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REVIEW ARTICLE

Extremity Magnetic Resonance Imaging in Rheumatoid Arthritis: Updated Literature Review

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Introduction

In April 2006, a white paper on extremity magnetic resonance imaging (MRI) in rheumatoid arthritis (RA) was published, based on a review of the literature by a task force commissioned by the American College of Rheumatology (ACR) (1). The document was well received for its scientific rigor and overview of the literature at that time. However, the report had unexpected consequences as certain insurers began to restrict coverage for extremity MRI, which was not the intent of the original scientific review. Over the last 4 years, research into the value of extremity MRI and its role compared with conventional radiography and high-field MRI has been ongoing.

In May 2009, the International Society of Extremity MRI in Rheumatology (ISEMIR) forwarded to the ACR publications they believed to be important in the field, requesting that the ACR review these new data and update the white paper with inclusion of the new information. The ACR Executive Committee and ACR Board of Directors thought that it was important to respond to this group, but due to the many efforts the ACR had ongoing, it was decided not to reconvene the original formal task force. Three members of the initial task force were asked to participate in this literature review: Atul Deodhar (an academic clinical rheumatologist with research interest in imaging modalities), to provide clinical perspective; Hollis Potter (a musculoskeletal radiologist with extensive experience in MRI), to provide technical expertise; and Stanley Cohen (a clinical rheumatologist in private practice with research interests in RA treatment). Paul Emery, who was not a member of the original task force, was asked to participate due to his expertise in MRI in RA as well as his involvement in the ISEMIR. Subsequent to the initial development of the manuscript, Philip Conaghan and Mikkel Ostergaard were invited to contribute to the review based on their expertise in the field and the desire of the working group as well as the ACR Board of Directors to broaden the perspective on this subject. This group reviewed the publications forwarded, as well as conducted a literature review of additional articles in Medline and PubMed involving MRI in RA published since 2006. This was not a formal evidence-based review such as the now-popular RAND-based methodology, but simply a literature review addressing the same questions raised in 2006 to determine if the conclusions reached at that time should be modified.

These publications can be broadly divided into 3 groups. The first group of publications deals with technical aspects, such as comparing low-field extremity units to high-field units, comparing the reproducibility of results obtained with low-field units in different centers, or addressing the Outcome Measures in Rheumatology Clinical Trials (OMERACT) MRI scoring systems. The second group consists of publications that confirm previously recorded observations, e.g., MRI scanning is more sensitive in detecting erosions compared with conventional radiography and predicts future radiographic erosions. The third group consists of publications that advance our knowledge of peripheral MRI further by breaking new ground. Although there are now extremity MRI units that are higher field at 1.0–1.5T, there was no available literature to determine the role of high-field extremity MRI in the diagnosis and management of RA.

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What are the extremity MRI systems that are presently commercially available?

Current extremity MRI systems include ONI (Ortho 1), which makes superconducting, helium-cooled 1.0T and 1.5T systems, Esaote (permanent 0.2T system; C-scan), and CompacT, which is an additional 0.21T permanent system (2). ONI products are superconducting, requiring cryogens, and provide a maximum field of view (FOV) of 16 cm. The available permanent systems noted above do not require cryogens and yield a variable FOV. Given the concerns regarding image quality and the cost of production of permanent MRI systems, many of the larger MRI manufacturers (e.g., Siemens, General Electric) have abandoned production and/or distribution of the permanent systems. MagneVu MV1000, a 0.2T permanent system (Applause), is no longer in production due to its reduced FOV, poor spatial resolution, and limited ability to detect synovitis.

How do images obtained with extremity MRI compare with high-field systems?

The literature has demonstrated that extremity MRI, likely due to its tomographic capabilities, is more sensitive than radiography in detecting erosive disease (3,4). It has been noted that an extremity MRI–estimated bone erosion volume of 20–30% would have to be present to allow for confident detection by conventional radiography (5). Despite the advantages over conventional radiography, low-field extremity MRI does not have diagnostic capabilities comparable with those of protocols optimized for high-field scanners due to an inherent diminished signal to noise ratio, limiting the ability to obtain consistent image quality in the face of high spatial and slice resolution.

