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Review

# Magnetic resonance imaging in early inflammatory arthritis: what is its role?

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## Abstract

Magnetic resonance imaging (MRI) has important applications in musculoskeletal medicine. It allows the visualization of bone and soft tissues in three dimensions using a multiplanar technique and is uniquely suited to imaging the rheumatoid joint. Bony erosions are seen well using MRI in early rheumatoid arthritis and are frequently detected before they appear on plain radiographs. Bone marrow oedema is another important MRI feature associated with inflammatory joint disease and may be a forerunner of erosion. Synovial membrane inflammation and hypertrophy are detected after contrast enhancement and also by the use of dynamic MRI techniques, which provide a non-invasive method to accurately measure the inflammatory process. This information can be analysed and collated using MRI scoring systems and ultimately may be used to improve diagnostic accuracy, predict prognosis and monitor therapy in these patients. This review examines the case for the use of MRI in early inflammatory arthritis, outlining its strengths and potential weaknesses as an imaging modality in this context and indicating its potential role in clinical practice.

Magnetic resonance imaging (MRI) has important applications in musculoskeletal medicine. It is now widely used by orthopaedic surgeons in the diagnosis of bone and soft tissue pathology. For rheumatologists, it may assist in the evaluation of back pain by imaging spinal structures such as intervertebral discs and spinal nerve roots, and it also has an important place in the diagnosis of aseptic necrosis [1]. However, the application of MRI to the investigation of inflammatory arthritis, and specifically rheumatoid arthritis (RA), remains less clear. Many clinicians are unwilling to request scans for their early RA patients because guidelines are lacking as to when scans are most cost-effective and likely to influence management. The purpose of this review is to summarize the literature regarding the use of MRI in RA and to provide some direction for its use in this context.

## Imaging the anatomy of the joint

MRI is unquestionably an excellent technique for imaging the anatomy of the rheumatoid joint. It allows visualisation of bone and soft tissue in three dimensions as it employs multiplanar tomography and therefore provides much better definition of bony detail than plain radiology in complex regions such as the carpus [2]. Cartilage can also be seen well by employing certain MRI sequences to maximize the differences in signal between this tissue and adjacent bone or synovial membrane. Fat suppression augments this contrast with soft tissue on $T_2$-weighted images and on $T_1$-weighted gradient echo images. At the knee, abnormalities of hyaline cartilage detected using these MRI techniques have been found to correlate well with findings on arthroscopy [3, 4]. However, at the wrist, the thin layer of cartilage overlying the carpal bones is much more difficult to see and cartilaginous thinning or erosions may not be defined accurately [5].

MRI has a clear advantage over other imaging modalities, such as plain X-ray imaging and CT, in its ability to image soft tissues and fluid within the joint. This often involves the use of a contrast agent, gadolinium–diethylenetriamine pentaacetic acid (Gd-DTPA), given i.v. Gadolinium is a heavy metal that exerts a paramagnetic effect on nearby water protons, causing them to relax more rapidly on $T_1$-weighted sequences. Signal intensity increases proportionate to the concentration of Gd-DTPA, which distributes rapidly to vascular tissues. Thus, highly vascular inflamed synovium enhances brightly [6, 7]. The technique of dynamic MRI allows measurement of synovitis by examining the uptake of gadolinium over time.

Joint effusions may be distinguished from synovium using gadolinium enhancement because they appear as areas of low signal intensity on $T_1$-weighted images.

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Contrast medium later diffuses into synovial fluid at a rate dictated by factors such as the volume of synovial fluid, the rate of blood flow to the synovium and the amount of joint movement which is occurring. Thus, equilibration between synovial membrane and fluid is much more rapid for small, highly inflamed MCP joints than for large, quiescent knee joints [6]. The integrity of tendons can also be assessed, as can the presence of synovitis and effusion within the tendon sheath. Acute tendon inflammation is often associated with signal change as well as swelling, which may be followed by attenuation and rupture if chronic inflammation persists. Changes in the anatomical location of tendons may be of relevance when joints have become subluxed or deformed [8].

