Clinically suspect arthralgia and early rheumatoid arthritis: advances in imaging and impact on daily life

Boer, A.C.

III

General discussion and summary

10

Discussion and summary

In this thesis, in **part I** we discussed the role and implications of inflammation observed by imaging, in particular MRI and to a lesser extent ultrasound, for the early detection and recognition of Rheumatoid Arthritis (RA). For this purpose we used patients of two population based cohorts: the Clinically Suspect Arthralgia (CSA) cohort and the Leiden Early Arthritis Clinic (EAC) cohort and we also assessed MRI data from healthy symptom-free controls. In **part II**, we focussed on several patient-reported outcomes during the phase preceding and in the early disease phase of RA. We examined the prevalence and course of symptoms and also emphasized to improve our understanding of certain symptoms by investigating its relationship with local MRI-detected joint inflammation.

PART I: Advances in imaging

In **Chapter 2**, we investigated the application of a reference based on healthy volunteers, to define the presence of inflammation at MRI in patients with CSA for the development of clinically detectable inflammatory arthritis and also in patients with undifferentiated arthritis (UA) for the development of RA. In these patient populations, the value of inflammation detected by MRI (i.e. synovitis, tenosynovitis, bone marrow oedema (BMO)) has been demonstrated previously and the presence of any MRI-detected inflammation was associated with an increased risk at RA.[1–3] As MRI is a highly sensitive tool, it harbours the risk of 'false-positive MRI results'. Consequently the question arose whether inflammation may also be present in a healthy control population. As this was only scarcely examined in previous research [4], Mangnus et al examined for this purpose, 193 symptom-free persons from the general population were recruited and indeed, certain types of low grade inflammation at MRI were present, at preferential locations and increasing with age.[5] For example, BMO in the lunate was present in 19% of persons aged 40-59 and also grade 1 synovitis in the wrist was frequently present, 35% of persons aged ≥60 had synovitis at the radiocarpal joint.[5] Tenosynovitis was infrequently observed in the healthy controls. In this chapter, we investigated the implications of these findings by analysing whether taking the prevalence of inflammation of healthy volunteers into account, could improve the predictive accuracy of MRI. We evaluated two different cut-off points and compared these results to the presence of any MRI-detected inflammation (without the use of a cut-off). The cut-offs explored were called '1% corrected definition' and '5% corrected definition'. For example, the '5% corrected definition' entails that when a certain type of inflammation, at a specific location, within an age category (<40, 40-59, ≥60) was present in less than 5% of the age-matched controls it was considered 'positive' for MRI-detected inflammation, but if it was present in 5% or more of healthy controls, it was considered negative. As the use of this cut-off resulted in a reduced amount of false positive results that coincided with an increased specificity, while maintaining a stable sensitivity, and also an increased accuracy of MRI, this convincingly suggests that a cut-off based on healthy volunteers is beneficial in the setting of early and pre-RA. We also investigated a more stringent cut-off of 1%. Then, an MRI was considered positive if it was present in 1% or more of healthy controls. For this cut-off, the specificity increased, but now at a considerable loss in sensitivity. Consequently, the current findings suggest convincingly that inflammation detected in healthy volunteers should be considered