In a cross-sectional study of 20 patients with active severe RA, low-field extremity MRI using the now-abandoned MagneVu unit was compared with radiography and high-field (1.5T) MRI. Using high-field MRI as the standard, low-field MRI had a sensitivity of only 46% and an accuracy of 55% for detecting erosions (6). In an additional study, 20 patients with RA and 5 healthy control subjects underwent conventional radiography, high-resolution computed tomography (CT), and two separate low-field extremity MRI evaluations (Esaote Artoscan and MagneVu MV1000) (7). With high-resolution CT as the standard, the sensitivity of the Artoscan for detecting erosions was higher than that of the MagneVu MV1000 or conventional radiography, but was only 68% for the metacarpophalangeal (MCP) joints and 50% for the wrist joints. Furthermore, a study assessing interclass correlation coefficients on a 0.2T extremity MRI system demonstrated acceptable reproducibility for erosion and synovitis, but not for the presence of bone edema (8). Duer-Jensen et al evaluated the ability of two different dedicated low-field extremity MRIs to detect bone erosions compared with conventional radiography (9); however, the acquisition parameters were not standardized, making comparison between the two MR systems difficult. An additional study comparing a 0.2T MR unit with a 1.5T MR unit showed excellent agreement between the two MR field strengths for detecting synovitis and erosion, and moderate agreement for tenosynovitis. Of note, the high-field pulse sequences were not optimized, with relatively poor in-plane resolution, and no cartilage-sensitive pulse sequence was provided (10).

It should be noted that while it is attractive to provide a large FOV to image the intercarpal, MCP, and interphalangeal joints simultaneously, this will inherently decrease the spatial resolution (pixel size) and thus the sensitivity for detecting marginal erosions. Illustrative images of erosions are not provided in much of the published literature, leaving it unclear how a distinction was made between true marginal erosions and the commonly encountered intraosseous ganglion cysts. In a recent multireader reliability study comparing high-field with low-field extremity MRI in the detection of disease activity in 15 patients with RA, intermachine reliability was excellent for the scoring of bone erosions; interreader reliability was also excellent at the MCP joints and good to very good at the wrist joint. For synovitis, however, as well as for bone edema, there was considerable variation in intermachine agreement (11).

The use of contrast will increase specificity for distinction between inflammatory synovitis and bland effusion; the use of contrast in a study with a 0.2T extremity MRI unit demonstrated high interclass correlation coefficients for erosion and synovitis (8). Other studies have suggested that the dose of contrast material influences synovitis scoring, as higher synovitis scores have been noted for double-dosed gadolinium compared with a single-dose evaluation (12). Given the current concerns, however, of nephrogenic systemic fibrosis potentially developing in patients with severely diminished renal function, high-dose gadolinium is now viewed with more caution than it had been prior to the recognition of nephrogenic systemic fibrosis (13). Consistent with this, a standard dose (0.1 mmole/kg) is generally used and recommended.

In this era of health care reform, diagnostic imaging has been placed under greater scrutiny with regard to cost-effectiveness, but also with regard to the need for accurate and reliable diagnosis that will have a direct impact on patient management. As such, it seems warranted that patients would benefit most from optimized imaging, performed in a standardized manner, with strict attention paid to technique. At this time, to our knowledge, there is no literature evaluating the impact of low-field or high-field MRI on utilization of health care resources. In theory, identification of patients at greater risk for disease progression and appropriate aggressive treatment intervention could decrease downstream costs such as hospitalizations and surgeries.