## Pathological changes within the rheumatoid joint

Plain radiography is not a useful investigation in early RA as X-ray images usually remain normal for at least 6–12 months after symptom onset [9]. The initial pathological changes develop unseen, leaving the clinician to manage the patient according to the degree of joint inflammation while guessing at the amount of underlying articular damage. In contrast, MRI provides a window through which we are able to witness the disease process unfold from the time of presentation. Bony erosions appear as focal areas within cortical bone where the normal signal intensity is reduced on $T_1$- and increased on $T_2$-weighted images. When viewed *en face* they may appear cystic, but when profiled an overlying cortical defect is seen. Erosions often enhance after i.v. Gd-DTPA, implying the presence of inflamed synovium within the defect. Studies of MRI at the hand and wrist in RA have revealed that bony erosions develop very much earlier than had been thought from plain radiography [10, 11, 12]. The exact time to the onset of erosion has not been defined and probably varies between individual patients, but McGonagle *et al.* [13] found that 18 of 19 patients with symptoms for $<1$ yr had erosions of the dominant hand on MRI. Our own studies of RA patients with symptoms for $\leq 6$ months revealed 45% to have carpal MRI erosions at presentation, rising to 74% at 1 yr [14, 15]. This compares with 15% having erosions on X-ray at baseline increasing to 29% at 1 yr. The capitate was the most common site for erosion, consistent with observations by other investigators [16, 17]. Studies of MCP and PIP joints have been less extensive, but suggest that erosions also appear early at these sites [18]. The earliest radiological erosions are frequently seen at metatarsophalangeal joints [19], but unfortunately there are no relevant reports of MRI of the feet in the literature.

Conahan *et al.* [20] reported an apparent progression of pathology within the rheumatoid joint during the first 6–12 months, and our own observations have confirmed this [15]. Synovitis develops initially, and is often followed by bone marrow oedema and finally by bony erosion, as seen on MRI scans. Radiographic erosions are recognized a further 6 months later, about 12–18 months after symptom onset [15]. The finding of bone marrow oedema was not recognized in the rheumatoid joint before the advent of MRI and has no radiological correlate. Specifically, it is not associated with periarticular osteopenia [6]. It appears as increased signal intensity of bone on $T_2$-weighted images after fat suppression, resulting from an increased amount of water in the marrow, and may represent the internal bony response to external attack by the inflamed synovium. Bone marrow oedema in early RA has been found to be strongly associated with subsequent erosion at the same site [15], and appears to be an important early pathological feature. It often accompanies the development of erosion and may subside once erosions become inactive, but proof of this awaits further longitudinal studies. Unfortunately, histological verification of the bone oedema seen in MR images is unlikely to be possible in early disease because of difficulties in obtaining appropriate biopsy tissue.

## Imaging synovitis using dynamic MRI

Synovitis in RA has been studied by a number of groups using MRI [21–24]. On static MRI, the inflamed synovial membrane is seen as thickened and it enhances prominently post-contrast. Not surprisingly, the majority of early RA patients have MRI evidence of synovitis; this was present in 93% of our series of 42 patients, most frequently involving the radiocarpal joint at the wrist [14]. Jorgensen *et al.* [16] also noted synovial thickening at the wrist in 11 of 15 early RA patients; it was localized to the distal radioulnar joint in nine, with pannus at the radiocarpal joint in seven. Dynamic MRI provides a means of quantifying synovitis, and this has been done in two ways. Firstly, the volume of the synovial membrane has been used as a surrogate measure. Ostergaard *et al.* [21] have employed manual and computer-assisted outlining methods to trace around the borders of synovial membrane within the joint, allowing the volume to be calculated. This has been found to correlate with clinical signs of inflammation as well as an overall histological score that incorporates estimates of polymorphonuclear leukocyte infiltration, blood vessel proliferation and villous hypertrophy [25]. These studies were performed at the knee in patients with established disease, but more recently the same technique has been applied to the wrist in early RA [26]. The second method is based on the finding that inflamed synovium enhances brightly after i.v. injection of Gd-DTPA [22–24]. A typical S-shaped curve of increasing signal intensity is observed after injection of contrast medium (Fig. 1), and the slope of this curve, over the initial linear phase, has been found by several groups [22–25] to correlate with histological evidence of synovitis. However, there is some debate as to whether this rate of enhancement (the E-rate) should be used as an absolute value [24] or whether it should incorporate an internal standard by dividing it by the baseline signal intensity [22, 23]. This results in a measure, known as