valid. Particularly the cut-off of 5% resulted in an improvement of test characteristics, due to mainly a decrease in false-positive results, while no major effect was observed on the sensitivity and thus the detection of correct positive results.
In the next chapter, in **Chapter 3**, we examined the additive value of imaging in another perspective. Namely, we used it for the determination of the number of involved joints for the classification of RA. Because early classification of RA is important for the enrolment of patients with RA as early as possible in clinical trials, the 2010 ACR/EULAR criteria have been developed.[6] During the development of the criteria, it was suggested that imaging modalities, in addition to swollen and tender joints could be used to determine the number of involved joints[7, 8] How to apply this notion, was however not clearly specified. Therefore, we investigated the value of the addition of inflammation detected by MRI, more specifically synovitis, to determine the number of involved joints for the 2010 ACR/EULAR classification criteria. The addition of imaging to determine the number of involved joints seems reasonable as it has been shown that MRI-detected inflammation is predictive of RA development and also that inflammation in early arthritis patients can be present in a considerable amount of joints that were neither swollen nor tender at clinical examination.[9] We selected patients with a clinical diagnosis of UA or RA and followed them for 1 year for the primary outcome of DMARD initiation. DMARD initiation implies that the rheumatologist is convinced that the patient will have a persistent disease course of their arthritis and was used as a proxy for RA, similar to outcomes used in other studies.[10] We showed that the addition of synovitis at imaging resulted in an increase of the number of involved joints of 48%, which resulted in an increase in points on the item 'involved joints' in 25% and finally an additional 10% increase in patients that now fulfilled the 2010 ACR/EULAR criteria. This addition concerned an increase of both false and correct positive results. Also the accuracy as measured by the AUC did not improve. When using a cut-off for MRI-positivity based on healthy volunteers, the addition of MRI remained unprofitable.[11] This suggests that at present there is no convincing evidence that the addition of imaging to determine the number of involved joints for the 2010 classification criteria is beneficial and that this notion should be handled with care as it lead to an a specific addition of patients that fulfilled the 2010 ACR/EULAR classification criteria for RA.
In **Chapter 4**, we critically evaluated the current MRI imaging protocol for the detection of RA, that includes next to imaging of the hand-joints (MCP2-5 and wrist) also the joints of the feet (MTP1-5). While MRI of the feet may be valuable, it leads to additional scan time and costs. Therefore, we examined the additive value of MRI of the feet in 357 patients with CSA. All patients underwent contrast-enhanced 1.5T MRI at baseline and were followed for progression to the development of clinically apparent inflammatory arthritis (IA). First, we examined the predictive value of inflammation at the feet joints. Then we observed, in line with studies on the joints of the hands,[1] that also for the feet, tenosynovitis was the most predictive feature of MRI-detected inflammation, which was independently from ACPA and CRP with an HR of 3.13 (1.48; 6.64). The next step was to evaluate its complementary value to MRI of the hands. The addition of MRI-feet to MRI-hands did not increase the predictive accuracy; the sensitivity remained 77% (64%-86%), while the specificity also did not improve as it remained rather stable with a change from 66% (60%-71%) to 62% (56%-67%) for the outcome IA-development within

the next year. Sensitivity analyses with RA-development as outcome showed similar results. Additionally a net reclassification index was calculated, which was -3.9% for any MRI-detected inflammation. This also showed no beneficial effect for addition of MRI of the feet. We expect that the lack of an additive effect was most likely caused by the fact that there were very few patients that developed clinical IA, that had inflammation at the feet only, without any MRI-detected inflammation at the hand-joints. When examining the prevalence of inflammation of joints in all included CSA-patients, 11% had inflammation in both the hands and the feet, 29% only in hands, and 3% only in the feet. Therefore we concluded that, tenosynovitis at the forefeet in CSA patients predicted IA- and RA-development. However, a foot-MRI in addition to a hand-MRI did not increase the accuracy. This was presumably caused by the fact that patients seldomly have inflammation at the feet joints only, without any inflammation at the hand joints. As the outcomes were similar by both test characteristics and the net reclassification index and our findings were similar to previously performed findings in patients with UA,[12] this strengthens our observation. Therefore, we concluded that foot-MRI can be omitted to reduce scan time and costs and increase the feasibility of MRI.

In **Chapter 5**, we addressed the issue of the comparability of different frequently used imaging techniques in the early detection of RA, MRI and ultrasound (US). Both are currently being recommended for the early detection of RA, without making a distinction which modality should preferably be used. As for both imaging modalities, tenosynovitis and synovitis have been shown to be of predictive value, it can be expected that both depict the same lesions, this has however never been examined on a joint-level. Thus, we examined whether US and MRI depict the same inflammatory lesions in 70 consecutive patients with early IA or CSA at a joint/tendon-level. MRI is considered as a highly sensitive and valid method to detect local joint inflammation. It enables a three dimensional examination of the joint and its results are reproducible. US is more easily available in many centres due to its lower costs and because it is less time consuming. However, its disadvantages are that its results can be difficult to reproduce due to operator and machine dependency. In this thesis, these imaging techniques were compared by using validated semi-quantitative scoring methods. These scoring systems differ for US and MRI, as they do not score inflammation of synovitis and tenosynovitis, which were studied here, in exactly the same manner for both imaging modalities. Each grade had different requirements for the different modalities. For MRI we used the OMERACT-RAMRIS method for synovitis and tenosynovitis.[13, 14] For US we applied two scoring methods, the method according to Szkudlarek et al,[15, 16] for grey scale (GS) and Power doppler (PD) synovitis and tenosynovitis, and the newly developed EULAR-OMERACT method for GS synovitis.[17] This was the first study that used the recently developed EULAR-OMERACT method for US in comparison to MRI, in patients with early IA and CSA.[17] Direct comparison of both US scoring methods showed that the modified Szkudlarek method scored the highest scores compared to the EULAR OMERACT method. The modified Szkudlarek method combines synovial effusion and hypertrophy.[16] Therefore the modified Szkudlarek method had more false positive results. As the scoring systems differ for US and MRI, we did not expect scores to correspond 1 on 1. It was compared whether increasing scores by MRI paralleled increasing scores by US and also if the presence of any synovitis or tenosynovitis, by