Low-field extremity MRI clearly can detect erosions better than conventional radiography, but to a lesser degree than high-field MRI. Limitations in the detection of bone edema and synovitis with low-field extremity MRI have been documented. Many of the published studies have utilized the MagneVu MV1000 system which, as noted above, is no longer available. The sensitivity of the Esaote (Artoscan) system in erosion detection is superior to that of the MagneVu, but is still less than that of high-field MRI. Whether larger-field extremity MRI will provide study quality similar to that of high-field conventional MRI is unknown, as publications addressing the 1.0T and 1.5T ONI technology were unavailable for review. At present,

high-field MRI with dedicated wrist and hand coils appears to provide the optimal means by which to assess the extent of the disease activity, as well as the presence of active versus inactive disease.

What is the predictive value of MRI-detected abnormalities, including synovitis, bone marrow edema, and erosions, for the subsequent development of radiographic erosions?

Several recent publications confirm findings of previous studies that certain MRI abnormalities (especially bone marrow edema) predict radiographic erosions. In the Cyclosporine, Methotrexate, Steroid in RA study, 130 patients with early RA that were aggressively treated with nonbiologic disease-modifying antirheumatic drugs (methotrexate or cyclosporine plus methotrexate; any swollen joints received intraarticular corticosteroid injection) were followed up for 1 year with contrast-enhanced MRI scanning (70% using low-field systems [Artoscan] and 30% using high-field systems [1.0–1.5T]) (14). Baseline total Sharp score, MRI erosion score, and MRI bone edema score were significantly associated with radiographic progression at 2 years in a univariate linear regression analysis. Utilizing multiple linear regression analysis, the baseline bone edema score of the wrist joints plus MCP joints, obtained using the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system (RAMRIS [OMERACT system]), was the only independent predictor of radiographic progression. Five-year followup data are now available and confirmed the independent predictive value of the baseline bone edema score (15). These results demonstrated that MRI findings in early RA can have independent predictive value for joint damage in early RA.

A second study evaluated the results of high-field MRI with contrast along with cyclic citrullinated peptide (CCP) antibody and IgM rheumatoid factor (RF) status to predict the development of RA in a population of patients with undifferentiated arthritis (16). The presence of bilateral or unilateral bone edema plus CCP antibody positivity had a predictive value of 100% for the development of RA at 1 year. Although the data were not presented, the authors state that high-field MRI predicted RA development even in patients with low Leiden Early Arthritis Cohort prediction scores.

What are the available data showing that MRI abnormalities are predictive of poorer functional outcomes or long-term disability?

Early in the RA disease process, functional capacity is considered to be more dependent on disease activity than on structural damage. In longstanding disease, especially in the prebiologics era, poor function has been more dependent on structural damage, even with improvement in inflammation (17). Therefore, prevention of joint damage has been a goal of treatment, and identifying those patients whose disease is more likely to progress is critical. Previous longitudinal studies utilizing high-field MRI have demonstrated that MRI-evidenced bone edema at baseline was predictive of the total Sharp score at 6 years (18). A model incorporating MRI erosion score, bone edema, synovitis, and tendinitis plus erythrocyte sedimentation rate and C-reactive protein level explained 59% of the variance in the total Sharp score at 6 years. These data suggest that MRI-evidenced damage could be used as a surrogate for radiographic damage.

One of the questions raised has been whether MRI erosions are true bone damage. Building on previous work, Dohn et al investigated whether erosions identified using 0.6T MRI are "real" by comparing them with CT-identified scan erosions, which are believed to be the gold standard (19). In 17 RA patients, 77 erosions were detected by CT scanning, of which 62 were also detected by MRI and 12 by radiography. The authors concluded that the specificity of MRI-identified erosions was 96%, even in joints that appeared nonerosive by conventional radiography.

Previous studies have demonstrated that patients with erosive disease seen on conventional radiography are more likely to develop structural progression. Do erosions seen on MRI have a similar predictive ability for the development of radiographic erosions? In the study by McQueen and colleagues using high-field MRI, 67% of patients with a high baseline composite score developed radiographic erosions at 2 years, whereas 90% with low baseline scores remained erosion free (18). To ascertain the importance of MRI abnormalities, we need to answer the following two important questions. First, what percentage of MRI abnormalities (especially erosions and edema) "disappear" without any new treatment? With the adoption of early aggressive treatment regimens targeting remission, studies to properly evaluate this issue will never be conducted, for ethical reasons. Second, in what percentage of healthy normal controls are "bone edema" and "erosions" seen on MRI scans?

