The evaluation of bone damage in rheumatoid arthritis with magnetic resonance imaging

R. Goldbach-Mansky[1], V. Mahadevan[1], L. Yao[2], P.E. Lipsky[1]

[1]Office of the Clinical Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases; [2]Department of Diagnostic Radiology, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, USA.

Please address correspondence and reprint requests to:Raphaela Goldbach-Mansky, MD, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Building 10, Room 9S205, 10 Center Drive, Bethesda, Maryland 20892, USA. E-mail: goldbacr@mail.nih.gov

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ABSTRACT
Magnetic resonance imaging (MRA) greatly improves the early detection and visualization of osseous and non-osseous joint changes over convention-al x-rays of involved joints in patients with rheumatoid arthritis (RA). Howev-er, the "pathophysiological correlate" of these MR imaging changes remains poorly defined. Careful validation of MRI findings and the evaluation of MRI as a tool to follow the effect of therapy remain to be performed before MRI may be used as a clinical tool to follow therapy or as a surrogate for evaluating osseous changes over time.

Introduction

Magnetic resonance imaging (MRI) of the joints has stimulated great interest as a research tool, because it can not only assess osseous changes but also extends the capacity to visualize the surrounding soft tissue with good contrast and high spatial resolution. Conventional radiographs limit visualization of the joint to the osseous structures and do not permit assessment of pathologic changes in joint tissues that may precede bone damage by months or even years (1, 2). These early changes include bone marrow edema and inflammation, synovial proliferation and early cartilaginous changes. In contrast, MRI permits detection of synovial proliferation and bone marrow changes early when special fat suppressed gadolinium-enhanced T1-weighted spin echo images are used (3, 4). Synovitis, the primary inflammatory lesion in rheumatoid arthritis (RA), can be detected by the increased uptake of contrast and monitored longitudinally. The early synovial membrane enhancement rate obtained by dynamic gadolinium-enhanced MRI was found to correlate with active inflammation on histology (5). Other soft tissues, such as the tenosynovium, tendons, entheses, joint effusions, and ligaments, can also be visualized.

Although MRI assessment of the inflamed synovium appears to be an important parameter in the assessment of RA (6), joint effusions detected by MRI are less specific, since they can be present in RA patients as well as patients with arthralgias and a few healthy controls (7). When MRI scores of the wrist and metacarpal bones of patients with RA are compared to radiographic scores of hands and feet one year later, patients with higher baseline MRI scores have significantly more subsequent radiographic erosions (8,9). More recently, bone marrow enhancement, but not synovitis, on the initial MRI scan predicted radiographic damage 6 years later; furthermore, although the synovitis score over time decreased, bone damage continued to increase (10). These results have suggested that MRI is superior to conventional radiographs in detecting osseous changes in joints early in the course of RA, and may detect bony lesions 6 to 24 months before conventional radiographs. In addition, early bone marrow changes rather than synovitis scores are associated with bone damage later on.

However, there are a number of caveats that must be considered when MRI studies are being evaluated.

What are MRI "erosions"?

A pathophysiologic term "erosion" is used to describe an MRI imaging abnormality. When individual MRI lesions are tracked over 2 years, only 25-50% of "erosions" detected on MRI progressed to become radiographic erosions (10, 11). This finding has raised a question about the true nature of "erosions" detected by MRI.

As the pathophysiologic basis of these "erosion-like lesions" has not been determined, the MRI lesions that are destined to become "radiographic erosions" remain uncertain, as is the significance of those MRI lesions that do

not progress to become radiographic erosions. One study has failed to document changes in erosions on MRI in the MCPs, even though radiographic scores of the hands progressed (12). Another study showed that 50% of MRI erosions at baseline did not progress to radiographic erosions in 5 years (10) highlighting the difficulty in interpreting the nature of early MRI lesions and the complexity of the use of MRI imaging in the clinical evaluation of patients.

