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## The use of MRI in early inflammatory arthritis

Nieuwenhuis, W.P.

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**Author:** Nieuwenhuis, W.P.

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**Summary, conclusions, discussion  
and future perspectives**

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## Summary and Conclusions

The main subject of this thesis is the exploration of the value of magnetic resonance imaging (MRI) in rheumatoid arthritis (RA). Because MRI has the ability to show inflammatory changes (i.e. synovitis, tenosynovitis and BME) in addition to structural changes (i.e. erosions), it might be valuable for multiple purposes, both clinical and research oriented. The studies in this thesis represent several different potential applications of MRI in the field of early arthritis.

All studies were performed in patients of the Leiden Early Arthritis Clinic (EAC). This is an observational cohort in which all patients that present at the rheumatologic outpatient clinic of the Leiden University Medical Center with inflammatory arthritis and symptom duration of less than two years are included. The EAC was started in 1993. At the start of the EAC, but also in the years after the start, the importance of early treatment initiation in early arthritis patients was accentuated by campaigns and guidelines. In **Chapter 8** we assessed whether RA patients were indeed recognized with shorter symptom duration during the existence of the EAC and whether this was accompanied with less severe RA at first presentation. We found that patients were identified earlier and that this was paralleled with less severe inflammation (less affected joints and lower levels of acute phase reactants). However, the severity of patient reported outcomes (PROMs: fatigue, pain, morning stiffness and disease activity) gradually increased over the same period. These findings appear paradoxical: why does the severity of PROMs increase, while patients present with less inflammation? Apparently, these PROMs are multidimensional: involving not only inflammatory, but also psychosocial factors. This is also reflected by other studies. It has been shown for example that fatigue is only limitedly explained by inflammatory variables, but does strongly correlated with variables like pain.<sup>1-3</sup> Presumably, the increase in severity of PROMs reflects a general increase in societal pressure, where smaller health problems could be experienced as more disabling. Furthermore, higher health expectations could lead to a shift of reference when reporting PROMs. These findings bring to light possible difficulties when comparing (differences in) PROMs between different study populations; not only when comparing populations from different countries, but also when comparing populations from the same countries but from different time periods.

MRI of the metacarpophalangeal (MCP), wrist and metatarsophalangeal (MTP) joints is performed in all newly presenting patients of the EAC since 2010. In combination with the other data collected in the EAC, this enabled us to study many questions regarding the use of MRI in early arthritis patients.

The original RAMRIS method included scores for erosions, bone marrow edema (BME) and synovitis. Later an additional scoring system for tenosynovitis at the wrist and MCP joints was developed.<sup>4,5</sup> However, the prevalence, discriminative value and prognostic value of MRI detected tenosynovitis in early arthritis was still limitedly studied. In **Chapter 2** we assessed tenosynovitis at the wrist and MCP joints in 178 early arthritis patients at baseline using this method. The prevalence of MRI detected tenosynovitis was high (65% of early arthritis patients had tenosynovitis). The prevalence was higher in RA patients than in other early

arthritis patients (75% vs 59%). However, when looking at the separately scored tendon locations, most locations were not specific for RA but also involved in patients with other arthritides. Tendons that were more often affected in RA-patients were the flexor tendons at MCP 5, the extensor tendons at MCP 2 and 4, and the tendons in wrist extensor compartments I, II, and IV. Nevertheless, the discriminative value of tenosynovitis at these specific locations was limited: specificity was high (>90%), but sensitivity was low (<20%). This means that the majority of RA patients did not have tenosynovitis at one of these locations, but that tenosynovitis at these locations was uncommon in non-RA patients.

Synovitis of the joint next to the affected tendons was seen in 70-100%. The majority of locations of tenosynovitis associated with RA, were associated with RA independent of local synovitis, thus the association between tenosynovitis and RA seems not to be driven by underlying synovitis. The severity of tenosynovitis was not significantly associated with more severe RA (radiographic progression or ACPA-positivity). An interesting observation in RA was that although the extensor tendons lack a synovial sheath at the level of the MCP joints, we also found inflammation at these tendons. A previous study named this periextensor tendon inflammation.<sup>6</sup> It might be difficult to differentiate synovitis of the joint and periextensor inflammation and the question could be raised whether detected periextensor tendon inflammation does not actually reflect joint synovitis. Interestingly, we also found periextensor inflammation without synovitis of the specific MCP joint. Although the numbers were small, we only found this in patients with RA. It might suggest an effect of RA on other tissue than the tenosynovium, for example a direct effect on the tendons.