using different cut-offs, detected by MRI was also identified by US on a joint and tendon level. Generally, our data showed indeed that increasing scores of MRI were paralleled by increasing scores at US. After dichotomization of scores, US had a good specificity, but was less sensitive when MRI was used as a reference on the joint and tendon level. Nonetheless, US sometimes also detected inflammation at sites that were negative for MRI-detected inflammation (tenosynovitis or synovitis). Importantly, the different definitions for the different scoring methods hamper direct comparison of the different semi quantitative scores. However, the current findings convincingly suggest that MRI cannot simply be replaced by US while maintaining its sensitivity on joint and tendon level. However, this was a cross sectional analysis and longitudinal research is better suited to point out which modality will be most preferably. Evidently replication in other studies is needed.

Future perspectives for MRI for the early detection of RA

In short **part I** of this thesis illustrated that:

- Caution should be taken to prevent overdiagnosis of patients at risk of RA development, based on a 'positive MRI' for MRI-detected inflammation. Not each inflammatory feature should be considered abnormal as it also can be present in patients that will not progress to clinically detectable inflammatory arthritis or RA. Taking inflammation of healthy volunteers into consideration when deciding on MRI positivity reduces false positive results.
- MRI as an addition to determine joint counts for the 2010 ACR/EULAR classification criteria for RA was not beneficial as it resulted in an increase of a specific patients that classified as RA while they did not require DMARD therapy during follow up.
- MRI-detected tenosynovitis of the foot-joints was independently associated with progression to RA in patients with Clinically Suspect Arthralgia. This finding was similar to findings obtained for the hand-joints. Nonetheless, MRI-detected inflammation of the feet in addition to the hands, was not of additive value and can be omitted to reduce scanning time and prevent additional costs.
- MRI and ultrasound are both recommended to be used in clinical daily practise to detect synovitis and tenosynovitis, as both have shown to be predictive of RA development. When examining its comparability of lesions of tenosynovitis and synovitis, we observed that increasing ultrasound scores were accompanied by increasing MRI scores, however both modalities did not identify the same lesions and cannot be used interchangeably. MRI was more sensitive, but longitudinal research should point out which modality predicts RA best and which modality has the best cost effectiveness.

The results on the determination of a cut off for a positive MRI were performed by a 1.5T MRI. Future research should point out whether these results can be generalized to other field strength machines as well. Also the data from the general population were gathered in the Netherlands and research should be performed to investigate how this corresponds to healthy individuals in other countries.[5] It is unknown whether the inflammatory lesions at MRI in the healthy population differ around the world. For RA it has been shown that globally the affected joints differ across countries and continents,[18] therefore it could also be true that inflammation at MRI for patients

with and without RA can be different around the world. Also the subject which specific lesions predict RA the best in certain patients, should be subject for future research. Then it is also important to keep in mind the risk of overdiagnosis in patients that never will have progressed to imminent RA. We showed that MRI-detected synovitis to determine the number of involved joints for classification of patients with RA was not beneficial. It could be suggested that more specific locations with certain types of inflammation could benefit the 2010-criteria. However, previous research has shown that tenosynovitis represents the feature with the highest predictive value of the different types of inflammation. But also for the addition of MRI-detected tenosynovitis, this yielded no beneficial effects. Evidently, our results require confirming in an independent cohort. We used the outcome, DMARD start, as proxy for RA. This outcome is not ideal and a more suitable outcome like disease persistency should be examined in future research. This outcome requires a longer follow up and was not feasible in our study. We showed that showed that tenosynovitis at the feet also predicts RA development in patients with CSA, but had no limited additive value when an MRI of the hands was also performed. Unfortunately, our research of inflammation at MRI concerned only scans that were performed unilaterally at the most painful sides. This may have resulted in an underestimation of the total burden of inflammation as measured by MRI. However, as symptoms often occur symmetrically and as RA is considered to be a systemic inflammatory disease, we do not expect this to have caused major problems in the analyses performed. Next to this, a frequently debated matter is our imaging protocol. According to RAMRIS BMO is scored on a T2 fatsat instead of a T1 post-contrast fatsat sequence that we performed in this thesis. Importantly, previous studies have shown that this performs similar and that it reduces scanning time. Also, this could not have affected the present results as all patients were scanned according to the same protocol. We compared MRI and US and found that both cannot simply be used interchangeably. For future research, the cut off point for positivity of MRI and US need to be established. As we found that a cut off based on healthy volunteers was beneficial for MRI,[11] this should also be examined for US to establish which inflammatory features are present in the general population. Our results showed that MRI was more sensitive than ultrasound, but future research comparing ultrasound and MRI should be performed to compare which of the two modalities truly predicts RA the best when analysing longitudinal data.

