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

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Clinically Suspect Arthralgia and Early Rheumatoid Arthritis

Advances in imaging and impact on daily life

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General introduction and outline

1 Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic disabling disease, due to recurrent joint inflammation. It is an auto-immune disease that is characterised by erosive polyarthritis with inflammation of mainly the small joints of hands and feet, but it can also affect large joints. The prevalence of RA is estimated as 0.5-1% in the population of adults in western countries.[1] In the Netherlands, approximately 12.400 patients were newly diagnosed with RA in 2017.[2] The disease can occur at any age but predominantly affects middle-aged persons, is more often present in woman than in men.[3] The aetiology of RA is still largely unknown and even though the disease often presents with joint inflammation, it is likely that it consists of a heterogeneous disease with several different risk factors. In general, joint inflammation in RA is caused by the activation of the immune system,[3] and although the disease primarily manifests the joints, it should be considered a syndrome that includes extra-articular phenomena like vasculitis, pulmonary involvement and other systemic complications.[4] Even though the exact causes of RA have not been elucidated yet, several risk factors have been identified. These may involve a combination of genetic, environmental and stochastic factors. Increased risks have been found for smoking, familiar predisposition and female gender.[5] Classically, RA lead to deformity of joints, consequently to destruction as a results of erosions in cartilage and bone. This had a major impact on daily life and physical functioning.[4] During the last decades treatment strategies have improved which resulted in a decreased prevalence of structural damage. However, irrespective of these improved therapeutic options, RA continuous to affect individuals tremendously. Chronic inflammation of the joints can still cause joint destruction with severe pain, loss of function, stiffness and fatigue as result.[6, 7] This significantly affects their contribution to society, through work loss and reduced daily functioning and it continuous to majorly impact a patients' quality of life.[8, 9]

Developmental stages of RA

The developmental course of RA is incompletely understood, it is however recognized that it consists of several phases.[10] The phase preceding that of clinically detectable (chronic) arthritis is already symptomatic, this stage is called Clinically Suspect Arthralgia (CSA). Patients with CSA can be recognized by rheumatologists via a combination of clinical characteristics. These 'CSA patients' are at increased risk to develop RA.[11] Their clinical characteristics were also described by a EULAR taskforce.[12] CSA patients have, based on their clinical characteristics, approximately 18-20% chance on RA development within the next 2 years,[11] which can increase in case of presence of certain laboratory of imaging findings. Also other pre-RA phases can be acknowledged. For example, it was established that systemic auto-immunity can be recognized by the presence of specific auto-antibodies (e.g. ACPA, RF), even years before symptoms have developed. Also genetic and environmental risk factors pose a certain risk on individuals.[13] However, these other 'pre-RA phases' can be challenging to identify and are not studied in this thesis. After the development of arthritis, a substantial part of these CSA patients can be diagnosed with RA. However, in certain patients with early inflammatory arthritis (IA), a specific diagnosis cannot yet be

established, at the onset of arthritis. These patients are called undifferentiated arthritis (UA), which is defined as IA not fulfilling the criteria for RA and also not caused by any other specific cause of arthritis. Part of the patients with UA develop RA during follow-up. A flowchart of these developmental stages of RA are illustrated by Figure 1.1.

Autoantibodies in RA

Factors that have been associated with RA development were different within certain subpopulations of RA patients. Therefore it has been recognized that RA is a heterogeneous disease that can be divided into (at least) two different subsets. Roughly, these groups are considered to consist of patients with auto-antibodies against anti-citrullinated protein antibodies (ACPA) or rheumatoid factor (RF) and patients without these auto-antibodies.[14] RF is detected in up to 60-80% of patients with RA, but can also occur in patients with other auto-immune diseases like systemic lupus erythematosus, mixed connective tissue disease, primary Sjögren and non-autoimmune diseases like chronic infections and even in patients with old age.[15] RF has long been used for the detection of RA. It is prevalent in 60-80% of RA-patients and has a sensitivity of approximately 54% and a specificity of 91%.[16, 17] More recently, ACPA has been recognized. These antibodies are prevalent in approximately 50-90% of RA populations.[16, 18–20] ACPA are considered equally sensitive as RF, but more specific for RA. Its specificity ranges up to 98%.[16] Next to the most commonly used antibodies, namely ACPA and RF, also other less prevalent antibodies can be recognized. Unfortunately, not all RA patients can be detected via laboratory testing of auto-antibodies, because in up to half of the patients with established RA they cannot be detected. Today, the major subsets of RA are divided as ACPA-positive and ACPA-negative RA. They are considered as two different disease entities with differences in etiopathology, as both subsets have differences in genetic and environmental risk factors.[5] ACPA-positive RA has always been considered as the more severe subset of RA, as the presence of ACPA is associated with more severe joint destruction and a higher mortality rate.[21–23]

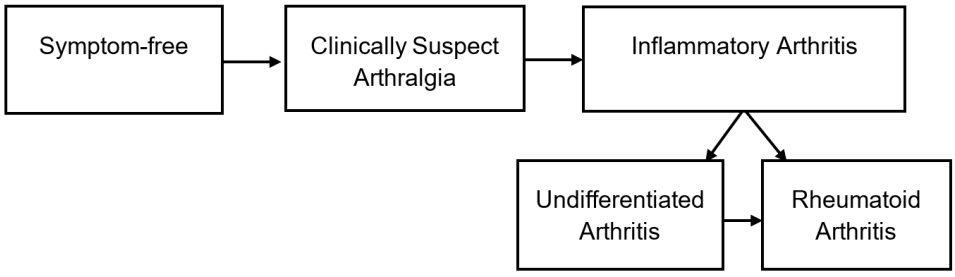

Figure 1.1: Clinically identifiable developmental stages of RA that were studied in this thesis.
A symptom-free control group; patients with arthralgia and without clinical arthritis with the clinically suspect arthralgia (CSA); patients were followed on the development of clinical inflammatory arthritis; part of these patients developed undifferentiated or rheumatoid arthritis.

Classification criteria

In RA, classification criteria have been developed with the aim to provide a more homogeneous subset of patients, particularly for research purposes. In this thesis, the 1987- and the 2010-classification criteria have been applied.[24, 25] The 2010 ACR/EULAR classification criteria have been developed with the aim to identify patients earlier in the disease course.[24] Thereby, it has been established that the 2010-criteria have indeed caused earlier classification of RA-patients, which enabled these patients to be enrolled in trials shorter after disease onset.[26] The criteria are more sensitive and slightly less specific than the 1987-criteria.[27] Both different sets of classification criteria and their differences are illustrated by Table 1.1. While in order to prevent damage and in light of research that has shown that earlier treatment leads to better disease outcomes, the 2010-criteria have been developed, these criteria also have certain drawbacks. Main differences between the 1987- and 2010-criteria are amongst others a stronger weight of autoantibodies in the 2010-criteria. Thus, a potential disadvantage of the 2010-criteria is that patients without auto-antibodies are recognized relatively later on in the disease course compared to patients with auto-antibodies. Moreover, autoantibody-negative patients require the presence of >10 involved joints to fulfil the criteria for RA.[10, 28] Currently, it is still challenging to appoint patients with joint complaints more precisely that will progress to imminent RA.

