ In the study by Benton *et al*, osteitis at baseline in patients with early RA was more predictive of bone erosions and functional outcome 6 years later than

were any other MRI features, clinical features, or CRP, alone or in combination.⁷⁰ Consistent with previous studies, erosive damage correlated with functional disability at 6 years but not in early disease, whereas osteitis correlated with disability in early disease, but not at 6 years. Interestingly, although DAS and the Health Assessment Questionnaire (HAQ) improved mildly during the first 2 years of the study, presumably due to treatment (no TNF α inhibitors or other biological agents), the median osteitis score remained relatively constant throughout the 6 years, and the bone erosion score increased relentlessly and almost linearly over that same period.

Examples of osteitis resolving before the development of frank erosion have also been reported in this group and others.¹⁵⁻³³ Accordingly, osteitis may be useful not only for predicting which patients are likely to progress but also for monitoring anti-erosive treatment in these patients. In contrast with bone erosion, which is typically used as a negative marker, in that it indicates efficacy by *not* happening,³⁴ recession of pre-existing osteitis provides direct evidence that the process driving erosion has ceased, and thus offers more rapid indication of therapeutic effect. Such a responsive marker would be useful for optimising treatment in clinical practice, and for short proof-of-concept trials and other internal decision making studies in clinical research.

"HEALING" OF EROSIONS

Filling in, or "healing", of pre-existing erosions, a phenomenon which has been seen both with radiography³⁵ and MRI (fig 2), similarly provides direct indication that the erosive process has stopped, and thus may also allow more rapid assessment of therapeutic efficacy. How frequently erosion "healing" occurs and whether or not it is accompanied by functional improvement is not known. It appears to be relatively uncommon on radiographs,³⁵ but it is not an infrequent finding on MRI, at least anecdotally. The reason for this discrepancy may be technical. As for other osseous lesions, most radiographic lucency associated with RA erosions is attributable to cortical bone loss. The intramedullary component of bone erosions (fig 2), unless associated with a calcified rim, is difficult to see with radiography. Penetrating erosions that have only small cortical components, therefore, are underestimated or occult on radiographs, particularly if the cortical defect is projected en face. These types of erosions, however, may be predisposed to reparative filling in, as they are surrounded by bone on