Some older studies have not defined criteria for so called MRI "erosions" and the distinction between bone marrow enhancement, called "bone marrow edema", and true bony erosions is often difficult to make with certainty. As our ability to optimize the acquisition of images increases, we may develop better sequences to distinguish true bone erosions from bone marrow edema and inflammation. Moreover, because high resolution MRI examinations are limited to evaluation of specific body areas, an unresolved question is the extent to which changes in a single joint or group of joints reflect a systemic, polyarticular disease process.

Technical challenges: Identifying appropriate MRI sequences and properly defining MRI lesions to allow for scoring

Differences in imaging sequences, changes selected to be scored, and scoring systems have confounded the interpretation and comparison of the various MRI studies (13). Some progress has been made to standardize image acquisition, nomenclature and scoring systems for MRI. At a consensus conference – OMERACT 5 (Outcome Measures in Rheumatoid Arthritis Clinical Trials) – a group of experts developed recommendations for image acquisition and scoring (14). The recommendations included the assessment of carpal bones as well as the metacarpal bases and the distal radius and ulna. "Erosion", "bone defect" or "bone edema" are each scored on a scale of 1-10 (1 meaning 10% bone involvement, and 10 being 100% involvement). Synovitis is graded on a scale from 0-3 at the radiocarpal joint and

intercarpal joints. Of note, standardization of the image acquisition is only loosely defined and the terminology used to describe image abnormalities is somewhat subjective and derived in part from non-validated pathological correlates. For example, bone marrow enhancement is not specific for RA and is present in degenerative joints (15, 16), post trauma (17,18) and also in some normal joints (19, and our unpublished observations). However, it is likely that the underlying histopathological changes vary in the different settings.

A major problem with any scoring system has been the large degree of inter-rater variability. In a recent publication (20), five international centers scored sets of images obtained by slightly differing techniques using different scoring methods. The inter-rater agreement was moderate at best, indicating the need to standardize the image acquisition technique, to develop a standard scoring system, and to improve training to achieve inter-rater reproducibility that is sufficient to assess synovial and osseous changes accurately (21). Centers that have trained staff to assess MRI scans in a standardized way have improved intra-reader and possibly inter-rater variability (22). However, it remains unclear at this time whether the composite score developed is sensitive to change (23).

Quantifying MRI abnormalities

To reduce the problem of inter-rater variability, quantitative rather than semi-quantitative methods to assess bone erosions and synovial changes have been explored. A recent study employed a semi-automated segmentation tool to outline and measure the volume of "erosions" (hypodense areas on the T1 weighted images) and the inflamed synovium (enhancing areas on the post-gadolinium images) (22). The analysis included 3 mm slices of the wrist from 12 patients with rheumatoid factor positive RA. Erosion and synovial volumes were calculated by summating all erosions and the area of the synovium outlined on each image and multiplying the sum by the slice thickness to generate a volumetric index.

The authors demonstrated that "erosion volumes" were reproducibly stable within a 2-day period, but synovial volumes showed more variability. However, the technical challenges of outlining regions of interest, such as an erosion or synovial tissue, also introduces operator dependence. An operator needs to decide whether a "dark area" on the T1 weighted image is an erosion and then draw a line around this area to measure its volume. The process of outlining an area of interest on the computer screen is called segmentation. To overcome the possible subjectivity implicit in this approach, several automatic and semi-automatic segmentation methods for multidimensional image analysis of objects of interest (i.e., bone and bone erosions) have been developed. Importantly, these methods differ in their degree of accuracy, precision and efficiency – i.e., the extent of operator dependence involved.

We have tried to address this problem by comparing bone lesion volumes detected by MRI with computerized tomographic (CT) images of the carpal bones in patients with erosive RA (24). As CT is considered to be the best method to assess bony changes, we felt that this would provide information to relate the MRI images to the best "gold standard" available. We have employed a boundary-based assisted segmentation method to outline the object boundary (25) and found that not all MRI lesions have a corresponding lesion on the CT. In addition, most of the MRI lesions are larger in volume than the corresponding lesion on the CT. The degree of size difference varies between individual lesions.