This study has shown that tenosynovitis is a common finding in early (rheumatoid) arthritis and that the presence of MRI detected tenosynovitis could have some diagnostic use. We were not able to show a relation with more radiographic joint damage. Still, tenosynovitis can cause pain, range of motion loss and (grip) weakness leading to disability. Therefore, the presence of MRI detected tenosynovitis can be of importance in early RA.

MRI also has potential prognostic use. It had been shown that patients with high BME and synovitis scores have more erosive progression during follow-up.<sup>7-19</sup> So far this was studied on patient level, i.e. the total BME, synovitis and erosion scores of a patient. In **Chapter 3** we assessed BME and synovitis lesions at bone level, i.e. we assessed per bone whether BME in that bone or synovitis around that bone (local synovitis) was present and whether there was erosive progression in that bone during follow-up. MRI was performed at three time points: at inclusion in the EAC, after 4 months and after 12 months of follow-up. This allowed us to not only study the association between baseline findings and erosive progression, but also to study the course of BME and synovitis lesions and whether the course of these lesions was associated with erosive progression.

The presence of BME and the presence of local synovitis at baseline were associated with erosive progression in that bone after follow-up in univariable analyses. Because BME and synovitis often occur concurrently, stratified analyses and multivariable generalized estimating equation (GEE) analyses were performed. In these analyses BME at baseline was still associated with erosive progression, however when adjusting for BME, the association of synovitis with erosive progression was weaker or lost.

The follow-up MRIs showed that the course of BME and local synovitis lesions were similar: lesions were most frequently present or absent at each time point. Lesions appeared or disappeared less frequently and only very rarely lesions disappeared and reappeared (or vice versa). This suggests that these inflammatory lesions are not very fluctuating or “waxing and waning”. To assess the association between the course of BME and synovitis lesions and erosive progression, the number of MRI scans where BME or local synovitis was present was determined for each bone (e.g. if BME was present at all 3 MRI time points in a given bone, the load of BME for this bone was 3). GEE analyses showed that both higher loads of BME and synovitis were univariably associated with erosive progression. However, multivariable analyses with both the load of BME and the load of synovitis showed that only BME was independently associated with erosive progression. Presence of BME in 2 or 3 time points was strongly associated with erosive progression (OR >55). Although the absolute number of bones with BME at all three time points that had erosive progression was not very high (15%), this study showed that persistent BME is predictive of erosive progression in the same bone.

Assumptions regarding the pathogenesis of bone erosions based on this study should be made with care. However, the findings could be in line with the hypothesis that synovitis of a joint leads to inflammation in the bone, seen on MRI as BME, which can lead to erosive changes of the bone. This could explain why synovitis is associated with erosive progression, but loses this association when adjusted for the presence of BME. Erosive progression was seldom in the absence of BME. It might be interesting to further study the presence of BME as a prognostic factor. BME could play a role in the selection of treatment, leading to more personalized medicine.

Because MRI is a very sensitive imaging modality, MRI could also play a role in the assessment disease activity in RA-patients. There is no gold standard to measure disease activity. Previously, radiographic progression and clinical decision making were used as surrogate measures to develop clinical composite scores to assess disease activity. In **Chapter 6** we used data obtained in patients diagnosed with RA that were included in the EAC to evaluate new disease activity scores that were derived by correlation to MRI findings. The new disease activity scores of Baker et al were derived using 2 different clinical trial populations.<sup>20</sup> In the first clinical trial population (GO-BEFORE) MRI-detected synovitis and BME were used to derive modified disease activity scores (M-DAS), this was done by using the regression coefficients of the independent predictors of MRI-synovitis. These predictors were selected from all commonly utilized components in the standard disease activity scores (DAS28-ESR, DAS28-CRP, SDAI and CDAI). The second clinical trial population (GO-FORWARD) was used to validate the M-DAS and to assess whether the M-DAS improved the prediction of radiographic progression. The M-DAS correlated stronger with MRI-detected synovitis than the standard disease activity scores (DAS28-ESR, DAS28-CRP, SDAI and CDAI). In addition, the M-DAS were stronger associated with radiographic progression within the first year. However, replication in the RA patients of the EAC did not show superiority of the different M-DAS over the standard scores (DAS28-ESR, DAS28-CRP, SDAI and CDAI) on the association with MRI-detected synovitis, MRI-detected BME, or radiographic progression association. Furthermore, similar to the findings in the study of Baker et al both the standard and modified scores correlated only

moderately to weakly with MRI-findings and predicted radiographic progression poorly. These findings are illustrative for the difficulty to assess the disease activity and relate different disease measures to each other. Another replication of this study in the French early arthritis cohort ESPOIR also didn't find a difference between M-DAS and DAS.<sup>21</sup> Nevertheless, the use of different study populations could also play a role here. Further research is needed to find out how MRI can be used to improve the assessment of disease activity.