We could find only one study with extremity MRI that employed "lesion-centric" analysis: in 24 patients who were followed up for 1 year from baseline (i.e., initiation of methotrexate treatment), utilizing the Artoscan low-field system (0.2T) with contrast (20). At baseline, 15 erosions in 6 patients were noted by radiography of the hands and wrists, and 21 erosions in 10 patients were noted by extremity MRI. At 12 months, 17 radiographic erosions were noted in 7 patients, with 5 patients exhibiting new involvement; 6 previous erosions were no longer visible, and 8 new erosions were seen. Fifteen new erosions in 8 patients were seen by extremity MRI. Four (19%) of the extremity MRI-evident erosions progressed to radiographically evident erosions at 12 months. Five percent of the MRI erosions had disappeared a year later.

Of 12 patients with baseline MRI erosion or bone edema, 4 (33%) developed radiographic progression at 1 year, compared with 1 (8%) without these findings at baseline: a relative risk of 4. Baseline pain and Health Assessment Questionnaire scores correlated positively with MRI synovitis score, and C-reactive protein levels correlated positively with MRI synovitis scores of >8.

To our knowledge, this was the first study to longitudinally evaluate low-field extremity MRI findings and the development of radiographic erosions. The authors concluded that extremity MRI could be used to predict which RA patients have disease that is more likely to progress to radiographic damage. However, the greatest advantage

may be for patients without erosions or bone edema, in whom the likelihood of developing radiographic disease is low, in contrast to patients with baseline involvement, as 67% of the patients with baseline abnormalities did not exhibit erosive radiographic disease at 12 months. The lack of additional clinical information, such as RF and CCP status, limits the ability to understand the incremental value MRI provides to patient management.

A 3-center international "reliability" study of extremity MRI was conducted, using MRIs from 15 patients (11). This was not a longitudinal study, and the same images were circulated among the 3 centers. The investigators found that the intraclass correlation coefficients for bone edema (the strongest predictor of radiographic erosions) were moderate to good (0.58 for MCP joints and 0.81 for wrists) in the hands of 3 experienced readers. In a longitudinal study by the same investigators, intraclass correlation coefficients for change scores were high for synovitis and erosions (0.89–0.91), but low for bone edema (0.24) (8). This illustrates that although detection of bone marrow edema is reliable, agreement on changes over time may be more difficult, warranting further research on this aspect.

A recent study examined the question of how specific the MRI findings of "bone edema" and "erosions" are for RA. Parodi et al studied the hands of 23 normal volunteers by extremity MRI (Artoscan), and 18 could be reevaluated after a mean period of 5 years. They found bone edema in 2 (8.7%) of these healthy volunteers, erosions in 6 (26%), and tenosynovitis in 4 (17%) (21). Solitary erosions were seen in 5 of the 6 subjects, with 2 erosions seen in the sixth. Five of these subjects had a RAMRIS erosion score of 1, and the sixth had a score of 2. A Canadian study investigating MRI (1.0T) without contrast of the MCP and wrist joints in 39 RA patients also included 2 groups of normal volunteers: a group of "older" controls (ages 49–74 years) and a "younger" control group (ages 19–33 years) (22). The investigators found bone edema in 27 joints, and found erosions in 65 joints of 27 controls in the older control group. The mean ± SEM erosion score in the older control group was 8.5 ± 1.7, compared with 24.6 ± 4.3 in the RA cohort. These research findings taken together would indicate that using extremity MRI in making treatment decisions may be hazardous in the setting of solitary lesions without accompanying bone edema or synovitis.

Summary

Low-field extremity MRI detects joint erosions better than plain radiography. Compared to high-field MRI, lesser ability to detect bone edema and lesser or similar ability to detect synovitis has been reported, with variable interreader reliability. However, the sensitivity for synovitis detection on low-field MRI remains greater than clinical examination, and bone edema cannot be detected on radiographs. No data to evaluate extremity MRI units with higher-field strengths, which are commercially available, were available for review.