Summary of research agenda:

- Development of a generally accepted definition of positivity for MRI that takes into regard inflammation that also occurs in a healthy symptom free population at preferential locations, increasing with age.
- Investigation if findings in healthy volunteers by 1.5T MRI can be generalized to other field strength MRI, like 3T.
- Further examination into for which patients MRI can be beneficial for increasing the probability of RA and in which patients MRI has only little or no additional value.
- Research to establish more precisely which locations and inflammatory features at MRI predict RA development the best, in which specific patient groups with CSA or UA.
- Further research on optimization of the MRI protocol to enable faster scanning time while maintaining the quality of images.

- For clinical daily practise, other methods than OMERACT RAMRIS should be examined as it is not suited for diagnostic purposes. Then, the most specific locations and types of inflammation can be taken into account. This was beyond the scope of our research.
- Longitudinal MRI research could be performed in early RA or patients at risk for RA, to investigate the order of development of different inflammatory factors more thoroughly and thereby increasing the understanding of the development of RA.
- Replication of our findings of the healthy volunteers in other countries and in a larger amount of persons to arrive at higher numbers per age category.
- Research into the causes why certain locations that are more prevalent at having inflammation at MRI, this could be for example mechanical or biological.
- Longitudinal study to compare which modality, US or MRI, predicts imminent (chronic) RA best.
- US examination of a healthy control group to examine the prevalence of inflammatory features at US in the general population.

PART II: Impact on daily life

The second part of this thesis focussed on measuring the impact of RA by other outcome measures than the traditional ones, which are important from a patients' perspective.[19] The traditional outcomes like damage have become less important due to a decreased prevalence of structural damage consequently to improved treatment strategies in RA.[20–24]

Chapter 6 discusses patient reported outcomes (PROs) including physical functioning and work disability in 982 RA patients, recently diagnosed and treated according to nowadays standard treatment regimen. Our aim was to compare the two main different disease subsets of RA, namely, patients with anticitrullinated protein antibodies (ACPA-positive) and those without (ACPA-negative). ACPA-positive RA is generally considered as the more severe subset as it is associated with more severe joint damage and higher mortality rates.[25–27] However, due to nowadays improved treatment strategies consisting of early methotrexate and disease activity score (DAS)-steered treatment strategies, joint damage has become infrequent.[20, 21, 24] Nonetheless, current research still has the tendency to focus more on ACPA-positive, rather than ACPA-negative RA. As joint damage has become infrequent, other outcomes have become increasingly relevant. For this reason, we emphasized to investigate if this focus on ACPA-positive RA can also be justified when other outcomes are considered. A study determined which parameters are important for patients' themselves.[19] Pain, fatigue and independence were considered the most significant parameters from a patients' perspective, to measure the perceived disease impact. Independence is closely related to physical functioning and also a patients' ability to work and perform daily activities. In this study we measured outcomes of pain, fatigue and general wellbeing, but also questions of productivity at work and at home. Our data showed that baseline PROs were slightly more severe for ACPA-negative compared to ACPA-positive patients, contrary to current general expectations. However, the observed difference was rather small and we hypothesized that it might have been caused by the setup of the 2010-criteria. Namely,

ACPA-negative patients need >10 joints affected to fulfil the 2010-criteria for RA and therefore may represent a more severe subset.[28] Indeed, when selecting RA patients by the 1987 instead of the 2010-criteria, ACPA-negative and ACPA-positive patients did not differ. Assessment of longitudinal data over 4 years of follow up, showed that ACPA-negative and ACPA-positive patients both had an improvement in PROs over time, which was similar between both disease subsets. The largest improvement in PROs occurred during the first year after diagnosis. We only observed a slight difference for fatigue, namely, ACPA-negative patients were somewhat more fatigued. It was 0.5 on a scale from 0-10. We also assessed other outcomes in a subset of patients as from 2010 onwards patients filled in a questionnaire on work ability. Baseline results showed also for these outcomes similar results for ACPA-positive and ACPA-negative RA patients. Longitudinal research revealed that the different disease subsets showed a comparable disease course over 4 years after diagnosis. However, also here we observed some slight differences to the detriment of ACPA-negative RA patients (2010-criteria). However, after applying corrections for baseline differences between ACPA-negative and ACPA-positive RA (e.g. swollen joint counts), in multivariable analyses these small differences were no longer present. Analyses of data of previous time periods (1993-1999) showed that ACPA-positive RA did represent a more severe disease subset compared to ACPA-negative RA, when measured by PROs and work disability. In conclusion, we no longer observed a more severe disease course for ACPA-positive, compared to ACPA-negative RA patients when treated according to current treatment regimen, consisting of early treatment initiation with a DMARD (preferably methotrexate) and DAS-steered treatment adjustments when the mentioned PROs, including restrictions at work and at home were considered. Thus, current research should focus equally on improving both ACPA-positive and ACPA-negative RA as both pose an equally severe burden of disease.