In 193 healthy, symptom-free controls it had been shown that MRI-detected inflammation increases with age.<sup>22</sup> In **Chapter 7** we studied the effect of age on MRI-detected inflammation in all 589 early arthritis patients and in a subgroup of 229 that fulfilled the 2010 ACR/EULAR classification criteria at presentation.<sup>23</sup> Next, we assessed whether the effect of age differed from that in healthy controls. Lastly, we compared the anatomic locations that were most commonly affected in RA-patients presenting at different age categories.

Both in all early arthritis patients and only those presenting with RA the total MRI-inflammation score was higher in patients presenting at higher age. The effect of age at presentation on the total inflammation score in all early arthritis patients and in RA patients was similar to the effect of age found in symptom-free controls (3% increase per year). Although the age-effect was similar, the total MRI-inflammation score in all early arthritis patients and RA-patients was higher (respectively 2.6 and 3.7 times higher). Comparing the localization of inflammation in RA patients presenting at different age categories (<40 years, 40-60 years, and >60 years) showed that at higher age more locations were affected. However, the locations that were most frequently inflamed were similar in younger and older age (e.g. synovitis at MCP 2 or BME at the first row of carpal bones).

The findings of this study suggest that there is a general effect of age on MRI-inflammation that is not disease specific, i.e. the effect in arthritis patients is similar to that in symptom-free controls. In RA-patients presenting at different ages, the most frequently affected locations are similar. Interestingly, these locations were also most frequently affected in symptom-free controls.<sup>22</sup> This study underlined the importance of taking age into account for the interpretation of MRI-findings.

The value of MRI in the early diagnosis of RA was assessed in **Chapter 4** and **Chapter 5**. Because early initiation of treatment increases the chance on a better disease outcome, the early identification of patients with RA is important.<sup>24-26</sup> The 2010 ACR/EULAR classification criteria for RA were developed to improve earlier identification of RA-patients.<sup>23</sup> Still, part of the RA-patients cannot be classified at first presentation. Up to 25% of patients presenting with UA (arthritis that cannot be classified by the 2010 RA criteria or by another disease) go on to develop RA.<sup>27,28</sup> MRI could be of value to identify these patients early.

In **Chapter 4** the addition of MRI-findings in the wrist and finger joints to the 2010-criteria, as described by Tamai et al, was evaluated.<sup>29</sup> Tamai et al studied whether MRI findings improved the diagnostic performance of the 2010 classification criteria in 166 early arthritis patients that did not fulfill the 1987 classification criteria for RA or criteria for other rheumatologic diseases (1987-UA).<sup>30</sup> Two outcome measures were used for the development of RA during follow up: fulfilling the 1987 criteria within one year and initiation of DMARDs

within one year. The test characteristics of only fulfilling the 2010-criteria were compared to the test characteristics of either fulfilling the 2010-criteria or the presence of specific MRI-findings. Their most interesting finding was the addition of the presence of BME to the 2010-criteria, this showed an increase in sensitivity, negative predictive value (NPV), and accuracy. However, the specificity and positive predictive value (PPV) decreased. In our study the addition of MRI-detected BME to the 2010-criteria also led to an increase in the sensitivity and NPV. However, this was at the cost of a considerable decrease in the specificity and PPV; overall this did not lead to an increase in accuracy. Our results suggested that using MRI for diagnostic purpose, with this method in patients not fulfilling the 1987 criteria is of limited diagnostic value. Moreover, with the used methods the results strongly depends on the prevalence of disease in the study population and how false positive and false negative tests are weighted.

In **Chapter 5** we chose a different approach; we aimed to assess the value of MRI to identify those arthritis patients that present with UA, but go on to develop RA. Furthermore, we hypothesized that false-positive MRI-findings would be reduced by using the MRI findings of the study in symptom-free controls as a reference to define an abnormal MRI. In symptom-free controls low grade MRI-detected inflammation was quite prevalent, especially at higher age and at preferential locations.<sup>22</sup> We used two outcome measures in this study: fulfillment of the 1987 criteria and initiation of DMARD-therapy within the first year of follow-up. First, we explored the discriminative value of MRI by comparing patients that presented with classifiable RA to symptom-free controls and patients that presented with other arthritides. We observed that patients that presented with other arthritides than RA also had high MRI-inflammation scores. Compared to BME and synovitis, tenosynovitis discriminated best between patients presenting with classifiable RA and symptom-free controls and patients presenting with other arthritides.