Baseline bone edema on low- and high-field MRI in patients with early RA is predictive of future radiographic damage. Recent studies have suggested that the edema seen by MRI is due to inflammation seen histologically. Bone edema in patients with undifferentiated arthritis may provide additional predictive value to RF and CCP antibody status for the development of RA.

The absence of bone erosions, edema, or synovitis by low-field extremity MRI is predictive of the lack of progression of radiographic damage in RA patients treated with methotrexate. Thirty-three percent of patients with baseline MRI abnormalities developed radiographic damage compared with only 8% without baseline MRI abnormalities at 12 months of followup.

Older patients with degenerative or posttraumatic arthritis may exhibit lesions resembling erosions and bone edema, and care should be taken in interpretation of solitary lesions seen on low-field extremity MRI, especially in older patients.

There are limited data on whether MRI abnormalities are predictive of poor functional outcome as opposed to being predictive only of future radiographic erosions. Radiographic erosions are considered a surrogate marker for poor functional outcome in longstanding RA. Findings on MRI could be considered a surrogate marker for radiographic erosions. Whether MRI erosions in the absence of radiographic erosions are associated with poor functional capacity has not yet been evaluated, and data from large ongoing clinical trials where MRI is being utilized are awaited.

High-field MRI with contrast provides the gold standard means by which to assess RA disease activity in the joints imaged, although this may not always be feasible; tradeoff in terms of field strength, use of contrast, and numbers of joints imaged should be tailored to particular requirements in clinical trials or clinical practice.

Research agenda

Several benefits from using MRI in RA have already been documented, as described above. However, unsolved questions remain and further methodologic and clinical research is very important.

As marked technical improvements have occurred since the data presented above were generated, it is relevant to evaluate the ability of state-of-the-art extremity MRI units with respect to detection and monitoring of various joint pathologies, particularly bone edema. This includes both the true low-field units and the 1.0–1.5T units available. Further studies of the ability of modern extremity MRI to reliably detect synovitis without the use of contrast agents are also highly relevant. Continued research of the performance of newer-generation extremity MRI in comparison to the standard 1.5–3T MRI units is indicated.

Further research to determine the exact role of MRI in the management of patients in clinical practice is essential. Given modern treatment paradigms that require very early detection and tight control of inflammatory arthritis, and given the increased sensitivity of MRI for detecting RA pathology over clinical examination and radiographs, MRI may benefit patients in several ways. A number of areas should be highlighted for further research.

First, the determination of clinical algorithms for when to use extremity MRI in early diagnosis of inflammatory arthritis is needed, such as has recently been suggested for

ultrasound (23). Of interest in the study of ultrasound in early undifferentiated arthritis, no additional predictive information on the risk of development of persistent inflammatory arthritis was reported in those patients seropositive for RF or CCP. For seronegative patients, findings on power Doppler ultrasound did increase the probability of developing persistent inflammatory arthritis.

Second, additional research into the role of MRI imaging in monitoring of existing RA is needed. It would seem logical that patients with disease activity would warrant change of therapy without recourse to imaging. In contrast, patients who appear to be responding well have been demonstrated to frequently have subclinical synovitis and bone edema visible on high-field MRI that is associated with subsequent erosion progression, and this group possibly would warrant the use of a modern imaging technique (24,25). We need studies from clinical practice to determine optimal algorithms for use and whether change in therapy based on imaging results in improvement in patient outcomes.

Finally, as well as understanding subclinical disease, we need to understand how imaging could aid in decision rules for stopping expensive biologic therapies, i.e., research into improving cost-effectiveness of current therapies.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Cohen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Cohen, Potter, Deodhar, Emery.

Acquisition of data. Cohen, Potter, Deodhar, Emery, Conaghan, Ostergaard.

Analysis and interpretation of data. Cohen, Potter, Deodhar, Emery, Conaghan, Ostergaard.

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