Earlier recognition and improved treatment strategies

Diagnostic delay is a major problem in many (chronic) diseases. In RA it has been shown that earlier treatment leads to better outcomes, and therefore general practitioners (GPs) are encouraged to refer patients with a (suspicion on) clinical synovitis within 6 weeks.[29] For the early detection and recognition, also laboratory findings of auto-antibodies have played an important role, as these aid earlier disease recognition. However, in a vast amount of patients these auto antibodies cannot be detected. Thus, when these patients present at disease onset, with an incompletely developed disease phenotype, it can be challenging to identify patients that will develop disease chronicity correctly. After diagnosis, modern advances in the medical treatment of RA, with earlier recognition and prompt initiation of treatment with disease-modifying antirheumatic drugs (DMARDs), preferably methotrexate, drastically improved disease outcomes in western countries. In combination with to treat-to-target approaches (disease activity (DAS)-steered treatment), this resulted in better disease outcomes.[21] Due to these improved treatment strategies, clinically relevant joint destruction has become infrequent.[30–34] In addition, patients' symptoms have been alleviated drastically in current rheumatology practice.[35–37] Therefore it is generally accepted that the disease has changed from a chronic disabling disease with severe malformations to a less severe disease. Nonetheless, patients do still experience symptoms like stiffness, pain and fatigue which lead to reduced performance at home and at work (Figure 1.2). Thus, although patients suffer less from severe chronic destruction and the disease has become less invalidating at first sight, the disease still severely affects the daily life of patients with RA.

Role of imaging in the early phases of rheumatoid arthritis

In some patients with early inflammatory arthritis (IA), it is not possible to establish a specific diagnosis during the first several weeks to months following symptom onset. However, it is desirable to set a diagnosis as early as possible and determine which patients will develop imminent (chronic) RA and which patients will have a self-limiting disease course without the need of a prompt therapeutic intervention. Imaging methods are considered as a more sensitive manner to detect joint inflammation than regular clinical examination.[38] MRI can depict synovitis, tenosynovitis, bone marrow oedema (BME or osteitis). Imaging techniques have shown to be useful to detect patients at risk to develop RA, both in patients with CSA and for patients with UA and therefore ultrasound (US) and MRI are both recommended in the diagnostic process of RA.[39] For these target populations validated scoring methods have been developed to provide valid and reproducible results. Even though RA is characterized by an influx of inflammatory cells and is frequently is accompanied by joint damage, MRI findings in early RA are found predictive on a group level, but yet have little predictive value in individual patients. Also in the pre-RA phase of CSA, imaging has been shown to be of value.[11] The risk to develop RA within the next two years increased in case of a positive MRI to about 30%. To improve this risk, it is currently being investigated how to optimize the MRI scanning protocol and also in which patients, MRI has the most added value.

The practicality of MRI

The MRI scans performed in this thesis, were scored according to semi-quantitative validated scoring methods and by two independent trained readers. Scoring was performed in line with the Outcome Measures in Rheumatology (OMERACT) RA MRI scoring (RAMRIS)-method.[40] RAMRIS was not developed to score MTP-joints, however others have previously adapted the RAMRIS to score MTP-joints as well.[41] Tenosynovitis was scored according to the method described by Havaardsholm et al, which was also applied at the flexor and extensor tendons at 2-5 MCP-joints. For practical reasons, like time efficiency and consequential additional costs, we scored BME on a post-contrast T1 fatsat sequence. We are aware of the fact according to RAMRIS BME is scored on a T2fatsat instead of a post-contrast, T1fatsat sequence.[42–45] But as several previous studies have shown that scoring BME on post-contrast T1, yields similar results for the detection of BME in several settings among which early arthritis and RA we deviated here from the RAMRIS BME protocol to provide more MRI scanning time.[43–46] As MRI can be costly and time-consuming for regular daily practice, we aimed to optimize the MRI scanning protocol even further. The RAMRIS-method is applied to the small joints of the hand and wrist, and also the feet are being scored. This requires repositioning of the hands and feet and thus considerable additional time. Therefore, we seek to define the additional value of MRI of the MTP-joints in addition to the hand-joints (MCP and wrist) in chapter 4. Next to MRI, ultrasound (US) is often performed in daily rheumatological practise in order to detect subclinical inflammation. Both imaging techniques are recommended in the diagnostic process of RA and no distinguishes are made between the two. By both imaging modalities, tenosynovitis and synovitis have been shown predictive for RA development.[11, 47–53]

Table 1.1: Classification criteria for Rheumatoid Arthritis

ACR 1987 criteria*	ACR/EULAR 2010 criteria**
1. Morning stiffness Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement	*1. Joint involvement* 1 large joint: 0 2-10 large joints: 1 1-3 small joints (with or without large joints): 2 4-10 small joints (with or without large joints): 3 >10 joints (at least one small joint): 5
2. Arthritis of 3 or more joint areas At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints	*2. Serology (at least one test result needed for classification)* Negative RF and negative ACPA: 0 Low-positive RF or low-positive ACPA: 2 High positive RF or high positive APA: 3
3. Arthritis of hand joints At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint	*3. Acute-phase reactants (at least one test result is needed for classification)* Normal CRP and normal ESR: 0 Abnormal CRP or normal ESR: 1
4. Symmetric arthritis Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)	*4. Duration of symptoms* <6 weeks: 0 ≥6 weeks: 1
5. Rheumatoid nodules Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician	
6. Serum rheumatoid factor Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5 of normal control subjects	
7. Radiographic changes Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)	

*Rheumatoid arthritis if he/she has satisfied at least 4 of the 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. ** Target population: patients who 1) have at least one joint with definite clinical synovitis (swelling); 2) with the synovitis not better explained by another disease. Definite score at least 6 of 10.

However, its usefulness in daily practise in individual cases has yet to be established. MRI is more expensive and time-consuming than US, nonetheless MRI also has its advantages like its high sensitivity to detect inflammation and its easily reproducibility. Another benefit of MRI is that it can depict bone marrow oedema (BMO). Advantageous for US is its easy availability in many hospitals due to lower costs, however, US scanning is machine and operator dependent and US cannot visualize BMO. Which modality of the two is superior needs to be determined in a longitudinal cohort. However, both are recommended in the early detection of RA due to their pros and cons. We analysed the comparability of US and MRI in a cross-sectional manner. By this first step that, we aimed to establish whether both modalities can be used interchangeably, or if this assumption is invalid.