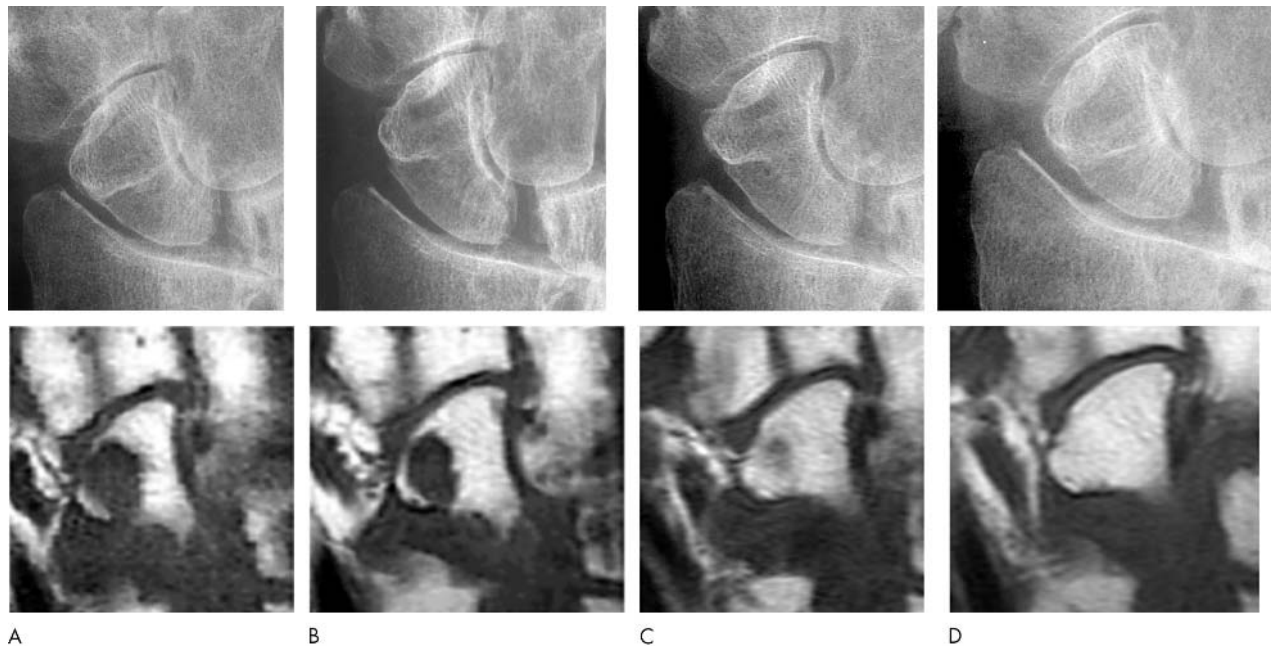


Figure 2 MRI is more sensitive than radiography for bone erosions. Radiographs and coronal T₁ weighted images at baseline (A); 3 months (B); 6 months (C); and 24 months (D) of a patient treated with methotrexate show a penetrating bone erosion in the distal pole of the scaphoid bone with a large intramedullary component. Despite the size of this erosion, it is barely visible with radiography. Follow up images show gradual filling in of the erosion over 2 years. Reproduced with permission of the copyright holder from Peterfy CG. *Magnetic resonance imaging of the wrist in rheumatoid arthritis. Semin Musculoskelet Radiol* 2001;5:275-88.

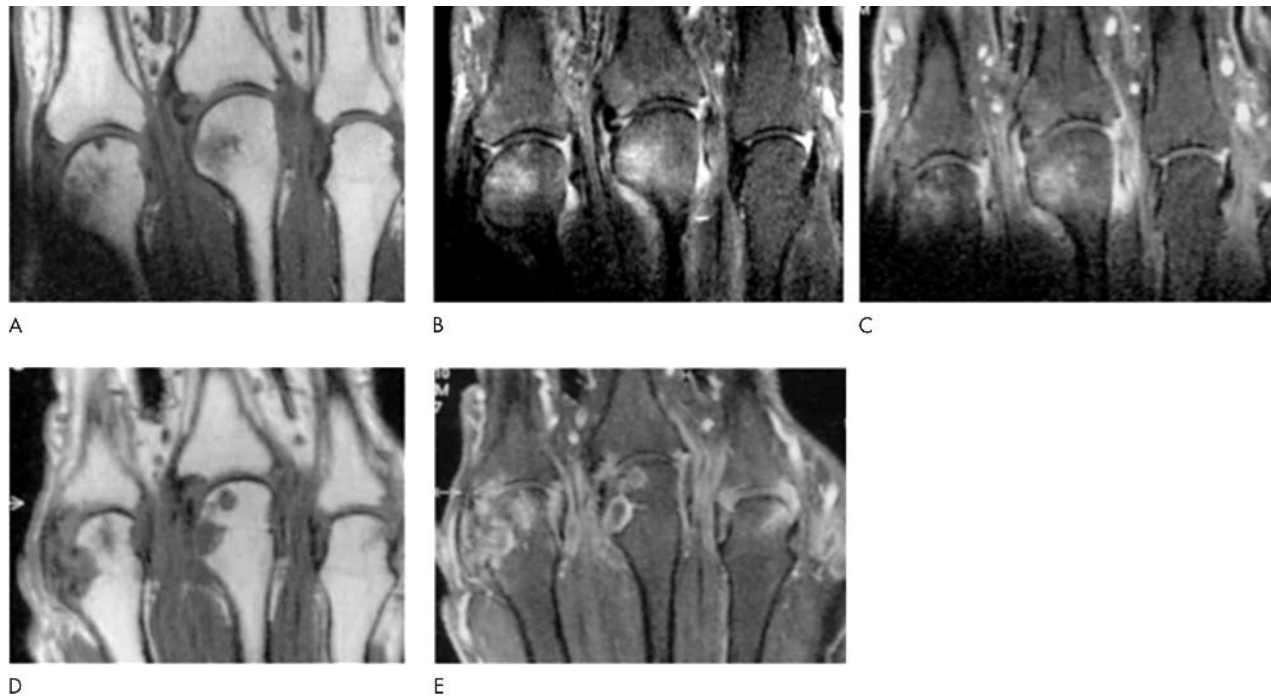


Figure 3 Pre-erosive osteitis. Coronal T₁ weighted (A) and fat suppressed T₂ weighted (B) spin echo images of the metacarpophalangeal joints of a patient with RA show areas of osteitis in the distal second and third metacarpals. The more sensitive fat suppressed T₂ weighted images also show these changes in the adjacent proximal phalanges. Fat suppressed T₁ weighted spin echo with Gd-DTPA (C) shows enhancement of these areas consistent with inflammation. Follow up images 17 months later (T₁ weighted images without (D) and with (E) fat suppression and Gd-DTPA) show development of bone erosions with sharply defined rim enhancing margins at these sites of previous osteitis, and a new focus of osteitis in the previously quiescent fourth metacarpal head. Reproduced with permission of the copyright holder from Peterfy CG. *Magnetic resonance imaging of the wrist in rheumatoid arthritis. Semin Musculoskelet Radiol* 2001;5:275-88.