Multiple factors may contribute to the apparent size difference in lesions shown on CT and MRI. The MRI likely depicts bone marrow abnormalities surrounding an area of bone loss or even filling an area of bone loss, and these marrow reactions may be variably depicted by other MRI sequences. Hence, caution must be used when referring to these MRI lesions as "erosions" or interpreting a change in erosion volume as "healing of an erosion" before more definitive validation has been completed. In addition, the mag-

nitude of signal changes on MRI is always influenced by the specific scan parameters; differences in MRI scanning methods must be strictly considered in applying any quantitative or semi-quantitative MRI method.

Does the MRI depict bone erosions?

This is a question of validity that describes how well an instrument or measurement procedure actually assesses what it proposes to measure. This issue is particularly important because mineralized bone does not give any signal on MRI, and is visualized as a "negative image" between surrounding tissues that contain mobile protons. Most of the "validation procedures" for MRI are based on the correlation of semi-quantitative MRI measures with radiographic scores or other imaging modalities (such as semiquantitative scoring of the MRI lesions of the wrist compared to radiographic scores of the hands or hands and feet) (2, 8,9,11, 12).

Although useful, these studies were not designed to relate MRI changes to pathophysiologic events. In fact, such true validation studies are difficult to conduct because of the difficulty of obtaining human tissue for analysis.

Ideally physical measurement of the erosion in the bone itself and comparison with the volume measured according to the MRI would provide validation of the MRI imaging technique to represent erosions. This kind of validation on cadaveric samples has obvious limitations and animal studies of MRI changes in early inflammatory arthritis with appropriate tissue validation have not been performed to date.

The question remains regarding the actual nature of the pathologic lesions detected on MRI. When comparing MRI lesions to CT erosions in our studies, we made some interesting observations. Large cystic CT lesions without a break in cortex or with only a small break in cortex may not have any MRI signal abnormality and could be completely overlooked on the MRI. Similarly a small number of CT lesions with definitive cortical defects do not have associated MRI changes. It is therefore

likely that only bony defects that encompass "filling defects" are visualized well by MRI. This could mean that the bone marrow in some bone cysts is replaced by normal marrow and therefore no signal abnormality can be detected on the MRI. On the other hand, the tissue filling a bony erosion may be abnormal marrow or tissue originating from outside the bone.

One may therefore ask whether the signal abnormalities that are detected in "bona fide" erosions indicate the state of bone marrow or other soft tissue abnormalities associated with a bony lesion, rather than an osseous defect itself. Interestingly, in a recent study that applied a more rigid definition of bone marrow edema and erosions, it was found that bone marrow edema rather than synovitis was the strongest predictor of osseous damage on radiographs at the 6-year follow up (26). Even though the imaging timepoints in this study were far apart, the data suggest that a careful unbiased observation of MRI lesions and abnormalities may permit a better understanding of the true pathophysiology of bone destruction.

One may hypothesize that bony erosions develop in patients who have a predilection for bone inflammation which can be detected by bone marrow enhancement ("bone edema") early in the course of the disease. We may therefore develop more predictive models of disease when accounting for persistent synovitis and bone marrow enhancement separately. Some clinical studies (27) and one imaging study (26) suggest that synovial inflammation and bone damage may be controlled separately and may synergistically contribute to joint damage. This does not contradict observations that link MRI lesions at the initial visit with radiographic damage at follow up, but points to the possibility that premature labeling of MRI lesions as "bona fide erosions" may interfere with objective analysis of the underlying pathophysiology of joint destruction.

How MRI might be used

Interest in the use of MRI in the diagnosis, establishment of prognosis, and

monitoring of RA has been stimulated by development of highly effective treatments, a need to monitor these therapies, and encouraging preliminary imaging results (28). The routine use of MRI in clinical practice has been advocated without studies demonstrating that this expensive modality adds significantly to the ability to diagnose or treat RA. Moreover, no guidelines have been developed regarding the use of MRI findings as a basis for treatment decisions.