Another frequently observed phenomenon in RA is morning stiffness (MS). This symptom encompasses the sensation of stiffness of the joints, which occurs mostly in the early morning or after prolonged periods of rest. Although the symptom is prevalent, its pathophysiology is still poorly understood. In **Chapter 7**, the relationship between MS and local MRI-detected inflammation was investigated in 286 patients with RA (2010-criteria) and UA (suspect for RA but not fulfilling the 2010-criteria) from the EAC cohort. MS has been part of classification and remission criteria, which illustrates it is considered a key symptom. The symptom has been linked to the circadian rhythm and the central regulation of cytokines via the hypothalamic-pituitary-adrenal (HPA)-axis and the autonomic nervous system.[29, 30] Moreover, it has been demonstrated that the administration of low-dose prednisone during the night could decrease the severity of MS.[31] However, as it is a local symptom which is essentially experienced the most pronounced at the joints of the hands, it can be hypothesized that local inflammation is also closely related to MS. Despite its relationship with circulating inflammatory factors, its relationship with local inflammatory factors is surprisingly scarcely investigated. Therefore, we conducted this study with the aim to investigate whether the presence of MS related to local inflammation measured sensitively by MRI, in patients with RA or UA. We examined synovitis and tenosynovitis, which were scored according to the validated OMERACT RAMRIS scoring method. MRI has been shown to be more sensitive than clinical examination.[9] Despite this sensitive method, we only observed

small associations with MS. The largest association was obtained for the simultaneous presence of synovitis and tenosynovitis, while the solitary presence of synovitis was not related to MS. The observed effect was surprisingly small, which implies that other unknown local factors may play an important role for the symptomatology of MS.

In **Chapter 8**, a recurrent question in daily clinical practice was discussed. Is there a role for perceived daily life stress in on the occurrence of RA? Although an observational study was conducted, we emphasized to investigate the role and time relationships of daily stress on RA emergence in patients with CSA. We could not investigate causality as this was an observational study, but the analyses were conducted to assess the presence of an association to investigate the relationship between perceived psychological stress and inflammation as measured by different measures, namely locally by MRI of the joints, systemically by c-reactive protein (CRP) and also by IA development during follow-up. Part of the patients with CSA will develop IA during follow-up and most of them then fulfil the 2010-criteria. Part of the patients will go on to never develop clinically detectable IA and symptoms often gradually disappear. We investigated the course of their perceived stress at baseline and during follow-up. Perceived psychological stress at baseline was measured by two questionnaires. Patients filled in the Cohen's perceived stress scale consisting of 10 questions (PSS-10),[32] and they filled in the Short Form 36 (SF-36) from which we extrapolated the scores of the Mental Health Index (MHI-5).[33, 34] At baseline and symptom-onset, we observed no relationship between perceived stress and local MRI-detected joint inflammation or systemic inflammation measured by CRP. Also for the outcome arthritis-development, we did not find an association. We observed that psychological stress at symptom onset was approximately similar to that of the general population. However, at arthritis-onset, and the moment of diagnosis of RA, their stress increased significantly. The year thereafter, it decreased to baseline values. In patients that never developed clinical arthritis, the prevalence of stress remained rather stable. An association between baseline stress and inflammation 1 year later, also was not related. Thus, we concluded that the data showed no clear association between inflammation or IA development and daily psychological stress. The course of stress and inflammation were in parallel rather than that one preceded the other. We cannot rule out that major psychological stress could have an impact on the emergence of RA, as we did not measure for example life events, but solely focussed on daily perceived stress. Also, small effects might have been missed in this subset of 241 CSA patients. However, the data convincingly showed that although patients with CSA do experience significant pain and physical impairments as measured by the HAQ,[35, 36] there was no clear relationship of perceived daily stress on the development of RA. This is a unique investigation, as the course of stress has never been investigated in this manner, in a cohort of CSA patients that are at risk of RA.

