# Magnetic resonance imaging: opportunities for rheumatoid arthritis disease assessment and monitoring long-term treatment outcomes

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## Abstract

Early diagnosis of rheumatoid arthritis (RA) combined with early initiation of an appropriate treatment regimen is acknowledged as an important factor in improving clinical outcomes in patients with RA. Early diagnosis allows treatment intervention to occur sooner in order to inhibit the progression of structural joint damage as well as providing improved patient quality of life. Unfortunately, early diagnosis has been challenging due to the non-specific signs and symptoms associated with many polyarthropathies and the lack of accurate definitive diagnostic tests that can accurately classify RA at presentation. The emphasis on early diagnosis has fueled the need for powerful, sensitive, non-invasive imaging techniques that not only accurately define RA and give an indication of prognosis, but can also serve as a tool to monitor long-term treatment outcomes. This article reviews the potential uses of magnetic resonance imaging as a tool for the classification, documentation, and clinical monitoring of RA.

**Keywords:** bone erosion, magnetic resonance imaging, radiography, rheumatoid arthritis, synovitis

## Introduction

Over the past several years, significant advances have been made in understanding the pathophysiology of RA in the joint. The earlier diagnosis of RA combined with an early initiation of an appropriate treatment regimen are acknowledged as important factors for improved clinical outcomes. Furthermore, the introduction of new, targeted therapies has significantly advanced the treatment of and quality of life of patients with RA [1,2]. The rationale for early diagnosis and availability of targeted aggressive therapy has fueled the need for powerful, sensitive imaging techniques that can be used not only to accurately diagnose and indicate the prognosis of patients with RA, but also to monitor the efficacy of long-term treatment. Radiographs, although able to detect structural joint damage in patients with established disease, have not been sensitive in detecting early RA disease pathology in the patient [3]. There has therefore been an increasing interest in magnetic resonance imaging (MRI), with the aim of providing more sensitive data and better predictive value [3]. This review will evaluate the use of MRI as a tool for the diagnosis, classification, and clinical monitoring of RA.

## Potential of MRI

The ability of MRI to assess both detailed changes in bone structure (i.e. erosions) and synovial inflammation combined with its multiplanar capability makes it a potentially valuable tool for assessing patients with RA. Such capabilities mean that MRI can be used in a variety of ways, as summarized in Table 1.



ACR = American College of Rheumatology; MRI = magnetic resonance imaging; RA = rheumatoid arthritis.

**Table 1**

**Potential uses for magnetic resonance imaging in rheumatoid arthritis (RA)**

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|---|
| Accurate diagnosis and classification of patients with RA at presentation |
| Early assessment of bony erosions to define patients who already have articular structural damage |
| Quantification of synovial inflammation at the primary site, potentially allowing prediction of further erosions and disease progression |
| Simultaneous assessment of synovitis and joint erosion pathologies, allowing for dissection of the relative importance of these two pathologies in RA disease progression |
| Long-term evaluation of treatment outcome in clinical trials and real-world settings |

## Early diagnosis of RA

RA is a progressive disease that, if left unchecked, results in irreversible joint damage. Early diagnosis is often difficult due to the non-specific symptoms and signs that develop relatively slowly. In particular, the conventional diagnostic criteria developed by the American College of Rheumatology (ACR) among patients, the slow development of signs and symptoms, and ambiguous symptoms similar to other inflammatory polyarthropathies. Furthermore, conventional diagnostic criteria developed by the ACR were derived from patients with established disease [4]. These criteria were not designed to detect early clinical symptoms of the disease process. In fact, recent data suggest that, in the first 3 months during disease onset, ACR criteria may well be misleading rather than helpful in making a definitive diagnosis of RA [5]. The natural history of RA is such that the early months of disease are a critical period during which irreversible joint damage occurs. The advantages of an accurate, early clinical RA diagnosis thus emphasize the need for more accurate methods of detection [6]. It should be noted, however, that currently the majority of patients do not present with a disease duration of less than 3 months, therefore ACR criteria would be valid. However, as indicated later, the majority of joint erosions are not detected by radiographic analysis in patients at presentation.