It is clear that MRI provides detailed and potentially quantifiable images of articular structures, and that varying changes on the MRI are seen during the course of the disease and in response to treatment. However, the enthusiastic embracing of this technology in clinical practice and clinical trials may be premature given the challenges of MRI data analysis and the uncertainty regarding their pathophysiologic meaning. MRI generates a large amount of information about bone, the marrow space and surrounding soft tissue, and may be a powerful tool for improving our understanding of the pathophysiology of RA and other arthritides (29). Careful validation of MRI findings is required before the importance and clinical interpretation of these findings is established with respect to disease activity and prognosis. In particular, whereas MRI may ultimately prove useful in the early prediction of outcome in RA, a rigorous validation of MRI findings as surrogates for established radiographic outcome measures is warranted before the routine inclusion of MRI in clinical trials can be recommended. Moreover, the quantitative interpretation of MRI results and the standards for MRI use must be predicated on well defined MRI protocols.

Nevertheless, as innovations in MRI technology evolve, our ability to obtain high resolution images of joints and surrounding soft tissue pathology will improve. If properly validated, MRI may become a powerful tool to examine the physiology of bone damage and remodeling, and the response to therapy, in RA and other inflammatory diseases.

References

1. GILKESON G, POLISSON R, SINCLAIR H *et al.*: Early detection of carpal erosions in patients with rheumatoid arthritis: A pilot study of magnetic resonance imaging. *J Rheumatol* 1988; 15: 1361-6.

2. FOLEY-NOLAN D, STACK JP, RYAN M *et al.*: Magnetic resonance imaging in the assessment of rheumatoid arthritis – a comparison with plain film radiographs. *Br J Rheumatol* 1991; 30: 101-6.

3. NAKAHARA N, UETANI M, HAYASHI K, KAWAHARA Y, MATSUMOTO T, ODA J: Gadolinium-enhanced MR imaging of the wrist in rheumatoid arthritis: value of fat suppression pulse sequences. *Skeletal Radiol* 1996; 25: 639-47.

4. SUENAGA S, OGURA T, MATSUDA T, NOIKURA T: Severity of synovium and bone marrow abnormalities of the temporomandibular joint in early rheumatoid arthritis: role of gadolinium-enhanced fat-suppressed T1-weighted spin echo MRI. *J Comput Assist Tomogr* 2000; 24: 461-5.

5. OSTERGAARD M, STOLTENBERG M, LOVGREEN-NIELSEN P, VOLCK B, SONNEHOLM S, LORENZEN I: Quantification of synovistis by MRI: Correlation between dynamic and static gadolinium-enhanced magnetic resonance imaging and microscopic and macroscopic signs of synovial inflammation. *Magn Reson Imaging* 1998; 16: 743-54.

6. POLEKSIC L, MUSIKIC P, ZDRAVKOVIC D, WATT I, BACIC G: MRI evaluation of the knee in rheumatoid arthritis. *Br J Rheumatol* 1996; 35 (Suppl. 3): 36-39.

7. SAVNIK A, MALMSKOV H, THOMSEN HS *et al.*: Magnetic resonance imaging of the wrist and finger joints in patients with inflammatory joint diseases. *J Rheumatol* 2001; 28: 2193-200.

8. MCQUEEN FM, STEWART N, CRABBE J *et al.*: Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. *Ann Rheum Dis* 1998; 57: 350-6.

9. LEE J, LEE SK, SUH JS, YOON M, SONG JH, LEE CH: Magnetic resonance imaging of the wrist in defining remission of rheumatoid arthritis. *J Rheumatol* 1997; 24: 1303-8.

10. OSTERGAARD M, HANSEN M, STOLTENBERG M *et al.*: New radiographic bone erosions in the wrist are detectable with magnetic resonance imaging a median of two years earlier. *Arthritis Rheum* 48: 2128-31.