Imaging in healthy symptom free individuals

The significance of findings at MRI have been put in a different perspective, when it was established that inflammatory characteristics found by MRI can also be found in the general symptom-free population.[54, 55] They largest study was performed by Mangnus et al. and they showed that these inflammatory findings increase with age. This finding had major implications, as it implies that inflammation found at MRI is not limited to inflammatory diseases only but can also occur in the healthy population, in persons that do not experience any joint symptoms, thus without arthralgia of any kind and certainly no arthritis. Based on the observation, a cut-off for positivity of an MRI is proposed in this thesis in chapter 2, which has the aim to prevent the detection of false positive MRI results.

Application of imaging methods for classification of RA

Imaging methods have shown to detect inflammation more sensitively than regular clinical examination. Thus, joints can be affected that are neither swollen nor tender at examination.[38] In light of these findings and due to the predictive value of imaging-detected inflammation, it was recommended to use imaging tools to ascertain the number of involved joints for the classification criteria for RA according to the 2010-criteria.[24] This notion suggests that next to the clinical finding of at least one swollen joint at physical examination, imaging tools are recommended to aid the detection of inflamed joints.[56] Although this addition seems logical, it was mainly based on expert opinion. Namely, its consequences have not been explored previously. Only a few (not peer-reviewed) abstracts have aimed to answer this question. We therefore examined the effects of the addition of imaging methods to determine the number of affected joints for the classification of RA patients by the 2010 ACR/EULAR classification criteria in chapter 3.

Patient reported outcomes

Due to the improved treatment strategies of the last decades there has been a shift in the importance of certain outcome measures in RA. While traditionally the severity of RA was measured by progression of joint damage and mortality. Joint damage has become increasingly infrequent,[30–34] and also increased mortality is no longer evidently present.[35–37] These traditional outcomes have become increasingly infrequent and

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a shift towards other outcomes, important for RA-patients have been investigated. In a study that aimed to determine these patient reported outcomes (PROs), it was found that according to patients, important outcomes are pain, fatigue and independence.[6] Independence is a key aspect of daily life, which can be reflected by for example physical functioning, but also activities in daily life and performance at work.[57] These outcomes are not solely important from a patients' perspective, but also for society, as decreased functioning in daily life activities can pose a substantial burden and lead to considerable costs. Next to the shift from the traditional outcomes due to an improved disease course, PROs also have become increasingly important due to shared decision making, which also places the patients central when deciding a treatment strategy.

Morning stiffness

RA patients often experience symptoms of the joints and besides pain and swelling also stiffness is often experienced. Their stiffness is characterized by its prominence during morning hours. This phenomenon is therefore called morning stiffness. It is considered as characteristic of RA and can be prevalent in 40-50% of patients.[58] In addition, the symptom has been a part of classification and remission criteria for years and it has been associated with functional disability. Morning stiffness poses a substantial burden on patients' perceived disease burden. Nonetheless, its underlying processes are still poorly understood.[58] It is presumed that both systemic and local inflammation underlie

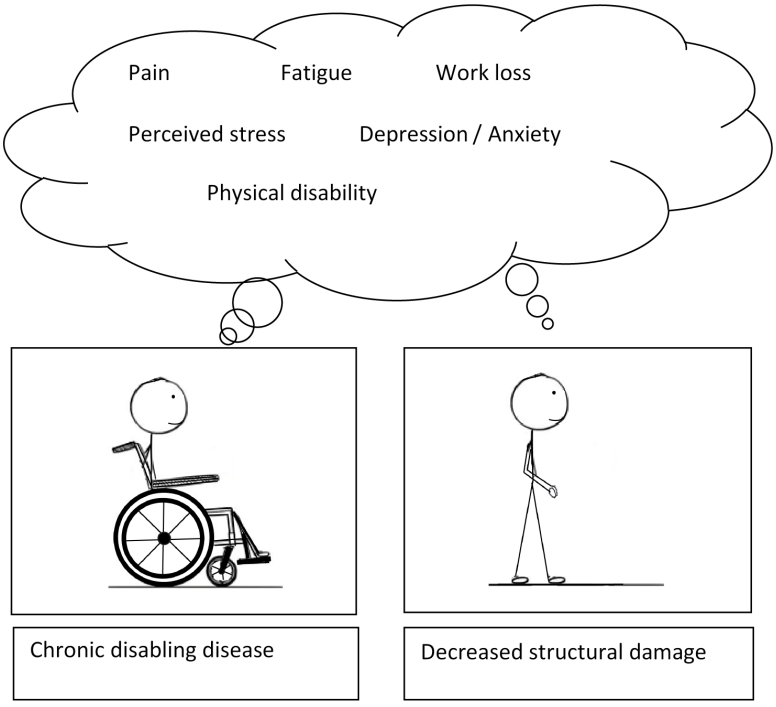

Figure 1.2: Phenotype of rheumatoid arthritis patients over the past decades.

morning stiffness.[59] Most studies focussed on systemic factors, which is intuitive as the circadian rhythm of symptoms parallels late night and early morning rises of pro-inflammatory markers. The time-relationship and observation that morning stiffness could be relieved by the application of low-dose prednisone during the night makes it likely that systemic inflammatory markers contribute to morning stiffness.[60] Morning stiffness is generally experienced as most pronounced at the hand-joints. In addition to joint stiffness being maximal in the early morning, grip strength is also lowest at this time-point.[61] Therefore it is presumable that local inflammation, besides systemic inflammation, is also important for the occurrence of morning stiffness. However, in proportion to the number of studies focussing on systemic markers, the association with local inflammation is less well studied. While morning stiffness is generally most pronounced at the hand-joints, it is presumable that local inflammation is important for the occurrence of MS. The fact that morning stiffness is a hallmark symptom of RA of which we do not fully understand the pathophysiology prompted us to perform a large cross-sectional MRI-study in which we aimed to determine if tenosynovitis, also in relation to synovitis, at small joints associated with MS in patients with UA and RA, in chapter 7.

Depression in relation to the emergence of RA

In addition to the symptoms of fatigue, pain and stiffness reported by patients, another frequently encountered adversity in chronic diseases are mental health disorders. Particularly anxiety and depression pose a burden on patients with RA. It has been reported that RA patients have an increased prevalence of psychological stress.[62] Generally, in chronic inflammatory diseases, psychological stress is considered to negatively affect the disease course.[63] The effects of psychological stress have been thoroughly investigated within patients with established RA. It is known that patients can have a deranged stress response, particularly in patients with a high disease activity.[64–66] The mechanism by which psychological stress affects inflammation is expected to work via activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, which thereafter is associated with the release of neurotransmitters (i.e. norepinephrine), hormones (i.e. cortisol) and activation of immune cells.[63, 67, 68] Thus, during increased psychological stress, the normal down regulation of the inflammatory response is hindered, possibly causing pro-inflammatory effects. However alternatively, stress can also be a consequence of symptoms and physical limitations without having exacerbating effects on inflammation in the phase of CSA. Patients themselves often experience stress and question whether this could have had an effect on the occurrence or flaring of their disease. However, until now, the stress response was unresearched in pre-RA phases and therefore it is currently unknown if daily stress can trigger or, more generally, precedes RA development.