The current ACR recommendations for diagnosing RA include radiographic analysis of selected joints. The sensitivity of radiography, however, is very limited. For instance, at presentation, the characteristic or pathognomonic radiographic-identified joint erosion was detected in only 15% of patients with RA [7]. In contrast, when imaged by MRI, abnormalities were detected in 70% of patients, involving 35% of the patients' joints. In another study, MRI was performed on 42 patients with early RA (median disease duration, 4 months) at baseline and at 1 year. Synovitis, measured by MRI, was predictive for the development of joint erosions at 1 year [8]. The use of imaging has allowed the distinction to be made between enthesseal-based disease and primary intrasynovial disease [9]. For example, MRI has been shown to be useful in differentiating polymyalgia rheumatica from RA by imaging extracapsular enhancement in the latter [10,11]. MRI has been used to determine whether recent-onset knee synovitis differed in RA patients compared with those who had spondyloarthropathy. Data showed that the non-RA patients had a periarticular location of entheseal inflammation and bone edema, while RA patients did not [12]. In another study, RA patients classified with a good prognosis (defined as acute onset [~24 hours] of disease) were shown to have the same characteristic entheseal pathology as opposed to the intrasynovial inflammatory pathology of RA and, importantly, MRI detection of enthesitis correlated closely with favorable clinical outcomes (not requiring disease-modifying therapy) in these patients [4]. The characteristic feature of the good-prognosis patients (all of whom fulfilled the ACR diagnostic criteria for RA) was that they lacked the intra-articular 'bare area' region lesions, whereas such a change was a universal feature of poor prognosis in other RA patients studied. This finding suggests that many RA patients with a good prognosis exhibit a unique pathology, an important clinical consideration. Unfortunately, these differences between diseases have been difficult to detect during routine clinical examination, providing further rationale for the use of MRI as a diagnostic tool in this subset of patients.

## Validation and imaging of MRI

Validation of MRI as a tool in RA has been undertaken in a variety of ways. These include evaluating biopsies of MRI bone erosions (obtained under ultrasound guidance), correlating the MRI bone erosions with ultrasound erosions (and radiographs), and conducting longitudinal studies to assess the long-term outcome of MRI studies.

Ultrasound and MRI modalities measure different physical characteristics of erosions, with ultrasound identifying the absence of a cortical echo and MRI detecting change in nuclear spin in response to a magnetic field. When MRI lesions are compared with ultrasound erosions, the two modalities act as a cross-reference for each other [13]. Studies undertaking these comparisons have shown that the cortical defects observed from ultrasound are closely correlated with MRI abnormalities on T1-weighted images [6] with all MRI lesions correlating with a cortical defect on ultrasound.

In one study, the presence of a MRI lesion was confirmed on ultrasound and then, under ultrasound guidance, tissue was obtained from the confirmed MRI erosion site [14]. Five patient biopsies were obtained, all of which contained bone, and three of which were also associated with cellular material. Furthermore, one patient biopsy had a distinct population of $CD34^+$ cells. The close correlation between ultrasound and MRI-detected bone erosions thus strongly supports the conclusion that MRI is measuring genuine abnormalities.

The sensitivity of MRI for detecting bone erosions has also been compared with radiography. In one comparison study, radiographic analysis detected bone erosions in 15% of RA patients (median symptom duration, 4 months), whereas MRI analysis detected erosions in 45% of RA patients [7]. Furthermore, longitudinal studies confirmed that lesions seen with MRI appear later as radiographic erosions. RA patient follow-up over 5 years showed that, at baseline, only 20% of MRI lesions were detected by radiographic analysis, while at 5 years 60% of MRI lesions were detected by radiographic analysis [9]. This reflects both the lack of sensitivity of radiography and the delay in the visualization of lesions using this technique. One potential explanation for this discrepancy may be that, at presentation, the majority of lesions detected are small in size; later, as the disease progresses, the lesions increase in size. Unfortunately, of all the bone erosions detected by radiography, only approximately 10% of these identified lesions were classified as small in size [6,9]. Thus, in addition to lacking the capacity for multiplanar imaging, radiographs do not detect early bone erosions because early RA is characterized by small erosions, which are below the threshold of radiographic detection.