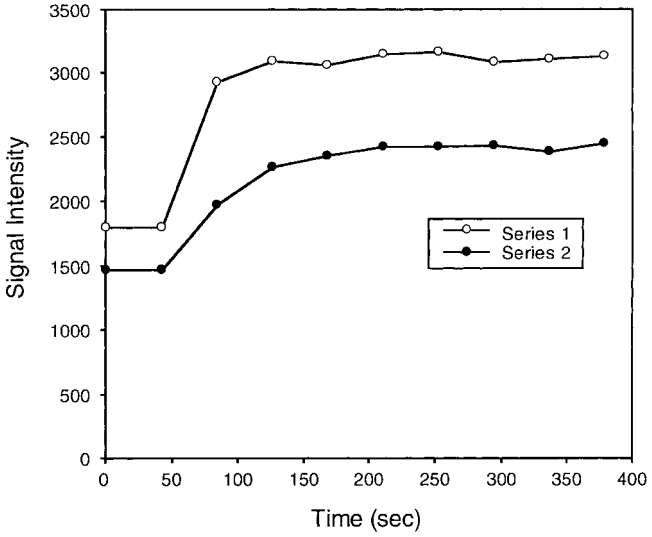


FIG. 1. Data derived from post-contrast (Gd-DPTA) dynamic MRI scans of the wrist in a patient with early RA. Signal intensity represents the degree of synovial enhancement and is plotted against time. Series 1, taken at the time of presentation (symptom duration 6 months), shows rapidly increasing signal intensity over the linear phase after the take-off point. E-rate ($SI_t - SI_0/\Delta t$, where $SI$ is signal intensity) = 26.9, implying active synovitis. Series 2 is from the same patient 1 yr after treatment with methotrexate. Synovitis was much reduced. E-rate = 12.7

the 'E-ratio', which also correlates with histological synovitis but may be spuriously elevated when baseline signal intensity is low [24, 27].

## Scoring of MRI scans

It is clear from the above that MRI has significantly advanced our understanding of the early pathology of RA. The information provided is of great clinical importance, but before it can be applied the features seen on MRI scans must be quantified in an accurate and reproducible manner by the use of a scoring system analogous to the methods described by Sharp [28] and Larsen [29] for plain radiography. A number of scoring systems for MRI have now appeared in the literature, the first of which was proposed by Rominger in 1993 [5]. This was devised for use at the wrist, and scored erosions at each of the individual carpal bones as 0–3 according to the number and size of the erosions. There was also a score for synovitis and joint effusion, which were assessed together in three compartments: the metacarpal articulations, the radioulnar joint and the ulnar styloid bursa. They were graded according to signal intensity and the extent of distension of the joint by synovial membrane and/or fluid. Tendon sheath inflammation was also scored according to the signal intensity of the material surrounding the tendon. No attempt was made to score changes in cartilage, as it could not be differentiated reliably from adjacent bone or synovial membrane. Ostergaard *et al.* [12] refined this system by adopting a more detailed assessment of synovitis, grading synovial membrane hypertrophy and post-contrast enhancement in six individual regions of the wrist. Our own system [14] has built on this background with the addition of a separate score for bone oedema and an expanded score for tendonitis which incorporates measures of the size and signal intensity of the tendon itself as well as the tendon sheath. Thus, joint erosion and bone oedema are scored at 15 sites, synovitis at seven sites and tendonitis at nine sites, and these scores are summed to give a total possible score of 124. This scoring system was validated by two blinded observers, and the interobserver and intraobserver reliabilities were found to be high [14, 15]. An international group, IMMRIC (International Musculoskeletal MRI Collaborators) is currently working within the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) framework [30] to produce a standardized MRI scoring system for RA, to be used in the context of clinical trials.