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Cohorts studied in this thesis

Clinically Suspect Arthralgia cohort

In 2015 the CSA cohort was started at the Leiden outpatient clinic. The CSA is a population-based inception cohort with patients with complaints of arthralgia of <1 year, of whom the rheumatologist think that it is suspect to progress to RA. Patients were followed for 2 years for the development of arthritis. Follow-up ended earlier when clinical arthritis had developed.[11] Patients were never treated with DMARDs in the phase of CSA. After arthritis-development, patients were mostly included in the early arthritis clinic cohort.

Leiden Early Arthritis Clinic cohort

In 1993, the Leiden Early Arthritis Clinic (EAC) cohort was started at the outpatient clinic. The EAC is a population-based inception cohort with patients that present for the first time at the outpatients clinic with recent onset IA, with a symptom duration of <2 years. They required clinical synovitis of at least 1 joint to be eligible for inclusion.[69]

Symptom-free volunteers

Symptom-free volunteers were examined by MRI and served as a reference for MRI-detected inflammation (n=193). They were recruited via advertisements in local newspapers and websites and had no history of inflammatory rheumatic diseases, no joint symptoms during the last month and no evidence of arthritis at physical examination, as described in reference.[55] The different sets of patients and the visits they had are schematically depicted in Figure 1.3. As illustrated, all patients underwent a baseline 1.5T gadolinium-enhanced MRI of unilateral MCP(2-5)-, wrist- and MTP(1-5)-joints.

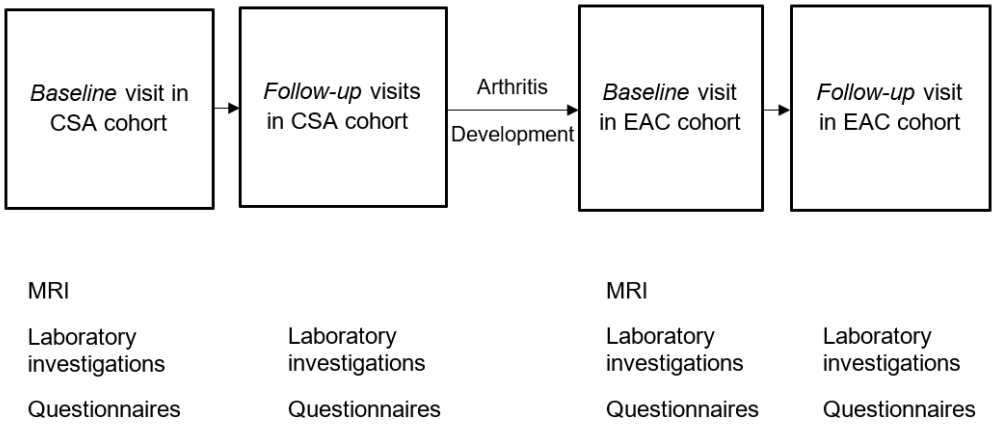

Figure 1.3: Overview of study protocol of cohorts for studies performed in this thesis.

Outline of this thesis

In **part I**, we investigated the value of imaging techniques in the early phases of RA.
In **Chapter 2** we start by examining the application of a cut-off for MRI-detected inflammation based on a reference population of healthy symptom-free controls. We propose a cut-off for 'MRI-positivity' for the early detection of RA. For this purpose, we used the previously published prevalence of low grade inflammation at MRI of healthy controls to determine the predictive accuracy of inflammation at MRI in patients with clinically suspect arthralgia for progression to inflammatory arthritis and also for patients with undifferentiated arthritis for progression to RA. Although a cut-off for positivity is common for other tests in medicine, this phenomenon is novel for MRI in the early detection of RA. In **Chapter 3** we examined the impact of joints detected by MRI for the determination of the number of involved joints for the 2010 ACR/EULAR classification criteria. Inflammation of joints at MRI were used to determine joint counts in addition to clinically affected swollen joints, as this was suggested in the original manuscript of the development of the 2010 ACR/EULAR classification criteria. Patients were followed for DMARD-initiation during follow-up as proxy for RA-development. In **Chapter 4** we examined the complementary value of MRI of the feet (MTP1-5) in addition to MRI of the hands (MCP2-5 and wrist) in patients with clinically suspect arthralgia in order to critically assess the time-efficiency of the current MRI scanning and scoring protocol. Thereafter we focussed on the comparability of two different imaging techniques in **Chapter 5**. Ultrasound is much more easy available than MRI in daily rheumatology practice, while MRI is considered more sensitive and provides more reproducible results. We compared cross-sectional data of semi-quantitative scores produced by both techniques in patients with early inflammatory arthritis and clinically suspect arthralgia.

In **part II**, we focussed on patient-reported outcomes in patients at risk of or with RA. Due to improved treatment strategies, these patient reported determinants of the disease have become more important, because due to improved treatment strategies the traditional outcomes (i.e. damage) have become infrequent.
In **Chapter 6** we explore the differences between ACPA-positive and ACPA-negative RA in terms of patient-reported outcomes including physical functioning and restrictions at work. Another commonly experienced symptom by patients with RA is morning stiffness. While this symptom is experienced by the majority of RA patients, its aetiology is still unknown. It is presumed that it reflects inflammation of the joints. Therefore, we examined in **Chapter 7** the relationship between morning stiffness and MRI-detected subclinical tenosynovitis in patients with RA. In these analyses we also took the presence of concomitant synovitis into account. Further, we investigated in **Chapter 8** the relationship between psychological stress and inflammation in the preclinical phase of RA. In general practise it is a commonly asked question whether daily stress could have caused a patients' RA. Therefore, we examined the relationship between daily psychological stress at inclusion in the cohort by two questionnaires with inflammation measured at MRI, by serology (CRP) and longitudinally on the development of clinically apparent inflammatory arthritis, in patients with CSA. After

arthritis onset, psychological stress and MRI data was examined after inclusion in the EAC cohort. In **Chapter 9** we further examined the impact of psychological stress on the disease activity of patients with early RA.

Finally, in **part III**, **Chapter 10** provides a summary and discussion of the results that are described in this thesis.

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I

Advances in imaging

2

Using a reference when defining an abnormal MRI reduces false-positive MRI-results - a longitudinal study in two cohorts at risk for rheumatoid arthritis

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Abstract

Objective

The use of hand and foot MRI in the diagnostic process of rheumatoid arthritis (RA) has been advocated. Recent studies showed that MRI is helpful in predicting progression from clinically suspect arthralgia (CSA) to clinical arthritis, and from undifferentiated arthritis (UA) to RA. Symptom-free persons can also show inflammation on MRI. This study aimed to evaluate if MRI findings in symptom-free volunteers are relevant when defining a positive MRI.