## Synovitis and intra-relationship with bony damage

The intra-relationship between synovitis and bony damage has also been addressed using patients with very early disease onset. The importance of studying this particular patient group is the lack of confounding influences of previous treatments, such as disease-modifying antirheumatic drugs (e.g. methotrexate). In a recent study, patients were randomized to receive treatments that had different timeframes for onset of action [11]. Bone damage and synovitis were measured by MRI. The MRI data suggested that the level of synovial thickness was critical in determining the amount of bone damage. In fact, the area under the curve for synovial thickness was the sole predictor of subsequent bony damage. Importantly, no damage occurred in joints without synovitis; thus, the presence of synovitis was prognostic for bone damage.

Synovitis is the primary abnormality in RA, and MRI, unlike radiology, can be used to image the synovium. Both the synovial volume and the level of inflammation can be independently assessed using MRI. The most common and extensively studied MRI method is the use of the magnetic contrast medium, gadolinium-diethylenetriamine pentaacetic acid. Early studies correlated the gadolinium-enhancing imaging properties in the synovium with the microscopic appearances on arthroscopic biopsies [15,16]. In one study, it was clearly demonstrated that the correlations between inflammation and histology held true for the site of biopsy, but the correlation diminished when random sites were assessed [16]. Other studies have evaluated dynamic imaging using multiple slices across the joint and have shown the ability of this technique to distinguish between two active therapies [17].

Although clinical examination has been a cornerstone in identifying and monitoring disease progression in RA patients, MRI has been shown to be more sensitive than clinical examination for identifying synovitis. Studies from a Japanese group correctly diagnosed 25 out of 26 patients at RA disease onset using MRI criteria, which was 23% more patients than were identified using ACR criteria [18]. In a recent study comparing MRI, ultrasound, and clinical examination, results again confirmed the sensitivity of MRI in RA. These data suggest that, as MRI becomes more widespread, it will serve as a more accurate measure for identifying key pathologic features of RA that are not readily identified using standard ACR criteria, such as synovitis.

## Predicting disease progression and monitoring treatment outcome

A key issue in RA patient management is whether MRI imaging of RA patients at disease onset can accurately predict the rate of disease progression. This issue is further complicated by the fact that the natural history of the disease is now rarely observed and because treatment is being administered earlier in the disease process. Despite the complexities inherent in predicting disease progression, some generalizations can be made. While the T1-weighted lesions (the anatomical cortical lesions conventionally called bony erosions) correlate best, the T2-suppressed lesions represent bony edema and a response to bone inflammation. It would be reasonable to predict that these latter lesions are the ones that will progress. However, unequivocal evidence is lacking, in part due to the institution of aggressive treatment in RA patients. Nevertheless, there is sufficient evidence to suggest that untreated patients with characteristic disease at onset with T1-weighted lesions surrounded by edema on T2-fat suppressed images are likely to progress. Therefore, MRI is valuable in predicting disease progression at least in a subset of RA patients.

MRI has the ability to assess bone damage, which has been crucial in allowing increased sensitivity for assessing therapeutic regimens. It is unlikely in the near future that MRI will replace radiographic analysis in established

disease, since radiographs are a better tool for imaging multiple affected joints. However, the ability to measure synovial volume may be more important over the long term to assess the efficacy of new or modified therapies designed to significantly decrease the rate of radiologic structural damage. If rheumatologists concur that synovitis is the primary abnormality in RA, then the accurate assessment of synovial volumes may replace structural damage as the most pertinent long-term clinical endpoint.