Chapter 9 precedes with the investigations on the effects of psychological distress in a different cohort comprising of early RA patients. Here, we aimed to replicate recent findings Michelsen et al. that disease activity as measured by the disease activity score (DAS) at follow-up, was related to baseline depression/anxiety.[37] Their findings implied that baseline increased depression or anxiety could lead to a lower degree of improvement in DAS.[37] In our study, baseline depression/anxiety was as measured by the mental component summary and the mental health index, both part of the SF-36.

We were able to confirm the findings of Michelsen et al. as also in our cohort of patients with early RA, baseline depression and anxiety, were related to a lower chance on DAS-remission (defined as DAS ≤2.4). The highest associations were observed between depression/anxiety and the more subjective components of the DAS, like the patient global assessment, implying that further efforts to improve psychological wellbeing of RA patients could also have a benefit on the disease activity and thereby preventing (unnecessary) treatment adjustments due to a higher DAS.

Future perspectives:
In short, the studies in **Part II** of this thesis showed that:
- ACPA-positive and ACPA-negative RA pose an equally severe burden of disease when treated according to current up-to-date treatment strategies in current rheumatology practise, on both subsets when compared by patient-reported outcomes like pain and fatigue, but also work ability. Further efforts to improve the disease should focus on both disease subsets.
- Local inflammation as measured by MRI contributes to the symptom MS, with the largest effect for the simultaneous presence of tenosynovitis and synovitis. Its effect was however small and other local factors may play a more important role in its symptomatology.
- When increased anxiety and depression are suspected at the moment of diagnosis of RA, it was related to a lower chance on DAS-remission 1 year later. Thus, it could have detrimental effects on the disease course later on, with (unnecessary) treatment intensifications and additional costs as a consequence.
- Perceived psychological stress in daily life daily was not associated with inflammation (as measured by MRI of the joints, CRP or IA or RA development later on). The time relationship of psychological stress did not precede, but paralleled RA development. The lack of an association and its time relationship advocate against psychological stress being a eliciting factor, but more as being a consequence of diagnosis.

In current rheumatology practise there is a tendency to focus more on ACPA-positive RA. The thought that ACPA-negative RA is less seriously disabling than ACPA-positive RA plays a role in this reasoning. Although we acknowledge that ACPA-negative RA might represent a more heterogeneous disease, we did show convincingly here that ACPA-negative RA also poses a substantial burden of disease on society and patients' themselves, it should be our aim to also further improve the perspectives of ACPA-negative RA patients, similar to efforts for improving disease outcomes in ACPA-positive RA. Importantly, the present findings need to be seen in light of currently standard treatment strategies comprising of early methotrexate and DAS-steered treatment adjustments. It could be true that ACPA-positive RA required a more intensive treatment strategy, but to compare treatment steps among both groups was not the aim of the present study. Further, we found a relationship between MS and local MRI-detected inflammation and observed that the simultaneous presence of synovitis and tenosynovitis had largest association with MS. Despite the high prevalence of MS, it was surprising to find that the biologic mechanisms underlying the local occurrence of MS are still poorly understood because previous research focused more on systemic rather than local inflammation. In our study the effect sizes were smaller than expected based

on the local character of the symptom. They might have been somewhat underestimated as it was our protocol to only scan one side by MRI. However, the most severely affected side was usually scanned and therefore we believe this may have had only minor effects. Future research could focus more on local factors in relation to the occurrence of MS. The symptom could also be examined in patients in the pre-RA phase, to assess if then the association with local MRI-detected inflammation is already present and to estimate its effect size. With regard to the psychological stress response in the symptomatic pre-RA phase of Clinically Suspect Arthralgia, we suggested that psychological stress is rather a consequence of symptoms than a causal factor of inflammation and subsequent RA development. This was studied in a unique large cohort of patients at risk for RA. Unfortunately, we did not collect data on major life events and cannot rule out that these may play a role in the emergence of RA. Also coping strategies were not assessed. Therefore, these factors should be examined in future research in the pre-RA phase in a larger cohort to assess if life events or coping strategies do play a role in the emergence of RA. Finally we were able to replicate recently published findings that showed the relationship between baseline depression/anxiety with a lower chance on DAS-remission later on in an independent cohort. We also found that this was mostly related to the more subjective components of the DAS. Therefore we agree that efforts to improve psychological wellbeing could also prevent additional medical costs. The effects of psychological support to improve the DAS, should however be examined in a separate study.

Summary of research agenda:

- Replication of our findings of the comparison between ACPA-negative and ACPA-positive RA by severity of disease impact as measured by patient reported outcomes in an independent cohort.
- Assess replicability of findings of association between morning stiffness and MRI-detected tenosynovitis and synovitis in patients with RA and in patients with Clinically Suspect Arthralgia.
- Trials to investigate whether psychological support in distressed or anxious patients with RA could benefit the disease activity as measured by the DAS.
- Examinations to the role of psychological stress in the pre-RA phase in an independent cohort, with more attention to major life events.