Methods

225 CSA patients and 201 UA patients underwent MRI of MCP, wrist and MTP joints at baseline and were followed for 1 year on progression to arthritis and RA, respectively, as reported previously. MRI was considered positive if ≥1 joint showed inflammation (called uncorrected definition), or if ≥1 joint had inflammation that was present in <5% of persons of the same age category at the same location (called 5% corrected definition). Test characteristics were compared for both definitions.

Results

By using MRI data of symptom-free volunteers as reference, specificity of MRI-detected inflammation increased from 22% to 56% in CSA patients, and from 10% to 36% in UA patients. The sensitivity was not affected; it was 88% and 85% in CSA patients and 93% and 93% in UA patients. The accuracy also increased, from 32% to 60% in CSA patients and 22% to 44% in UA patients.

Conclusion

The use of a reference population resulted in a substantial reduction of false-positive results, without influencing the sensitivity. Although common for other tests in medicine, this phenomenon is novel for MRI in the early detection of RA.

Introduction

Magnetic resonance imaging (MRI) is sensitive in detecting local inflammation in hand and foot joints. Although compelling evidence suggests that early treatment of RA is associated with a better outcome, an early disease presentation is frequently accompanied by an incompletely developed clinical phenotype. In this light, the EULAR imaging taskforce has recommended that hand and foot MRI can be used to facilitate the diagnostic process of RA.[1] Several studies have shown that MRI-detected subclinical inflammation is associated with progression from clinically suspect arthralgia (CSA) to clinical arthritis and from undifferentiated arthritis (UA) to RA, independent of other predictors.[1–6]

Acknowledging the value of MRI, the subsequent question is how to define a positive MRI result. Several groups have evaluated MRI-detected joint inflammation in the healthy population.[7–12] The largest study up to now included almost 200 symptom-free persons of different age categories.[13] In line with findings of earlier smaller studies, this study observed that low-graded MRI-detected inflammation occurs in the general population, especially in older persons, and at preferential locations (e.g. MTP1, MCP2, 3 and wrist for synovitis; MTP1, lunate and scaphoid for bone marrow oedema (BMO); extensor carpi ulnaris tendon and flexor digitorum tendon of MCP3 for tenosynovitis).[8] It has been questioned whether MRI-detected inflammation of a reference population is relevant to consider when defining an MRI positive for local inflammation, or whether this is irrelevant (for instance noise induced by sensitive scan protocols or inadequate readers).[14] If findings observed in symptom-free persons are irrelevant, then taking these into consideration when defining a positive MRI, this can result in a decreased or unchanged accuracy to predict arthritis or RA development. In contrast, if symptom-free persons truly have low-grade inflammation at certain locations at a certain age, then considering this information will result in reduced numbers of false-positives and an increased predictability.

In medicine, the definition of a positive test result often incorporates findings of a reference population. For instance, the cut-offs for several auto-antibody tests were determined relative to findings done in healthy controls.[15] The ESR is another example. A normal population of different ages was explored 50 years ago and resulted in a definition of an abnormal ESR that is age-dependent.[16] The question arose of whether a similar process is required to determine a positive MRI. Therefore, this study evaluated the validity of taking inflammation detected in a symptom-free population into consideration when defining a positive MRI. MRI data of two previously published cohorts of CSA and UA patients were studied to this end.[2, 6]

Methods

Participants

CSA cohort

The CSA cohort was a population-based inception cohort that started at the rheumatology outpatient clinic in Leiden, The Netherlands, with the aim of studying

the symptomatic phase of RA that precedes clinical arthritis. Inclusion required the presence of arthralgia of small joints for <1 year that, because of the character of the symptoms, a rheumatologist suspected would progress to RA; a detailed description is provided elsewhere.[2] Patients included between April 2012 and March 2015 with available baseline MRI data were studied (n = 225). Follow-up ended when clinical arthritis had developed, or else after 2 years. Outcome here was arthritis development, identified at joint examination by experienced rheumatologists, within 1-year follow-up.

Early arthritis cohort

This longitudinal inception cohort includes patients with clinically confirmed arthritis and symptom duration <2 years that presented to the Leiden rheumatology outpatient clinic. The cohort was initiated in 1993 and baseline MRI was added to the study protocol in August 2010. Patients that presented with UA (n = 201) between August 2010 and October 2014 were studied on progression to RA (1987 criteria) during 1-year follow-up, as described in detail in [17].

Symptom-free volunteers

Symptom-free volunteers that served as a reference (n = 193) were recruited via advertisements in local newspapers and websites and had no history of inflammatory rheumatic diseases, no joint symptoms during the last month and no evidence of arthritis at physical examination, as described in.[13] The age ranged from 19 to 89 years; volunteers were divided into three age groups (18–40 years, n = 51; 40–59 years, n = 90; ≥60 years, n = 52). From these data, percentages were calculated for the prevalence of synovitis, BMO and tenosynovitis for different severities, joints and age categories as described in [12].

The different sets of participants are schematically depicted in supplementary Figure 2.2. All studies were approved by the local Medical Ethical Committee (Leiden University Medical Centre). All participants signed for informed consent.

MRI and scoring

Patients and volunteers were scanned on the same scanner (an MSK Extreme 1.5 T extremity MR system (GE Healthcare, Wisconsin, USA). MRI scans of the second to fifth MCP and wrist joints and first to fifth MTP joints were made of the most affected side, or the dominant side in the case of equally severe symptoms and in the symptom free volunteers. Patients were asked not to use any NSAIDs 24 hours before MRI. Sequences acquired were coronal pre-contrast T1-weighted fast spin-echo and coronal and axial post-contrast T1-weighted fast spin-echo with frequency selective fat suppression of MCP and wrist, and post-contrast coronal and axial sequences of MTP. More details are provided elsewhere.[2, 13, 17]

Synovitis and BMO were scored as described previously and in the supplementary methods, available at Rheumatology Online.[2, 13, 17] Total inflammation scores consisted of the sum of synovitis, BMO and tenosynovitis scores. Trapezium and base metacarpal-1 (CMC-1) was excluded. Scans of symptom free volunteers were evaluated

with the same methodology as scans of patients. All inter- and intraclass coefficients were > 0.93 (see supplementary methods, also available at Rheumatology Online).