all sides. Non-penetrating erosions associated with extensive cortical bone loss may lack sufficient scaffolding to guide bone synthesis. Because MRI is disproportionately more sensitive to penetrating erosions, MRI would be expected to detect more "healing" erosions than radiography does. Again, erosion "healing" does not necessarily imply biomechanical recovery. However, it is a direct indication that the erosive process has stopped, and therefore it is a potentially useful marker of therapeutic efficacy. However, no reported studies have systematically examined erosion "healing" on MRI thus far.

SYNOVITIS

Synovitis is another hallmark feature of RA that is visible with MRI. In the absence of fatty infiltration (lipoma arborescens),³⁶ fibrosis, or iron accumulation (haemosiderosis), however, thickened synovial tissue can be difficult to differentiate from adjacent synovial fluid with conventional MRI pulse sequences,³⁷ and intravenous contrast material containing Gd is typically required.^{21 37-44} Various segmentation techniques can be used to measure the volume of this enhancing, inflammatory compartment in the wrist or fingers.^{45 46} In a recent study Savnik *et al* measured similar synovial volumes with low field (0.2 T) dedicated extremity MRI as with conventional 1.5 T MRI.⁴⁷ A number of studies have found that synovial volume correlates with joint swelling and tenderness,^{21 45 46 48 49} and is predictive of bone erosion on follow up images.^{15 21 28 33 50} In one of these studies clinical examination detected only 49% of cases of synovitis demonstrable with low field dedicated extremity MRI.²⁸ In the study by Benton *et al* the synovitis score did not correlate with clinical features at any time point, but it did predict erosions on MRI at 6 years.⁷⁰

In addition to volume, the rate and magnitude of synovial enhancement on sequential MR images after bolus intravenous injection of contrast material containing Gd has been shown to correlate with the histological severity of inflammation in the synovium⁵¹⁻⁵³ and with clinical markers of disease activity.⁵⁰ Enhancement of synovium can be accurately quantified by dynamic MRI of single sections through the wrist.⁵⁴ In a recent randomised clinical trial, the knees of 34 patients with RA were examined with dynamic, gadolinium enhanced MRI at baseline and after 4 months of treatment with leflunomide¹⁷ or methotrexate.^{17 55} Despite the small number of patients and short study duration, measurements of the rate of synovial enhancement showed a statistically significant difference between

the two treatment groups, whereas the clinical examinations could not. In an earlier report, histological findings from synovial biopsies of the same joints correlated well with these MRI results.⁵⁶ Several other studies have also shown that synovial volume and synovial enhancement decrease with treatment, but the follow up interval in many of these was 6 months or longer.^{21 49 50 57-60}

ARTICULAR CARTILAGE

Another unique strength of MRI is its ability to directly visualise articular cartilage.⁶¹⁻⁶⁴ Direct imaging of this tissue is more specific than radiographic joint space width, and tomography provides greater anatomical coverage of the joint surface than projection does. A number of morphological and compositional MRI markers of cartilage integrity have been developed,^{61 65-67} but most of this work derives from the knee, because the articular cartilage in the hand and wrist is extremely thin, and high resolution imaging techniques are required.

TENDON PATHOLOGY

In addition to monitoring changes in the bones, cartilage, and synovium, MRI can directly visualise the full spectrum of tendon pathology, and has been shown to identify tendonitis and tendon rupture with greater accuracy than clinical examination.^{68 69} In Benton's study, tendon score was not itself predictive of either bone erosion or functional disability, but when combined with bone erosion, osteitis, and synovitis both were predictable.⁷⁰ Ligaments and the triangular fibrocartilage complex can also be examined directly with MRI. However, to date, very little attention has been given to imaging these structures in RA.

SUMMARY

In summary, as effective structure modifying treatments for RA begin to enter mainstream clinical practice, and early aggressive treatment becomes more widespread, the use of conventional radiography for managing patients with RA will continue to diminish. As Benton's report demonstrates, MRI offers a powerful alternative to radiography in this circumstance. It is far more sensitive than radiography for bone erosion in patients with early RA, and can detect pre-erosive features, such as osteitis and synovitis, along with tendonitis and potentially other MRI features that can be used to predict which patients will go on to severe destructive joint damage and irreversible functional disability. Being able to predict this accurately at the time of initial presentation is crucial to effective patient management.

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