We continued by assessing the value of an abnormal MRI in the clinical relevant group of patients: the 201 that presented with UA. Within one year of follow up, 29 (14%) UA patients fulfilled the 1987 RA criteria (RA development) and 75 (37%) were prescribed DMARD-therapy. An abnormal MRI for any inflammation was associated with RA development. Of the individual inflammation types synovitis and tenosynovitis were associated with RA-development, but BME was not. UA patients frequently had a positive MRI for several types of inflammation. Only an abnormal MRI for tenosynovitis was associated with RA development independent of the other types of inflammation. Also after adjusting for age, swollen joint count, and CRP an abnormal MRI for tenosynovitis was significantly associated with RA-development. Assessing the test characteristics of an abnormal MRI for tenosynovitis revealed a PPV of 25% and a NPV of 95%. Thus, whereas 95% of UA-patients with a normal MRI for tenosynovitis did not develop RA, only 25% of UA-patients with an abnormal MRI for tenosynovitis developed RA.

Lastly, we also assessed the test characteristics of an abnormal MRI for tenosynovitis in UA patients presenting with mono-, oligo- or polyarthritis. Because the differential diagnosis can differ in these patients the value of MRI might also differ. This revealed that an abnormal MRI for tenosynovitis was only associated with RA-development in patients with oligoarthritis. Of the 83 UA-patients that presented with oligoarthritis, 15 (18%) developed RA. In these patients the PPV



of MRI was 36% and the NPV was 98%. The outcome DMARD-initiation revealed similar findings.

The findings of this study suggest that MRI can contribute to the early identification of UA-patients that go on to develop RA. Although an abnormal MRI did not yield high risk for RA development, the absence of MRI-detected inflammation made progression to RA highly unlikely.

## Discussion and future prospects

### Diagnostic use of MRI

With the knowledge that early aggressive treatment in RA prevents joint damage and increases the chance of achieving remission on the one hand and overtreatment of patients on the other hand there is a need for adequate diagnostic tools in patients presenting with recent onset arthritis. Using MRI to depict inflammation in the hand and foot, we observed that tenosynovitis was of most diagnostic value (compared to synovitis and BME). Still, when using MRI as a diagnostic test to identify which UA-patients develop RA, the posttest odds only slightly improved compared to the pretest odds. The biggest improvement was seen in UA-patients that presented with 2-4 swollen joints. MRI especially had a high negative predictive value, i.e. in the absence of MRI-inflammation in the MCP, wrist and MTP joints RA-development in UA patients was rare.

Remarkably, BME was not associated with the development of RA in early UA patients. This finding might seem contradictory to previous studies and even our own study which show clear associations between BME and the development of erosions in RA patients.<sup>7-10,12</sup> The development of articular bone erosions is a hallmark of RA and histological studies have shown that BME lesions in RA patients reflect inflammatory infiltrates in the subcortical bone, which could be involved with the development of erosions.<sup>31-33</sup> However, UA patients that go on to develop RA are a different group of patients than patients with (longstanding) RA. These patients are in an early phase of disease in which erosive joint damage is not (yet) present and BME might be less specific for the development of erosions and thus less specific for RA-development. The MRI-finding of BME can indeed be caused by inflammatory causes, but can also occur with other underlying processes (trauma, degenerative, vascular, infectious, neoplastic, metabolic and neurological)<sup>34</sup> and has also been found in symptom-free controls.<sup>22,35</sup> Similarly to BME, the presence of MRI-erosions was also of limited value to discriminate between UA patients that developed RA and those that did not.