Different definitions for a positive MRI were compared. First, an MRI was considered positive when each of two readers indicated inflammation in at least one joint (a score ≥1 for synovitis, BMO or tenosynovitis), referred to as the uncorrected definition. Second, an MRI was positive if each of two readers indicated inflammation in at least one joint (synovitis, BMO or tenosynovitis) that was present in <5% of the healthy persons in the same age-category at the same location,[13] referred to as the 5% corrected definition. In addition to the evaluation of a reference population, we also evaluated the cut-off used. Therefore, a more stringent definition was also explored with a cut-off of <1%, meaning that MRI was considered positive when two readers indicated inflammation in at least one joint that was present in <1% of the reference population, referred to as the 1% corrected definition. For example, a 65 year old patient with grade 1 synovitis in MCP-4 was indicated positive for the uncorrected definition, positive for the 5% corrected definition as it was seen in 4% of controls in this age category on this location, and negative for the 1% corrected definition. Likewise, a 65 year old patient with grade 1 tenosynovitis of the flexor of MCP-3 was positive for the uncorrected definition and for negative the 5% and 1% corrected definitions as it was seen in 12% of controls.[13]

Statistics

Test characteristics and predictive accuracies with corresponding 95% CIs were calculated. SPSS Statistics v23 was used (IBM, Armonk, NY, USA).

Results

Patients with CSA and UA had a mean age of 44 and 54 years, 77% and 61% were female, and they had a median MRI-inflammation score of 2.5 and 7.0, respectively. Further characteristics are shown in supplementary Table 2.3.

Comparing definitions of MRI positivity for inflammation

MRI had a high sensitivity for both the uncorrected and the 5% corrected definition, which was 88 and 85% in CSA patients and 93 and 93% in UA patients, respectively. Using the 5% corrected definition, the specificity improved from 22 to 56% in CSA patients and from 10% to 36% in UA patients. The accuracy increased from 32 to 60% in CSA patients and from 22% to 44% in UA patients, as illustrated in Fig. 2.1. Predictive values also increased when using the corrected definition instead of the uncorrected definition (Table 2.2).

Sub-analyses for different MRI features and age categories

To explore the different features incorporated in the cutoff, analyses were split based on inflammation feature, location and age category, as shown in Table 2.2 for CSA and UA patients. Overall, results for the sub-analyses were similar in both cohorts. For the 5% corrected definition compared with the uncorrected definition this resulted in increased specificities and stable or lower sensitivities. The accuracy and positive predictive value

Table 2.1: Test characteristics of MRI to detect development of arthritis and RA for uncorrected and corrected definitions

	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
CSA patients						
Main analysis for total MRI inflammation						
Uncorrected	88 (73, 95)	22 (17, 28)	16 (12, 22)	91 (80, 97)	32 (26, 38)	0.55
Corrected (<5%)	85 (69, 93)	56 (49, 63)	25 (18, 34)	96 (90, 98)	60 (54, 67)	0.71
Corrected (<1%)	67 (50, 80)	72 (65, 78)	29 (20, 40)	93 (87, 96)	71 (65, 77)	0.69
Sub-analyses per MRI feature						
BMO						
Uncorrected	48 (33, 65)	48 (41, 55)	14 (9, 21)	84 (76, 90)	48 (42, 55)	0.48
Corrected (<5%)	30 (17, 47)	82 (76, 87)	22 (13, 36)	87 (82, 91)	74 (68, 79)	0.56
Synovitis						
Uncorrected	73 (56, 85)	44 (37, 51)	18 (13, 26)	90 (83, 95)	48 (42, 55)	0.58
Corrected (<5%)	52 (35, 67)	78 (71, 83)	28 (19, 41)	90 (85, 94)	74 (68, 79)	0.65
Tenosynovitis						
Uncorrected	70 (53, 83)	70 (64, 76)	29 (20, 39)	93 (88, 96)	70 (64, 76)	0.70
Corrected (<5%)	70 (53, 83)	76 (70, 82)	33 (23, 45)	94 (89, 96)	75 (69, 80)	0.73
Sub-analyses per location						
MTP						
Uncorrected	42 (27, 59)	68 (61, 74)	19 (11, 29)	87 (81, 92)	64 (58, 70)	0.55
Corrected (<5%)	33 (20, 50)	89 (83, 92)	33 (20, 50)	89 (83, 92)	80 (75, 85)	0.61
MCP						
Uncorrected	70 (53, 83)	58 (51, 65)	22 (15, 31)	92 (85, 95)	60 (53, 66)	0.64
Corrected (<5%)	64 (47, 78)	72 (66, 78)	28 (19, 40)	92 (87, 95)	71 (65, 77)	0.68
Wrist						
Uncorrected	67 (50, 80)	45 (38, 52)	17 (12, 25)	89 (81, 94)	48 (42, 55)	0.56
Corrected (<5%)	42 (27, 59)	76 (70, 82)	23 (14, 35)	88 (83, 93)	71 (65, 77)	0.59
Sub-analyses per age group						
18–40 years						
Uncorrected	77 (50, 92)	39 (29, 51)	19 (11, 31)	90 (75, 97)	45 (35, 56)	0.58
Corrected (<5%)	77 (50, 92)	59 (48, 70)	26 (15, 41)	93 (82, 98)	62 (51, 72)	0.68
40–60 years						
Uncorrected	93 (70, 99)	13 (8, 21)	14 (9, 22)	93 (69, 99)	24 (17, 32)	0.53
Corrected (<5%)	87 (62, 96)	54 (44, 63)	22 (13, 34)	96 (88, 99)	58 (49, 67)	0.70
60+ years						
Uncorrected	100 (57, 100)	5 (1, 22)	19 (9, 38)	100 (21, 100)	22 (11, 41)	0.52
Corrected (<5%)	100 (57, 100)	50 (31, 69)	31 (14, 56)	100 (74, 100)	59 (41, 75)	0.75

Different definitions for a positive MRI were compared for CSA patients and for UA patients. First, an MRI was considered positive when each of two readers indicated inflammation (in ≥ 1 joint a score ≥ 1 for synovitis, BMO or tenosynovitis), called the uncorrected definition.
Second, an MRI was positive if inflammation was present in ≥1 joint and in <5% of the healthy persons in the same age category at the same location, the 5% corrected definition.
Additionally, an MRI was considered positive if inflammation was present in ≥1 joint and in <1% of the healthy persons in the same age category at the same location, the 1% corrected definition.
Data were also split on inflammation feature, location and age group.