## Using MRI to diagnose early RA

One of the possible practical applications of MRI in early RA is to help differentiate this condition from other inflammatory arthropathies. McGonagle *et al.* [31] reported a study of 20 patients with recent-onset knee effusion and found that prominent peri-entheseal bone marrow oedema was a feature in six of ten spondyloarthropathy patients but was not found in the RA patients studied. In another study by the same group [18], MRI scans of the MCP joints of the dominant hand were used to try to distinguish between acute-onset RA, which carries a good prognosis [32] and insidious-onset disease, which does not. Bone marrow oedema at the articular margin was found to be a useful differentiating feature, being present in 13 of 22 patients with a poor prognosis (insidious onset) and in none of a group of patients with a good prognosis. However, capsular enhancement was more common in the group with a good prognosis. The authors hypothesize that these early MRI changes may define two distinct locations for pathology in patients satisfying criteria for early RA. Intrasynovial inflammation may characterize those with a poor prognosis (who go on to develop true RA), and extrasynovial, capsular inflammation may be a marker of good prognosis, associated with remission or possibly evolution into one of the spondyloarthropathies.

## MRI and the prediction of outcome in RA

Can MRI be used for prognostication in early RA? If so, it could be a crucial investigation at the time of presentation, allowing drug regimens to be tailored according to disease severity for individual patients. To explore this question, Ostergaard *et al.* [26] studied MRI of the wrist in 26 patients over a period of 1 yr and found a high correlation between the synovial membrane volume at baseline and the rate of erosive progression. Our own studies of early RA patients, using

static and dynamic MRI, have also revealed a strong association between the synovitis score at baseline and the development of erosion at 1 yr [15, 27]. Site-specific data analysis confirmed that synovitis adjacent to a carpal bone at baseline doubled the risk of subsequent erosion at that bone. However, the strongest individual predictor of erosion was bone marrow oedema, which, if present at a specific site at baseline, was associated with a 6-fold increase in the risk of erosion at that site after 1 yr [15]. The total baseline MRI score (including synovitis, tendonitis, bone oedema and erosions) was also highly predictive of MRI erosion at 1 yr with a positive predictive value (ppv) of 93%, but was less predictive of X-ray erosions in the same patients (ppv = 53%). This may reflect the slower rate of development of X-ray erosions, and analysis of 2-yr data is awaited. A baseline MRI scan which is negative for erosions may be more useful, as such a scan was highly predictive for the absence of X-ray erosions at 1 yr (negative predictive value = 92%), implying a good prognosis. Such patients might be spared treatment with potentially toxic and expensive disease-suppressing agents. Figure 2 shows MRI scans and radiographs from a patient in this cohort who had completed a 2-yr follow-up, illustrating bone marrow oedema involving the triquetrum on baseline MRI scan with a normal baseline X-ray (although this area is not well seen). Erosions became apparent at this site on MRI and X-ray at 1 yr and had progressed by 2 yr on X-ray.

## Using MRI to monitor the response to therapy

A third potential application for MRI in early RA is to monitor disease activity and the progression of erosions during treatment with disease-suppressing therapy. Lee *et al.* [33] used MRI to monitor disease in 10 patients newly treated with methotrexate and hydroxychloroquine. Four patients achieved clinical remission [34] and their scans revealed a decrease in synovial proliferation and bone marrow oedema, with no new erosions over 12 months. In contrast, new erosions developed in five of the six patients who did not achieve remission. Dynamic MRI of several joints (wrist, knee or ankle) was used to monitor synovitis in 18 patients receiving therapy with anti-tumour necrosis factor-$\alpha$ monoclonal antibody [35]. Those given the higher dose of antibody (10 mg/kg) demonstrated a marked improvement in clinical parameters as well as a highly significant reduction in gadolinium uptake. Changes in signal intensity of the synovium on MRI correlated with clinical indicators of inflammation, and the authors concluded that this technique was suitable for monitoring biological response modifiers in RA. Ostergaard *et al.* [36] used dynamic MRI to monitor changes in synovitis at the knee after intra-articular methylprednisolone and recorded a decrease in synovial volume, implying a reduction in synovitis. Sugimoto *et al.* [37] also found the synovial volume to fluctuate in parallel with disease activity in their study of 11 patients, but no direct correlation was found with clinical parameters. Clearly, this application of MRI is in its infancy but is likely to assume increasing importance given the plethora of new biological and pharmacologic agents currently being developed for use in RA.

