MR imaging in early rheumatoid arthritis : techniques and applications

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Chapter 11

Summary and general conclusion
Samenvatting en algemene conclusie
List of abbreviations
List of publications
Dankwoord
Curriculum vitae

Summary and general conclusion

The main aim of this thesis is to determine the role of magnetic resonance imaging (MRI) in early rheumatoid arthritis (RA). We set out to improve the MRI protocol and sequences used in arthritis patients, to detect subclinical inflammation in various patient groups and to describe the clinical implications of MRI. Chapter 1 provides a general introduction to this thesis, in chapter 2 the earliest disease stages of rheumatoid arthritis and the concept of pre-rheumatoid arthritis are further explored.

Technical developments and protocol optimization

In chapters 3-5 various ways are described to optimize the scanning protocol for arthritis patients. We evaluate the effect of leaving out gadolinium (Gd)-chelate contrast administration, leaving out T2-weighted sequences and replacing a conventional T1-weighted sequence with a rapid out-of-phase gradient echo sequence.

In Chapter 3 we evaluated whether intravenous Gd-chelate contrast administration can be eliminated when evaluating synovitis and tenosynovitis in early arthritis patients, thereby decreasing imaging time, cost, and invasiveness of the procedure. Wrist MRIs of 93 early arthritis patients were evaluated by two readers for synovitis of the radioulnar, radiocarpal, and intercarpal joints, according to the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) score, and for tenosynovitis in ten compartments. Scores of MRI images without Gd-chelate contrast enhancement were compared to scores obtained when evaluating all, including contrast-enhanced, MRI images as reference. Subsequently, a literature review and pooled analysis of data from the present and two previous studies were performed. At the individual joint/tendon level, sensitivity to detect synovitis without Gd-chelate contrast was 91 % and 72 % for the two readers, respectively, with a specificity of 51 % and 81 %. For tenosynovitis, the sensitivity was 67 % and 54 %, respectively, with a specificity of 87 % and 91 %. Pooled data analysis revealed an overall sensitivity of 81 % and specificity of 50 % for evaluation of synovitis. Variations in tenosynovitis scoring systems hindered pooled analyses. These results show that eliminating Gd-chelate contrast administration results in low specificity for synovitis and low sensitivity for tenosynovitis, indicating that Gd-chelate contrast administration remains essential for an optimal assessment.

In Chapter 4 we determined whether T1 post-Gd chelate images (T1Gd) could replace T2-weighted images (T2) for evaluating bone marrow edema (BME), thereby allowing a shorter MRI protocol in RA. In 179 early arthritis patients and 43 advanced RA patients, wrist and metacarpophalangeal (MCP) joints were examined on a 1.5-T extremity MRI system with a standard protocol (coronal T1, T2 fat-saturated and coronal and axial T1 fat-saturated after Gd). BME was scored according to OMERACT RAMRIS by two observers with and without T2 images available. Agreement was assessed using intraclass correlation coefficients (ICCs) for semi-quantitative scores and test characteristics with T2 images as reference. Agreement between scores based on T2 and T1Gd images was excellent (ICCs 0.80-0.99). At bone level, sensitivity and specificity of BME on T1Gd compared to T2 were high for both patient

groups and both readers (all ≥80 %). Therefore T1Gd and T2 images are equally suitable for evaluating BME. Because contrast is usually administered to assess (teno)synovitis, a short MRI protocol of T1 and T1Gd is sufficient in RA.

In Chapter 5 we investigated the option of using opposed-phase gradient echo (OPGE) imaging to detect erosions. In magnetic resonance imaging for RA, demarcating erosions may be hard because of cortical destruction and similar signal intensity of adjacent synovium and bone marrow with edema. OPGE imaging might improve delineation of the bone-tissue interface. Wrist and MCP joints of fourteen early arthritis patients were imaged on a 1.5T extremity MRI. Coronal T1, T2 fatsat and post-Gd-chelate T1-fatsat as well as OPGE pre- and post-Gd-chelate sequences were obtained. T1-based and OPGE-based image sets were assessed for image quality and scored according to OMERACT RAMRIS score for erosions in consensus by two observers. A reference score was established using all available images. Image quality, absence of motion artifacts and sharpness were better on OPGE than on T1-weighted images (all scored 5 versus 4 on a 1-5 scale). Homogeneity, signal-to-noise ratio, RAMRIS erosion scores and confidence did not differ between sequences. There was a trend towards higher sensitivity of OPGE images for detection of erosions (85.6% vs 68.0%). Acquisition time was shorter for OPGE (43s vs 3m30s). These results show that the use of OPGE imaging to assess erosions reduces imaging time while providing better image quality. It might increase sensitivity for small erosions compared to T1-weighted images.