Table 2.1: *continued*

	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
UA patients						
Main analysis for total MRI inflammation						
Uncorrected	93 (78, 98)	10 (7, 16)	15 (10, 21)	90 (70, 97)	22 (17, 29)	0.52
Corrected (<5%)	93 (78, 98)	36 (29, 43)	20 (14, 27)	97 (89, 99)	44 (38, 51)	0.65
Corrected (<1%)	79 (62, 90)	51 (44, 59)	21 (15, 30)	94 (87, 97)	55 (48, 62)	0.65
Sub-analyses per MRI feature						
BMO						
Uncorrected	76 (58, 88)	32 (25, 39)	16 (11, 23)	89 (78, 94)	38 (32, 45)	0.54
Corrected (<5%)	41 (26, 59)	56 (48, 63)	14 (8, 22)	85 (77, 90)	54 (47, 60)	0.49
Synovitis						
Uncorrected	93 (78, 98)	22 (17, 29)	17 (12, 23)	95 (83, 99)	32 (26, 39)	0.58
Corrected (<5%)	62 (44, 77)	58 (51, 65)	20 (13, 29)	90 (83, 94)	59 (52, 65)	0.60
Tenosynovitis						
Uncorrected	83 (65, 92)	45 (38, 53)	20 (14, 28)	94 (87, 97)	51 (44, 58)	0.64
Corrected (<5%)	83 (65, 92)	58 (51, 65)	25 (17, 35)	95 (89, 98)	62 (55, 68)	0.70
Sub-analyses per location						
MTP						
Uncorrected	52 (34, 69)	48 (41, 56)	14 (9, 22)	86 (77, 91)	49 (42, 56)	0.50
Corrected (<5%)	24 (12, 42)	77 (70, 82)	15 (7, 28)	86 (79, 90)	69 (62, 75)	0.50
MCP						
Uncorrected	86 (69, 95)	43 (36, 50)	20 (14, 28)	95 (88, 98)	49 (42, 56)	0.65
Corrected (<5%)	79 (62, 90)	60 (52, 67)	25 (17, 35)	94 (89, 97)	63 (56, 69)	0.70
Wrist						
Uncorrected	83 (65, 92)	33 (27, 40)	17 (12, 24)	92 (82, 97)	40 (34, 47)	0.60
Corrected (<5%)	69 (51, 83)	62 (55, 69)	24 (16, 34)	92 (86, 96)	63 (56, 70)	0.66
Sub-analyses per age group						
18–40 years						
Uncorrected	33 (6, 79)	19 (9, 35)	4 (1, 18)	75 (41, 93)	20 (10, 36)	0.26
Corrected (<5%)	33 (6, 79)	50 (34, 66)	6 (1, 27)	89 (67, 97)	49 (33, 64)	0.42
40–60 years						
Uncorrected	100 (68, 100)	14 (8, 23)	10 (5, 19)	100 (74, 100)	22 (14, 31)	0.57
Corrected (<5%)	100 (68, 100)	44 (33, 55)	15 (8, 27)	100 (90, 100)	49 (39, 59)	0.72
60+ years						
Uncorrected	100 (82, 100)	2 (0, 9)	23 (15, 34)	100 (21, 100)	24 (16, 35)	0.51
Corrected (<5%)	100 (82, 100)	18 (11, 30)	27 (18, 39)	100 (74, 100)	37 (27, 48)	0.59

Age groups in both groups ranged from 18 to 40 years (CSA, n = 84; UA, n = 35), 40 to 60 years (CSA, n = 114; UA, n = 88) and 60+ years (CSA, n = 27; UA, n = 78);33 of 225 CSA patients developed clinical arthritis; 29 of 201 UA patients developed RA (according to 1987-criteria). Percentages with 95% confidence intervals are shown, except for the AUC. AUC: area under the receiver operating characteristic curve; BMO: bone marrow oedema; LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value.

also increased in all sub-analyses and the negative predictive value remained stable. The least increase in specificity was seen for tenosynovitis, compared with synovitis and BMO. For data of total MRI inflammation based on age group, specificities were very low when using the uncorrected definition in patients aged above 60 years and increased considerably after application of the 5% corrected definition (e.g. from 5 to 50%, Table 2.2).

Discussion

Early recognition of patients with imminent RA is essential. Early treatment of RA has been associated with better outcomes. It has been suggested that this also applies for the earlier phases of UA and CSA.[1] An early diagnosis is difficult if the phenotype is incompletely developed, and it has been suggested that MRI-detected inflammation is useful in the diagnostic process, though insufficiently accurate when used alone.[1, 18] MRI is a relatively novel technique and although it is not regularly used in daily clinical practice, it is sometimes used in certain patients or in some places. This study evaluated different definitions for a positive MRI, and in particular the effect of the use of a reference population of symptom free individuals. The data showed that a definition that incorporates a reference population drastically improved the discriminative ability of MRI: it yielded an improved specificity without major influences on the sensitivity. Thus, the number of false-positive test results decreased.

In the field of laboratory tests (for instance autoantibodies, ESR), data for a reference population are generally used to define a positive test result. For instance a recent auto-antibody test was developed with the 5% definition and earlier an ESR test with ~ 1% definition.[15, 16] Also in imaging this is a frequently used principle. For example an MRI made to detect a hernia nuclei pulposi can only be interpreted in light of the clinical presentation, as healthy subjects also show MRI abnormalities without clinical consequences.[19] The current study is the first demonstrating the value of knowledge of a symptom free reference population for MRI of hand and foot joints. In clinical practice the risk of false-positive results is presumably most relevant in the setting of UA, as a positive MRI result may influence the decision to initiate disease modifying anti-rheumatic medication.

In general, when a cut-off changes, an increased specificity is paralleled by a decreased sensitivity. However,in the main analyses in this study, we did not change a cut-off point, but incorporated data of a reference population in the definition of a positive MRI. Then the number of false-positives reduced without affecting the sensitivity. Next, in addition to incorporating a reference population, a more stringent cut-off was evaluated. Then, as expected when changing cut-offs, the specificity and predictability increased even more, but now at the cost of a decreased sensitivity, indicating that patients that later on developed arthritis were missed.

The main analysis was split on the different inflammation features, revealing similar results, with the least increase in specificity for tenosynovitis. This is explained by the fact that tenosynovitis was least prevalent in controls.[13] Specificity of MRI-detected

inflammation in the age group >60 years was very low in both cohorts and increased considerably with the use of a reference population. This is in line with previous findings that MRI detected inflammation increases with age;[13, 17] in other words, in a general older population some MRI-detected inflammation occurs in certain joints. Without correction, this was considered abnormal, whereas after correction for the reference population, the false-positive rate decreased and specificity increased. Of note, some subanalyses within age groups were done on small patient groups per age category.

We are aware of the fact that the OMERACT RA MRI scoring (RAMRIS) system was not derived for diagnostics and that according to RAMRIS BMO is scored on a T2fatsat instead of a post-contrast, T1fatsat sequence.[20] However, all patients and participants were scanned and scored according to the same methodology. Hence, these choices do not affect the comparisons made. Nonetheless, if MRI were to be regularly used in the diagnostic process, evaluation scoring methods other than RAMRIS might be useful, and the number of symptomfree persons serving as reference should be increased to arrive at higher numbers per age category.