## Is MRI too sensitive to be reliable?

One of the concerns about the use of MRI to monitor clinical progress in RA is that its high sensitivity for detecting erosions may be associated with low specificity, so that false positives could occur. There is little control data available because of cost issues, but benign lesions such as intraosseous cysts are present in normal subjects and those with degenerative joint disease [17]. These can usually be distinguished from erosions as the latter often contain synovium, which enhances on post-contrast $T_1$-weighted images. Partial volume artefacts can also be responsible for false positives when scoring erosions, but this risk is reduced if images are obtained in the axial and coronal planes.

Studies from our cohort of early RA patients have confirmed that MRI erosions are generally persistent lesions, being present at 1 yr in 95% of those patients who had erosions at baseline [15]. The one false positive in this group was due to the presence of enhancing synovium adjacent to an area of bony irregularity. This was initially scored as an erosion but had disappeared on the follow-up scan. The impression to date has been that MRI erosions are not usually benign or reversible, but are likely to be followed by X-ray erosions after a 6- to 12-month period. However, tracking individual lesions has not been performed and further data are required.

## Low-cost office-based MRI systems

A major impediment to the use of MRI in the investigation of common rheumatic disorders is cost. At more than US$300 per scan of the wrist (with contrast), MRI is expensive, but this cost would be more than recovered if it allowed identification of the patient with a good prognosis and prevented the unnecessary use of biological agents. New low-cost, low-field, dedicated-extremity MRI systems which are office-based are being developed [38]. Peterfy *et al.* [39] investigated the application of such a system to imaging of the wrist in RA and devised a method for scoring erosions and joint-space narrowing based on a radiographic scoring system. Whether these low-field, dedicated-extremity MRI units can provide the same quality of information as the larger machines has yet to be demonstrated, but they have the potential to improve access to this imaging modality for the clinician. MRI will be competing with other imaging techniques such as high-quality ultrasound, which has been shown to have promise in assessing synovitis at the finger joints in inflammatory arthritis [40], and must be priced competitively if it is to become widely used.