Subclinical inflammation

In chapters 6-8 we looked at the presence of inflammation on MRI when no inflammation can be detected at physical examination, i.e. subclinical inflammation.

In Chapter 6 we determined the association and concordance between inflammation of small joints measured with MRI and physical examination. 179 patients with early arthritis underwent a 68 tender joint count and 66 swollen joint count and 1.5T MRI of MCP (2-5), wrist and MTP (1-5) joints at the most painful side. Two readers scored synovitis and BME according to the OMERACT RAMRIS scoring method and assessed tenosynovitis. The MRI data were first analyzed continuously and then dichotomized to analyze the concordance with inflammation at joint examination. 1790 joints of 179 patients were studied. Synovitis and tenosynovitis on MRI were independently associated with clinical swelling, in contrast to BME. In 86% of the swollen MCP joints and in 92% of the swollen wrist joints any inflammation on MRI was present. In 27% of the non-swollen MCP joints and in 66% of the non-swollen wrist joints any MRI inflammation was present. Vice versa, of all MCP, wrist and MTP joints with inflammation on MRI 64%, 61% and 77%, respectively, were not swollen. BME, also in case of severe lesions, occurred frequently in clinically non-swollen joints. Similar results were observed for joint tenderness. These results indicate that inflammation on MRI is not only present in clinically swollen but also in non-swollen joints. In particular BME occurred in clinically non-inflamed joints.

Anticitrullinated peptide antibodies (ACPA) and acute phase reactants may be increased before arthritis becomes clinically detectable, suggesting that the processes underlying RA start preclinically. Whether local inflammation occurs in the preclinical phase is unknown. In Chapter 7, we studied the small joints of ACPA positive arthralgia patients for local subclinical inflammation. Imaging was performed using 1.5 T extremity MRI. Painful hand or foot joints of 21 ACPA positive arthralgia patients without clinical arthritis were imaged. For comparison, hand and foot joints of 22 ACPA positive RA patients and 19 symptom free controls were studied. Within ACPA positive arthralgia patients, painful and symptom free joint regions were imaged. Scoring was performed according to the OMERACT RAMRIS method. Analyses were performed on joint region level and focused on inflammation (synovitis plus BME). The mean combined inflammation scores of the MCP/proximal interphalangeal (PIP) joints of controls, painful joints of ACPA positive arthralgia patients and ACPA positive RA patients were 0.1, 0.7 and 3.7, respectively ($p<0.001$). Likewise, the mean combined inflammation scores of the wrist were 0.9, 2.3 and 10.3, respectively ($p<0.001$) and that of the metatarsophalangeal joints 0.5, 0.9 and 3.8, respectively ($p=0.10$). At the MCP joints, the combined inflammation score was significantly correlated with C reactive protein and erythrocyte sedimentation rate levels ($rs=0.83$ and $rs=0.78$, respectively). These data suggest that local subclinical inflammation occurs in ACPA positive arthralgia patients.

In Chapter 8 we assessed whether subclinical inflammatory changes are present on magnetic resonance imaging (MRI) in patients with inflammatory bowel disease (IBD) and arthralgia. In this pilot study, painful hand joints [MCP, PIP and/or distal interphalangeal (DIP)] of 11 IBD patients (age 18-45 years) with continuous pain for > 6 weeks were scanned on a 1.5-T extremity MRI system. A control group of 11 IBD patients without joint pain who were matched for type and disease duration of IBD, gender, and age was included. All patients were clinically examined by a rheumatologist for the presence of pain and arthritis. Imaging was performed according to a standard arthritis protocol with intravenous Gd-chelate contrast administration on the same day. Images (blinded for clinical information) were evaluated by two readers in consensus for the presence of joint fluid, synovitis, tenosynovitis, enthesitis, erosions, cartilage defects, and bone marrow oedema. Enthesitis was seen in three hand joints (MCP 2, MCP 3, PIP 3) of 2/11 (18%) arthralgia patients and in none of the control group ($p = 0.48$). A small amount of subchondral bone marrow oedema was seen in the metacarpal head of two controls. No other abnormalities were observed. Several young IBD patients with chronic hand pain had subclinical inflammation on MRI, which invites for further study in a larger group of patients.

Clinical value

In chapters 9 and 10 we explore some of the clinical implications of the MRI findings.