MRI may also be beneficial in functional status assessment for patients in which joint erosions have been minimized due to advances in early diagnosis and treatment modalities. For example, MRI has been shown to be a sensitive tool for the detection of inflammation of periarticular tendons and tendon sheaths [19]. Although MRI tendon imaging would not add to the assessment of structural damage, as rheumatologists are able to minimize joint erosion, damage to tendons may contribute significantly to functional status. MRI could a play a key role in detecting and measuring decreased functional status due to tendonitis or tendon rupture and MRI would provide greater accuracy than physical examination.

## Limitations of MRI

A major concern with the use of MRI in RA has been the validation of bone erosion scoring. The European League Against Rheumatism and the Outcome Measures in Rheumatoid Arthritis Clinical Trial working groups have both undertaken cross-sectional (and the former group also longitudinal) analyses of RA bone erosion scoring using MRI [20,21]. When the strict criteria for the definition of bone erosions (lesion observed in two imaging planes involving a cortical break in at least one) are applied to scoring, there is a 97% consistency in the recording of such lesions by MRI [20].

## Summary

MRI is a sensitive, accurate, non-invasive tool that allows simultaneous assessment of all the components of diarthrodial joints. MRI-imaged abnormalities can be identified in the majority of RA patients at disease presentation. Furthermore, MRI provides the unique opportunity to assess RA disease progression since new efficacious agents such as infliximab (cA2, Remicade®; Centocor, Inc., Malvern, PA, USA) and etanercept (Enbrel®; Immunex Corporation, Seattle, WA, USA) have been shown to inhibit the progression of structural damage. Preventing progression of structural damage will limit the utility and need for long-term patient monitoring by radiographic analysis as RA patients are diagnosed early and treated aggressively. In conclusion, the implementation of MRI will provide clinicians with a powerful imaging tool for long-term, periodic monitoring of the RA disease state.