FINAL CONCLUSIONS

A large part of this thesis focussed on the additional value of MRI in the early detection of RA. In contrast to showing its additional value, we also found that MRI can also be too sensitive and appoint patients with MRI-detected inflammation that never will go on to develop imminent, chronic RA. In clinical practise the exact role of imaging for the early detection of RA still needs to be established further. Also the causes of inflammation at MRI in patients with CSA or early IA are not fully understood yet. It needs to be specified in which individual patients, MRI has the most beneficial effects and in combination with which clinical characteristics. In addition to this, also its cost effectiveness needs to be determined. The second part of this thesis focussed more on

subjective components of the disease, which is highly valuable for patients' themselves. But next to this, a patients' perspective is increasingly being taken into account for decisions on treatment options. Although current treatment strategies have resulted in improved disease outcomes and chronic damage can be prevented in a large amount of patients, patients still experience problems in daily life and at work. As we observed that despite improved therapies, many important outcomes remain present, like fatigue and pain, these should also be incorporated in future treatment aims as they pose a burden on patients' wellbeing as well as on society.

References

[1] Nieuwenhuis WP, van Steenbergen HW, Mangnus L, Newsum EC, Bloem JL, Huizinga TWJ, et al. Evaluation of the diagnostic accuracy of hand and foot MRI for early Rheumatoid Arthritis. Rheumatology (Oxford). 2017;56:1367–1377.

[2] van Steenbergen HW, van Nies JA, Huizinga TW, Bloem JL, Reijnierse M, van der Helm-van Mil AH. Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI. Ann Rheum Dis. 2015;74:1225–32.

[3] Tamai M, Kawakami A, Uetani M, Fukushima A, Arima K, Fujikawa K, et al. Magnetic resonance imaging (MRI) detection of synovitis and bone lesions of the wrists and finger joints in early-stage rheumatoid arthritis: comparison of the accuracy of plain MRI-based findings and gadolinium-diethylenetriamine pentaacetic acid-enhanced MRI-based findings. Mod Rheumatol. 2012;22:654–658.

[4] Mangnus L, Schoones JW, van der Helm-van Mil AH. What is the prevalence of MRI-detected inflammation and erosions in small joints in the general population? A collation and analysis of published data. RMD Open. 2015;1:e000005.

[5] Mangnus L, van Steenbergen HW, Reijnierse M, van der Helm-van Mil AH. Magnetic Resonance Imaging-Detected Features of Inflammation and Erosions in Symptom-Free Persons From the General Population. Arthritis Rheumatol. 2016;87:31–7.

[6] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham r C O, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580–8.

[7] Funovits J, Aletaha D, Bykerk V, Combe B, Dougados M, Emery P, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. Ann Rheum Dis. 2010;69:1589–95.

[8] Neogi T, Aletaha D, Silman AJ, Naden RL, Felson DT, Aggarwal R, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. Arthritis Rheum. 2010;62:2582–91.

[9] Krabben A, Stomp W, Huizinga TW, van der Heijde D, Bloem JL, Reijnierse M, et al. Concordance between inflammation at physical examination and on MRI in patients with early arthritis. Ann Rheum Dis. 2015;74:506–12.

[10] Radner H, Neogi T, Smolen JS, Aletaha D. Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review. Ann Rheum Dis. 2014;73:114–23.

[11] Boer AC, Burgers LE, Mangnus L, ten Brinck RM, Nieuwenhuis WP, van Steenbergen HW, et al. Using a reference when defining an abnormal MRI reduces false-positive MRI results-a longitudinal study in two cohorts at risk for rheumatoid arthritis. Rheumatology. 2017;56:1700–1706.

[12] Dakkak YJ, Boeters DM, Boer AC, Reijnierse M, van der Helm-van Mil AHM. What is the additional value of MRI of the foot to the hand in undifferentiated arthritis to predict rheumatoid arthritis development? Arthritis Res Ther. 2019;21:56.

[13] Ostergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis. 2005;64:i3–7.

[14] Haavardsholm EA, Ostergaard M, Ejbjerg BJ, Kvan NP, Kvien TK. Introduction of a novel magnetic resonance imaging

tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study. Ann Rheum Dis. 2007;66:1216–20.

[15] Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Østergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis & Rheumatism. 2003;48:955–962.