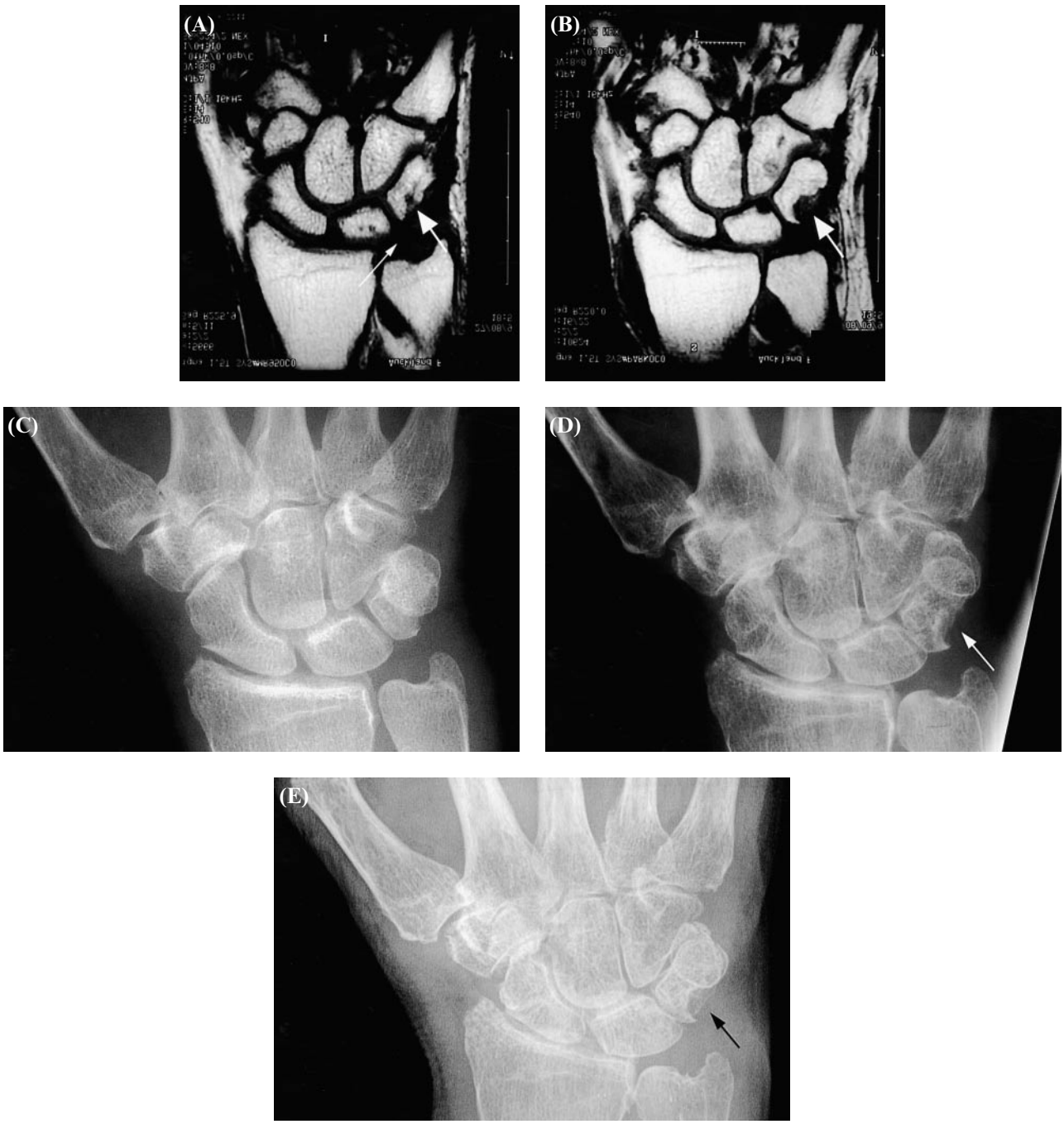


FIG. 2. MRI scans ($T_1$-weighted coronal images) and X-rays of the dominant wrist from a 63-yr-old woman with early RA. (A) Baseline MRI scan taken 3 months after symptom onset, showing bone marrow oedema within the triquetrum (thick arrow) and adjacent synovial thickening (thin arrow). (B) MRI scan taken 1 yr later shows a large erosion within the triquetrum (arrow). (C) X-ray at baseline did not reveal an abnormality at this site. (D) X-ray 1 yr later revealed the erosion at the triquetrum (arrow). (E) X-ray at 2 yr revealed further erosive change at this site (arrow).

## Conclusions

To summarize, MRI is an exciting imaging modality and is particularly suitable for application to musculoskeletal medicine. For rheumatologists, it provides a window through which the rheumatoid process can be observed. The sequence of pathology leading to bony erosion is yet to be fully elucidated, but oedema of the bone marrow is a frequent precursor, suggesting that this might be the site for crucial early immunopathological events. Scoring systems have been developed for MRI, analogous to the radiological scoring systems of Sharp [28] and Larsen [29], and are being standardized so that they can be used universally to measure joint

inflammation and damage. MRI has clinical applications in the diagnosis of inflammatory arthritis and in the prediction of prognosis, which could influence management decisions in early disease. It is also likely to assume crucial importance in monitoring responses to disease-modifying agents, so that efficacy can be assessed within weeks of starting therapy rather than having to wait months or years before radiological changes become apparent. MRI is unlikely to replace plain radiography, as this remains the better tool for imaging multiple joint areas in established disease. However, MRI is emerging as an important imaging technique in the context of early inflammatory arthritis and promises to be a useful addition to the rheumatologist's armamentarium for the new millennium.

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