No large studies had yet evaluated the accuracy of MRI to differentiate early RA from other patients with early arthritis. In Chapter 9 we report on our large cross-sectional study to determine whether patients who are clinically classified with RA differ in MRI features compared to patients with other diagnoses. In our study, 179 patients presenting with early arthritis (median symptom duration 15.4 weeks) underwent 1.5T extremity MRI of

unilateral wrist, MCP, and metatarsophalangeal joints according to our arthritis protocol, the foot without contrast. Two independent readers scored images according to OMERACT RAMRIS. Tenosynovitis was also assessed. The main outcome was fulfilling the 1987 American College of Rheumatology (ACR) criteria for RA. Test characteristics and areas under the receiver-operator-characteristic curves (AUC) were evaluated. In sub-analyses, the 2010 ACR/EULAR criteria were used as outcome, and analyses were stratified for ACPA antibodies. The ACR 1987 criteria were fulfilled in 43 patients (24.0%). Patients with RA had higher scores for synovitis, tenosynovitis, and bone marrow edema (BME) than patients without RA ($p < 0.05$). ACPA-positive patients had more BME (median scores 6.5 vs. 4.25, $p = 0.016$) than ACPA-negative patients. For all MRI features, the predictive value for the presence of RA was low (< 50%). For all MRI features the AUC were < 0.70. Patients who fulfilled ACR/EULAR 2010 criteria but not ACR87 criteria for RA had less synovitis than patients who were positive for RA according to both sets of criteria ($p = 0.029$). Although patients with RA had higher scores of MRI inflammation and ACPA-positive patients had more BME, the severity of MRI inflammation assessed according to RAMRIS does not accurately differentiate patients with RA from other early arthritis patients.

In Chapter 10, we assessed the relevance of this subclinical inflammation with regard to radiographic progression. 1130 joints (unilateral MCP 2-5, wrist and metatarsophalangeal 1-5) of 113 early arthritis patients underwent clinical examination and 1.5 T MRI at baseline, and radiographs at baseline and 1 year. Two readers scored the MRIs for synovitis, bone marrow oedema (BME) and tenosynovitis according to the OMERACT RAMRIS method. Radiographic progression over 1 year was determined using the Sharp-van der Heijde scoring method. On patient level, BME, synovitis and tenosynovitis were associated with radiographic progression, independent of known risk factors ($p=0.003$, 0.001 and 0.011, respectively). Of all non-swollen joints ($n=932$), 232 joints (26%) had subclinical inflammation (≥1 MRI-inflammation feature present). These joints were distributed among 91% of patients. Radiographic progression was present in 4% of non-swollen joints with subclinical inflammation compared to 1% of non-swollen joints without subclinical inflammation (relative risks (RR) 3.5, 95% CI 1.3 to 9.6). Similar observations were done for BME (RR5.3, 95% CI 2.0 to 14.0), synovitis (RR3.4, 95% CI 1.2 to 9.3) and tenosynovitis (RR3.0, 95% CI 0.7 to 12.7) separately. Radiographic progression was infrequent, but joints with subclinical inflammation had an increased risk of radiographic progression within year 1. This demonstrates the relevance of MRI-detected subclinical inflammation.

Discussion and conclusion

Our studies on imaging sequences show that there are several opportunities to optimize and shorten the MRI protocol, but that at least for now administration of Gd-chelate remains necessary for an optimal assessment. The most feasible option is leaving out T2 weighted sequences and relying on T1 weighted post-Gd-chelate sequences for evaluation of BME. In practice, implementing this resulted in reduction of approximately 25% of the imaging time, or 15 minutes on a total examination time of around one hour. Out-of-phase gradient echo sequences might further shorten the imaging protocol by approximately 20%, however this needs confirmation in further studies.

There are additional options to optimize the scanning protocol that we have not yet explored. Diffusion weighted MRI (DWI) might be able to visualize inflammation without the use of Gd-chelate, which would be a great improvement for patients.[1] It was not possible to perform DWI on the extremity MRI that was used for the research described in this thesis, but this is readily possible on most whole-body systems. This also opens up the possibility to perform whole-body imaging, overcoming the limitation of extremity MRI to image only a limited number of joints and enabling assessment of total disease activity analogous to the currently used disease activity scores based on clinical examination.[2] Arterial spin labelling (ASL) is another advanced MRI technique that could potentially be used to non-invasively visualize inflammation and in addition quantify it in a objective and repeatable manner. We have performed some initial experiments with ASL, but these were hindered by technical challenges, others, however, have shown some initial success with it.[3]

For subclinical inflammation, we have shown that this is a common finding in early arthritis patients, that it is present in patients at high risk of developing RA and that MRI is a sensitive method to detect it. Furthermore, we determined its clinical relevance by showing that the presence of subclinical inflammation does actually predict worse radiographic outcome. Future studies should determine whether it useful to target treatment at subclinical inflammation, for example by treating patients with BME more aggressively, because BME is indicative for a worse outcome.