Tenosynovitis has a high sensitivity for the development of RA in UA-patients and interestingly it has also been shown that tenosynovitis is most predictive for development of clinically apparent arthritis in patients presenting with clinically suspected arthralgia.<sup>36</sup> However, although it has been shown that tenosynovitis is seldom in healthy controls,<sup>22</sup> the specificity of tenosynovitis is limited. We and others have shown that tenosynovitis is not only prevalent in RA patients, but also in other inflammatory arthritides.<sup>37</sup>

To truly evaluate a diagnostic test, the clinical consequences need to be taken into account. Does the test improve certainty of the presence or absence of a disease? Does it change the decision to initiate treatment or refrain from treatment? Does it lead to earlier initiation of DMARD-therapy than without the test? And most

importantly: does the use of the test improve disease outcome? The results of our study showed that MRI changed the post-test odds most in UA-patients that presented with 2-4 clinically inflamed joints. Still, our study was an observational study. A diagnostic trial should be performed to study whether adding MRI to the diagnostic process truly improves the outcome for patients presenting with UA and of course whether this is cost-efficient.

For diagnostic purposes in clinical practice, US might be a more interesting imaging modality than MRI. It is cheaper than MRI, has logistical advantages over MRI and can also be used to detect synovitis and tenosynovitis. However, it is more operator dependent. The interpretation of US examinations performed by others and the comparison US examinations at multiple time points can be more complicated than when using MRI. Previous studies have shown that the sensitivity of ultrasound to detect inflammation is only slightly lower than contrast enhanced MRI.<sup>6,38,39</sup> Future research is needed to assess the diagnostic value of ultrasound in this setting, because similar questions as for the value of MRI also hold up for US.

### **Monitoring disease activity**

With the improvement in treatment of RA, the current goal is not only to prevent joint damage but also to achieve (DMARD-free) clinical remission. To achieve this treat-to-target strategy is recommended: the adaptation of therapy based on regular assessment of clinical disease activity.<sup>40</sup> Although there is no gold standard to measure disease activity in RA, several composite measures have been developed as surrogate measures for disease activity. Most of these composite scores contain a measure for the number of clinically involved joints. Because MRI and ultrasound are more sensitive to detect inflammation than physical examination it has been suggested that the use of these imaging modalities could be beneficial in the monitoring of disease activity.<sup>41</sup> Several studies have shown that ultrasound detected inflammation in patients in remission predicts clinical flare and progressive radiographic damage.<sup>42-45</sup> Moreover, it has been proposed that aiming for imaging remission in addition to composite measures might lead to better outcome of patients.

Recently the results of the TASER and ARTIC studies have been published, these studies compared a clinically monitored step-up treat-to-target strategy with a combination of clinically and ultrasound monitored step-up treat-to-target strategy in early arthritis patients.<sup>46,47</sup> Both studies showed a good response to treatment in both study arms, but the addition of US to disease monitoring did not lead to an improvement in outcome measures, despite more aggressive treatment in the ultrasound monitored group. This suggests that intensifying treatment based on inflammatory findings on ultrasound in the absence of clinical inflammation does not lead to better disease outcome and might even lead to overtreatment.

Whereas the additional value of imaging in step-up treat-to-target seems to be of limited help, some studies have shown that the presence of joint inflammation on imaging has predictive value to identify RA patients in clinical remission that are not able to stop or taper biological treatment without getting a relapse.<sup>48,49</sup> With more patients achieving clinical remission, side-effects and high costs of some DMARD-treatments, proper identification of patients who are able to taper or stop DMARD-therapy is a very interesting research topic.

Still, it is important to keep in mind that RA is an autoimmune disease and clinically detected joint inflammation or MRI-detected inflammatory findings are symptoms.

Although it is important to treat joint inflammation, the absence of joint inflammation (both clinical and subclinical) does not guarantee that the autoimmune processes related to RA are contained. Ideally (the disruption in) the immune system would be followed up and DMARD-therapy would be aimed to achieve new homeostasis of the immune system. By increasing our understanding of the pathogenesis of RA, new ways to observe disease activity might arise.

### **Other prospects for future research**

We did some interesting MRI findings which could be explored further and might help in our understanding of RA.

First of all, the anatomical locations most often showing inflammatory features on MRI in symptom free controls were similar to those in arthritis patients (e.g. synovitis at the second and third MC-joint). These locations also had higher inflammation scores (i.e. more severe inflammation) most often. It could support the hypothesis that mechanical strains play a role in starting an inflammatory response in RA. A possible explanation for why RA patients develop joint complaints and healthy individuals do not could be that in healthy individuals this response is regulated and asymptomatic, where in RA this might lead to symptomatic joint inflammation and possibly even to joint destruction. A better understanding of why some joints/tendons/bones are more often involved in RA than others might help further unravel the pathophysiology of RA.