[16] Scheel AK, Hermann KGA, Kahler E, Pasewaldt D, Fritz J, Hamm B, et al. A novel ultrasonographic synovitis scoring system suitable for analyzing finger joint inflammation in rheumatoid arthritis. Arthritis & Rheumatism. 2005;52:733–743.

[17] D'Agostino M, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn G, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. RMD open. 2017 Jul;11:e000428.

[18] Bergstra SA, Chopra A, Saluja M, Vega-Morales D, Govind N, Huizinga TWJ, et al. Evaluation of the joint distribution at disease presentation of patients with rheumatoid arthritis: a large study across continents. RMD Open. 2017;3(2).

[19] van Tuyl LH, Sadlonova M, Hewlett S, Davis B, Flurey C, Goel N, et al. The patient perspective on absence of disease activity in rheumatoid arthritis: a survey to identify key domains of patient-perceived remission. Ann Rheum Dis. 2016;.

[20] Sokka T, Kautiainen H, Hakkinen A, Hannonen P. Radiographic progression is getting milder in patients with early rheumatoid arthritis. Results of 3 cohorts over 5 years. J Rheumatol. 2004;31:1073–1082.

[21] Pincus T, Sokka T, Kautiainen H. Patients seen for standard rheumatoid arthritis care have significantly better articular, radiographic, laboratory, and functional status in 2000 than in 1985. Arthritis Rheum. 2005;52:1009–19.

[22] Heimans L, Wevers-deBoer KV, Ronday HK, Collee G, de Sonnaville PB, Grillet BA, et al. Can we prevent rapid radiological progression in patients with early rheumatoid arthritis? Clin Rheumatol. 2015;34:163–6.

[23] Ajeganova S, van Steenbergen HW, van Nies JA, Burgers LE, Huizinga TW, van der Helm-van Mil AH. Disease-modifying antirheumatic drug-free sustained remission in rheumatoid arthritis: an increasingly achievable outcome with subsidence of disease symptoms. Ann Rheum Dis. 2016;75:867–73.

[24] Minichiello E, Semerano L, Boissier MC. Time trends in the incidence, prevalence, and severity of rheumatoid arthritis: A systematic literature review. Joint Bone Spine. 2016;83:625–630.

[25] Farragher TM, Goodson NJ, Naseem H, Silman AJ, Thomson W, Symmons D, et al. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. Arthritis Rheum. 2008;58:359–69.

[26] Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, et al. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. Joint Bone Spine. 2013;80:29–33.

[27] Akdemir G, Verheul MK, Heimans L, Wevers-de Boer KV, Goekoop-Ruiterman YP, van Oosterhout M, et al. Predictive factors of radiological progression after 2 years of remission-steered treatment in early arthritis patients: a post hoc analysis of the IMPROVED study. RMD Open. 2016;2:e000172.

[28] Boeters DM, Mangnus L, Ajeganova S, Lindqvist E, Svensson B, Toes REM, et al. The prevalence of ACPA is lower in rheumatoid arthritis patients with an older age of onset but the composition of the ACPA response appears identical. Arthritis Res Ther. 2017;19:115.

[29] Straub RH, Cutolo M. Circadian rhythms in rheumatoid arthritis: Implications

for pathophysiology and therapeutic management. Arthritis & Rheumatism. 2007;56:399–408.

[30] Cutolo M. Glucocorticoids and chronotherapy in rheumatoid arthritis. RMD Open. 2016;2.

[31] Arvidson NG, Gudbjörnsson B, Larsson A, Hällgren R. The timing of glucocorticoid administration in rheumatoid arthritis. Annals of the Rheumatic Diseases. 1997;56:27–31.

[32] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24:385–96.

[33] Berwick DM, Murphy JM, Goldman PA, Ware J J E, Barsky AJ, Weinstein MC. Performance of a five-item mental health screening test. Med Care. 1991;29:169–76.

[34] Friedman B, Heisel M, Delavan R. Validity of the SF-36 five-item Mental Health Index for major depression in functionally impaired, community-dwelling elderly patients. J Am Geriatr Soc. 2005;53:1978–85.

[35] Ten Brinck RM, van Steenbergen HW, Mangnus L, Burgers LE, Reijnierse M, Huizinga TW, et al. Functional limitations in the phase of clinically suspect arthralgia are as serious as in early clinical arthritis; a longitudinal study. RMD Open. 2017;3:e000419.

[36] van Steenbergen HW, Mangnus L, Reijnierse M, Huizinga TW, van der Helm-van Mil AH. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. Ann Rheum Dis. 2016;75:1824–1830.

[37] Michelsen B, Kristianslund EK, Sexton J, Hammer HB, Fagerli KM, Lie E, et al. Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. Ann Rheum Dis. 2017;76:1906–1910.