11. MCQUEEN FM, BENTON N, CRABBE J *et al.*: What is the fate of erosions in early rheumatoid arthritis ? Tracking individual lesions using x rays and magnetic resonance imaging over the first two years of disease. *Ann Rheum Dis* 2001; 60: 859-68.

12. KLARLUND M, OSTERGAARD M, JENSEN KE, LYSGARD MADSEN J, SKJODT H, LORENZEN I: Magnetic resonance imaging radiography, and scintigraphy of the finger joints: one year follow up of patients with early arthritis. *Ann Rheum Dis* 2000; 59: 521-8.

13. MCQUEEN FM: Magnetic resonance imaging in early inflammatory arthritis: What is its role ? *Rheumatology (Oxford)* 2000; 39:700-6.

14. CONAGHAN P, EDMONDS J, EMERY P *et al.*: Magnetic resonance imaging in rheumatoid arthritis: summary of OMERACT activities, current status, and plans. *J Rheumatol* 2001; 28: 1158-62.

15. FELSON DT, CHAISON CE, HILL CL *et al.*: The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med* 2001; 134: 541-9.

16. LINK TM, STEINBACH LS, GHOSH S *et al.*: Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* 226: 373-81.

17. YAMAMOTO T, SCHNEIDER R, BULLOUGH PG: Subchondral insufficiency fracture of the femoral head: histopathologic correlation with MRI. *Skeletal Radiol* 2001; 30: 247-54.

18. KRAMPLA W, MAYRHOFER R, MATCHER J, KRISTEN KH, URBAN M, HRUBY W: MR imaging of the knee in marathon runners before and after competition. *Skeletal Radiol* 2001; 30: 72-6.

19. GIGENA LM, CHUNG CB, LEKTRAKUL N, PFIRRMANN CW, SUNG MS, RESNICK D: Transient bone marrow edema of the talus: MR imaging findings in five patients. *Skeletal Radiol* 2002; 31: 202-7.

20. OSTERGAARD M, KLARLUND M, LASSERE M *et al.*: Inter-reader agreement in the assessment of magnetic resonance images of rheumatoid arthritis wrist and finger joints – an international multicenter study. *J Rheumatol* 2001; 28: 1143-50.

21. LASSERE M, MCQUEEN F, OSTERGAARD M *et al.*: OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Exersice 3: an international multicenter reliability study using the RA-MRI Score. *J Rheumatol* 2003; 30: 1366-75.

22. BIRD P, LASSERE M, SHNIER R, EDMONDS J: Computerized measurement of magnetic resonance imaging erosion volumes in patients with rheumatoid arthritis: A comparison with existing magnetic resonance imaging scoring systems and standard clinical outcome measures. *Arthritis Rheum* 2003; 48: 614-24.

23. MCQUEEN F, LASSERE M, EDMONDS J *et al.*: OMERACT rheumatoid arthritis magnetic resonance imaging studies. Summary of OMERACT 6 MR Imaging Module. *J Rheumatol* 2003; 30: 1387-92.

24. BEDAIR H, MURPHEY M, FLEMMING D *et al.*: A comparison of MRI and CT in detecting bone erosions in early rheumatoid arthritis. *Arthritis Rheum* 2001; 44: S222 (abstr.).

25. FALCAO AX, UDUPA JK, SAMARASEKERA S, SHARMA S: User-steered image segmentation paradigms: Live wire and live lane. *Graphical Models and Image Processing* 1998; 60: 233-60.

26. MCQUEEN FM, BENTON N, PERRY D *et al.*: Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 1814-27.

27. LIPSKY PE, VAN DER HEIJDE DM, ST CLAIR EW *et al.*: Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; 30: 1594-602.

28. OSTERGAARD M, SZKUDLAREK M: Magnetic resonance imaging of soft tissue changes in rheumatoid arthritis wrist joints. *Semin Musculoskelet Radiol* 2001; 5:257-74.

29. MCGONAGLE D, GIBBON W, EMERY P: Classification of inflammatory arthritis by enthesitis. *Lancet* 1998; 352: 1137-40.