## References


1. Feldmann M, Maini RN: **Anti-TNFα therapy of rheumatoid arthritis: what have we learned?** *Annu Rev Immunol* 2001, **19**:163-196.
2. O'Dell JR: **How is it best to treat early rheumatoid arthritis patients?** *Baillieres Best Pract Res Clin Rheumatol* 2001, **15**: 125-137.
3. McGonagle D, Conaghan PG, Wakefield R, Emery P: **Imaging the joints in early rheumatoid arthritis.** *Bailleres Best Pract Res Clin Rheumatol* 2001, **15**:91-104.
4. McGonagle D, Gibbon W, O'Connor P, Green M, Pease C, Ridgway J, Emery P: **An anatomical explanation for good-prognosis rheumatoid arthritis.** *Lancet* 1999, **353**:123-124.
5. Green M, Marzo-Ortega H, McGonagle D, Wakefield R, Proudman S, Conaghan P, Gooi J, Emery P: **Persistence of mild, early inflammatory arthritis: the importance of disease duration, rheumatoid factor, and the shared epitope.** *Arthritis Rheum* 1999, **42**:2184-2188.
6. Wakefield RJ, Gibbon WW, Conaghan PG, O'Connor P, McGonagle D, Pease C, Green MJ, Veale DJ, Isaacs JD, Emery P: **The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography.** *Arthritis Rheum* 2000, **43**:2762-2770.
7. McQueen FM, Stewart N, Crabbe J, Robinson E, Yoeman S, Tan PL, McLean L: **Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevelance of erosions at four months after symptom onset.** *Ann Rheum Dis* 1998, **57**:350-356.
8. Huang J, Stewart N, Crabbe J, Robinson E, McLean L, Yeoman S, Tan PL, McQueen FM: **A 1-year follow-up study of dynamic magnetic resonance imaging in early rheumatoid arthritis reveals synovitis to be increased in shared epitope-positive patients and predictive of erosions at 1 year.** *Rheumatology (Oxford)* 2000, **39**:407-416.
9. Albers JMC, Paimela L, Kurki P, Eberhardt KB, Emery P, van't Hof MA, Schreuder FH, Leirisalo-Repo M, van Riel PL: **Treatment strategy, disease activity, and outcome in four cohorts of patients with early rheumatoid arthritis.** *Ann Rheum Dis* 2001, **60**:453-458.
10. McGonagle D, Pease C, Marzo-Ortega H, O'Connor P, Gibbon W, Emery P: **Comparison of extracapsular changes by magnetic resonance imaging in patients with rheumatoid arthritis and polymyalgia rheumatica.** *J Rheumatol* 2001, **28**:1837-1841.
11. Ostergaard M, Hansen M, Stoltenberg M, Gideon P, Klarlund M, Jensen KE, Lorenzen I: **Magnetic resonance imaging-determined synovial membrane volume as a market of disease activity and a predictor of progressive joint destruction in the wrists of patients with rheumatoid arthritis.** *Arthritis Rheum* 1999, **42**:918-929.
12. Gaffney K, Cookson J, Blake D, Coumbe A, Blades S: **Quantification of rheumatoid synovitis by magnetic resonance imaging.** *Arthritis Rheum* 1995, **38**:1610-1617.
13. Tamai K, Yamato M, Yamaguchi T, Ohno W: **Dynamic magnetic resonance imaging for the evaluation of synovitis in patients with rheumatoid arthritis.** *Arthritis Rheum* 1994, **37**:1151-1157.
14. McGonagle D, Gibbon W, O'Connor P, Blythe D, Wakefield R, Green M, Veale D, Emery P: **A preliminary study of ultrasound aspiration of bone erosion in early rheumatoid arthritis.** *Rheumatology (Oxford)* 1999, **38**:329-331.
15. Ostergaard M, Stoltenberg M, Lovgreen-Neilsen P, Volck B, Jensen CH, Lorenzen I: **Magnetic resonance imaging-determined synovial membrane and joint effusion volumes in rheumatoid arthritis and osteoarthritis: comparison with the macroscopic and microscopic appearance of the synovium.** *Arthritis Rheum* 1997, **40**:1856-1867.
16. Veale DJ, Reece RJ, Parsons W, Radjenovic A, O'Connor PJ, Orgles CS, Berry E, Ridgway JP, Mason U, Boylston AW, Gibbon W, Emery P: **Intra-articular primatised anti-CD4: efficacy in resistant rheumatoid knees. A study of combined arthroscopy, magnetic resonance imaging, and histology.** *Ann Rheum Dis* 1999, **58**:342-349.
17. Reece RJ, Canete JD, Parsons WJ, Emery P, Veale DJ: **Distinct vascular patterns of early synovitis in psoriatic, reactive, and rheumatoid arthritis.** *Arthritis Rheum* 1999, **42**:1481-1484.
18. Sugimoto H, Takeda A, Kyodoh K: **Early-stage rheumatoid arthritis: prospective study of the effectiveness of MR imaging for diagnosis.** *Radiology* 2000, **216**:569-575.

19. Kainberger F, Trattnig S, Czerny C, Seidl G, Kritz H, Imhof H: **MRI in assessment of the systemic manifestations of rheumatological disease.** *Br J Rheumatol* 1996, **35(suppl 3)**:40-44.
20. Ostergaard M, Klarlund M, Lassere M, Conaghan P, Peterfy C, McQueen F, O'Connor P, Schnier R, Stewart N, McGonagle D, Emery P, Genant H, Edmonds J: **Interreader agreement in the assessment of magnetic resonance images of rheumatoid arthritis wrist and finger joints—an international multicenter study.** *J Rheumatol* 2001, **28**:1143-1150.
21. Conaghan P, Edmonds J, Emery P, Genant H, Gibbon W, Klarlund M, Lassere M, McGonagle D, McQueen F, O'Connor P, Peterfy C, Schnier R, Stewart N, Ostergaard M: **Magnetic resonance imaging in rheumatoid arthritis: summary of OMERACT activities, current status, and plans.** *J Rheumatol* 2001, **28**: 1158-1162.