Secondly, inflammation at the extensor tendons at the MCP joints was an interesting finding because these tendons lack a synovial sheath at the level of the MCP joints and thus the ability to develop tenosynovitis. The inflammatory findings around these tendons could be explained by peri-arthritis or secondary to the swelling of the underlying joint. However, in some patients the extensor tendons were also involved without underlying synovitis. Interestingly, this was only seen in patients with RA, this could be some rest inflammation or inflammatory involvement of tendons. Further exploration could give more insight in some of the pathophysiological process of RA.

Furthermore, most studies have focused on erosions, bone marrow edema, synovitis and tenosynovitis in the wrist and MCP-joints; the features that are represented in the RA MRI scoring system (RAMRIS), the only validated scoring system.<sup>4,5</sup> The RAMRIS has recently been updated and a recent systematic literature review has shown its validity for the use in clinical trials.<sup>50,51</sup> However, RAMRIS has some disadvantages and there are other joints, MRI findings and MRI techniques that can be studied (more extensively).

RAMRIS is a semi-quantitative scoring method and has its limitations. For example, with RAMRIS the location of an erosion within a specific bone is not assessed (e.g. in the central portion of the joint, the margins of the joint or away from the joint). Also, the assessment of inflammatory findings with RAMRIS could be hampered by a floor effect: there is a broad range of inflammatory findings that fall under a RAMRIS score of "1" (e.g. BME in 1% of the scored bone is scored similarly as BME in 32% of the bone) and scores of "2" or higher are uncommon. It is likely that in clinical practice MR scans would be assessed more qualitatively, leading to different interpretation of the MR findings. However, it is hard to use qualitative assessment of MRIs for research purposes because of limitations to the comparability and reproducibility of these findings.

Most studies have assessed the wrist and MCP joints; we have also studied the MTP joints. Recently there have also been studies in which whole-body MRI has been performed.<sup>52,53</sup> It is not yet clear which joints should be scanned, which, of course, also greatly depends for which purpose an MRI would be performed (e.g. diagnostic, disease monitoring, etc.). MRI findings like enthesitis, cartilage damage and bursitis were not scored in our studies and also other have only limitedly studied these findings. Furthermore, there also are MRI techniques that are not included in the RAMRIS which could prove useful for the assessment of inflammatory arthritides (e.g. dynamic contrast enhancement and diffusion weighted imaging). Finally, there are now also (semi)-automated quantification methods which can assist in the interpretation of MRI findings and can help assess the value of MRI.<sup>54,55</sup>

The knowledge on the use of MRI could be improved by using MRI to study clinically inflamed joints in RA patients and study the changes of these joints over time. This might learn us more on which findings on MRI are associated with inflammatory arthritis or, more specific, RA. The additive value of MRI to other (clinical) findings in the field of RA probably lies in the detection of inflammation or aspects of inflammation that cannot be detected otherwise. However, these inflammatory findings can be subtle, especially in early phases of disease, and differentiating which findings are related to RA and which findings are related to other processes (i.e. trauma, overuse, degeneration) can be problematic. Inflammatory MRI findings are also seen in symptom-free controls.<sup>22</sup> We have already shown that including the findings in symptom-free controls improves the specificity of MRI. Studying the MRI findings in clinically inflamed joints could further improve the interpretation of MRI findings. Additionally, the application of MRI in early arthritis patients could also improve if we succeed in further unraveling the pathophysiology of RA. When the disease processes of RA are better understood, it might be possible to perform MR examination focused on more specific findings.

In conclusion, over the past few decades the field of rheumatology has changed dramatically. With 1) the growing realization of the importance of early treatment of RA patients and thus of the importance of early recognition of RA patients and 2) new treatment options which can prevent joint destruction in most patients and make low disease activity and even remission realistic goals, there is a necessity for adequate tools to assess inflammatory and structural changes caused by RA. The studies in this thesis have assessed MRI findings in the important study population of patients with new onset arthritis and have shown that MRI provides valuable information.

Still, the additional value of MRI to other findings should be sorted out further. Future studies will need to show whether the information added by MRI is useful in clinical practice. It will have to be shown whether the information of MRI in trials is relevant in addition to the other observed parameters. It is not yet clear how MRI findings should influence clinical decision making and whether this would lead to better disease outcome for patients. For example, (the extent of) inflammation is detected more sensitively by MRI than physical examination; yet, it is not clear how this additional information should affect treatment. More aggressive treatment could lead to improved disease outcome, but also to overtreatment. In clinical trials,

MRI might help to detect smaller differences between treatment arms, but it should be kept in mind that these small differences might not be clinically relevant.

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