Recently, other studies have shown that even in remission subclinical inflammation is commonly present and negatively affects prognosis.[4] As also suggested by others, perhaps we should aim for imaging remission instead of clinical remission.[5–7] This would require defining acceptable maximal levels of inflammation to aim for with treatment and intensifying treatment when inflammation passes this threshold. Disappointingly however, preliminary results of the TASER and ARCTIC studies, both employing an ultrasound based treat-to-target strategy, failed to show improvement in clinical outcomes.[8, 9] Even though more patients in the intervention groups were treated with biologicals, this did not appear to improve rates of remission. One explanation why these studies failed to improve clinical outcomes might be that power-doppler based joint inflammation was targeted. A limitation of ultrasound is that BME cannot be studied; this can uniquely be demonstrated by MRI, and is a stronger predictor of eventual radiographic progression. As we have shown in chapter 6, as opposed to other forms of inflammation, BME is often observed in joints that do not exhibit clinical inflammation and therefore targeting this disease characteristic complements the current clinical remission criteria rather than merely increasing sensitivity for joint inflammation. Whether this is actually relevant in patients with remission remains to be determined, with present studies showing mixed results with regard to whether MRI-detected synovitis or bone marrow edema is more important in predicting progression during remission.[10, 11] Initial steps towards establishing a cut-off point for an acceptable state of synovitis scores have been made.[11] Furthermore, a first MRI-based randomized clinical trial testing an imaging-guided treat-to-target strategy is currently underway.[12]

As for now, the established clinical potential of MRI primarily lies in determining the prognosis and uncovering subclinical inflammation.[13] Its role in diagnosis is uncertain and probably very limited. Although our study on discernibility of early arthritis patients was not directly aimed at diagnostic performance, it clearly demonstrated the substantial overlap in imaging findings between different types of arthritis in their early stage, making it hard to use these findings to establish a diagnosis. MRI research in RA has focussed primarily

on synovitis, BME and erosions. Tenosynovitis is another prevalent finding which can be difficult to diagnose clinically but can be readily detected and differentiated from synovitis with MRI.[14] Its clinical relevance is still largely unclear but our data showed that, like other forms of inflammation, subclinical presence of tenosynovitis is associated with radiographic progression in early arthritis patients. Another feature that has been less well studied with MRI is cartilage damage and degradation, which is surprising considering that cartilage loss is the main factor determining physical disability. This is an area which deserves further attention.[15, 16]

Limitations and alternatives

Practical limitations of MRI include long examination duration, the need to administer an intravenous contrast agent and presence of contraindications in some patients. Another limitation might be its cost-effectiveness: MRI is relatively expensive, and a clear benefit of its adoption in treatment protocols for clinical prognosis has yet to be established.[17] Of the alternative imaging options to detect inflammation in rheumatic diseases, ultrasound has been most well studied.[18] Ultrasound is a comparatively low-cost technique that is well-suited to assess multiple joint regions which might be affected by RA. It can be performed directly by the treating physician in the outpatient clinic, however it is operator dependent and requires significant training. Compared to MRI it is more easily feasible to assess multiple joint regions with ultrasound and a set of joints and tendons can be selected to be examined for follow-up of inflammatory activity,[19] although ultimately whole-body MRI protocols might allow for an even more complete assessment of disease burden.[2] A major strength of MRI compared to ultrasound is the ability to detect BME which has been shown in many studies to be an important risk factor of erosive progression.[20] Other imaging techniques such as scintigraphy, PET and optical imaging have been less-explored but might one day prove to be viable alternatives for imaging inflammatory activity.[21–23]

When applied in a clinical context, paradoxically MRI can pose a diagnostic dilemma by being too sensitive. MRI detected erosions, synovitis and BME occur frequently in symptom-free persons and more frequently with increasing age.[24, 25] Therefore, robust studies are needed to better define the normal and abnormal MRI findings as found in healthy persons and patients.

In conclusion, the shift towards treating RA patients in earlier disease phases and the slower progression of disease due to more effective treatment necessitate more sensitive methods to assess inflammation and structural damage. MRI is one of the most sensitive methods available for this purpose and provides a wealth of extra information compared to clinical examination or conventional radiographs. Subclinical inflammation is prevalent and clinically relevant. Nevertheless, the exact role of MRI in clinical practice is yet to be determined. Improvements in imaging methods and protocols, and our understanding of implications of imaging findings, can and need to be made.

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