In conclusion, the current study performed in two population-based longitudinal cohorts demonstrated the value of a reference population in the definition of an abnormal MRI. If MRI were to be more commonly used for the early detection of (imminent) RA, a larger reference population may be required. The present finding of a 2 fold increase in specificity with a stable sensitivity underlines the relevance of further studies on MRI inflammation in persons from the general population to arrive at a data driven definition of an abnormal hand or foot MRI.

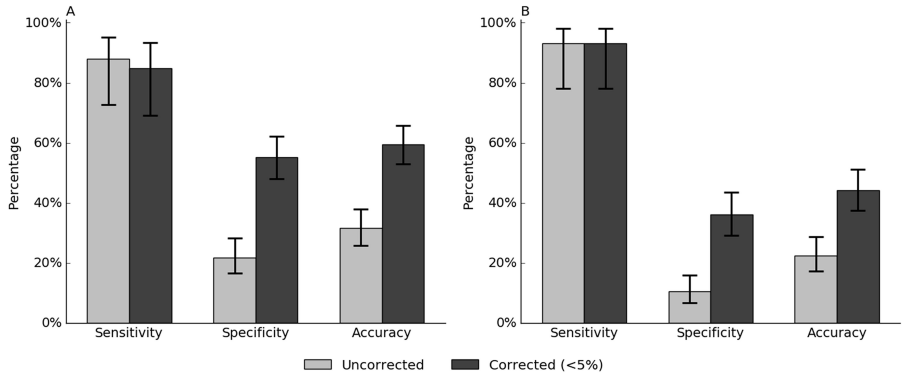

Figure 2.1: Test characteristics of MRI-detected inflammation for the development of arthritis in CSA patients (A) and RA in UA patients (B) during 1-year follow-up. Two definitions for a positive MRI were compared. First, an MRI was considered positive when each of two readers indicated inflammation (in ≥1 joint a score ≥1 for synovitis, BMO or tenosynovitis), called the uncorrected definition. Second, an MRI was positive if teach of two readers indicated inflammation in ≥1 joint that was present in <5% of the healthy persons in the same age category at the same location, called the 5% corrected definition. Error bars indicate corresponding 95% CIs.

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Supplementary data

Supplementary methods are available at *Rheumatology Online*.

Supplementary figure

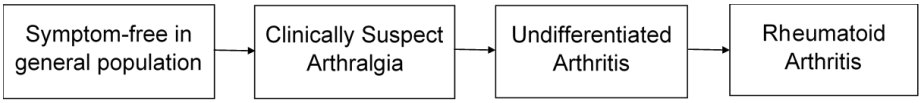

Figure 2.2: Clinically identifiable stages of RA-development and flowchart of patients studied. First, a symptom-free control group of 193 participants; second, 225 patients with arthralgia and without clinical arthritis from clinically suspect arthralgia cohort (MRI at baseline) were followed on the development of clinical arthritis within 1 year; third, 201 patients with UA from early arthritis cohort (MRI at baseline) were followed on progression of RA within 1 year.

Supplementary table

Table 2.3: Baseline characteristics of patients with undifferentiated arthritis and clinically suspect arthralgia.

	CSA (n=225)	UA (n=201)
Age, mean (SD)	44 (13)	54 (16)
Female, n (%)	174 (77)	123 (61)
68-Tender joint count, median (IQR)	6 (3-10)	3 (1-6)
66-Swollen joint count, median (IQR)	0 (0-0)	2 (1-4)
CRP (mg/L), median (IQR)	3 (3-5)	4 (3-10)
RF positive (≥3.5 IU/mL), n (%)	46 (20)	19 (10)
ACPA positive (≥7 U/mL), n (%)	28 (12)	8 (4)
Total MRI-inflammation score, median (IQR)	3 (1-6)	7 (3-15)

UA: Undifferentiated Arthritis not fulfilling 2010 RA criteria as described previously[6]; CSA: clinically suspect arthralgia.

3

The use of MRI-detected synovitis to determine the number of involved joints for the 2010 ACR/EULAR classification criteria for Rheumatoid Arthritis – is it of additional benefit?

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Abstract

Objective

To assess the value of MRI-detected synovitis to determine the number of involved joints on the performance of the 2010-ACR/EULAR classification criteria for rheumatoid arthritis (RA).

Methods

277 patients with a clinical suspicion of RA consecutively included in the Leiden Early Arthritis Clinic (EAC)-cohort underwent 1.5T MRI of MCP-, wrist- and MTP-joints. Test characteristics of the 2010-criteria were calculated when the number of involved joints was determined with and without including MRI-detected synovitis. Two outcomes were studied: disease modifying anti-rheumatic drug (DMARD)-initiation and 1987-criteria fulfilment during the first year.

Results

At baseline, 143 patients were classified as RA. When MRI-detected synovitis was considered, 14 patients additionally fulfilled the 2010-criteria. Of these, 64% (9/14) started DMARDs. When MRI-detected synovitis was also used to determine the number of involved joints the sensitivity changed from 62% to 67%, the specificity from 90% to 84% and the AUC from 0.76 to 0.75. The net reclassification index was -2.4%. When fulfilling the 1987-criteria was used as outcome, results were similar.

Conclusion

We found no scientific support that the use of MRI-detected synovitis is of additional benefit for the performance of the 2010 classification criteria.

Introduction

Because early classification is important in rheumatoid arthritis (RA), the 2010 ACR/EULAR classification criteria have been developed.[1] These criteria are more sensitive and slightly less specific than the 1987-criteria.[2] Differences between these criteria are amongst others a stronger weight of autoantibodies in the 2010-criteria. In addition, the 2010-criteria suggest the use of imaging tools to ascertain synovitis.[1] This addition seems reasonable as studies on Magnetic Resonance Imaging (MRI) have shown that synovitis in early arthritis patients can be present in a substantial amount of joints that were neither swollen nor tender at clinical examination.[3] Moreover, autoantibody-negative patients require the presence of > 10 involved joints to fulfil the criteria for RA.[4] The addition of advanced imaging modalities could substantially increase the number of involved joints and may therefore improve the accuracy of the criteria in the autoantibody-negative group in particular. Although the development of the 2010-criteria was primarily data-driven, the suggestion to also use advanced imaging modalities to detect synovitis was included in the criteria based on expert opinion.[5] Thus far there are no studies published in peer-reviewed journals that evaluated the effects of including information of synovitis detected by MRI on the performance of the 2010-criteria. Therefore, this study determined the effects of the inclusion of MRI-detected synovitis in the evaluation of the number of involved joints on the performance of the 2010-criteria.

Methods

Patients

We studied 277 patients with clinically evident inflammatory arthritis of ≥1 joint that were consecutively included in the Leiden Early Arthritis Clinic (EAC) cohort between 2013 and 2015, who when the results of regular laboratory investigations were known, had the clinical working diagnosis of RA or undifferentiated arthritis (UA) (Figure 3.1). The EAC is a population-based inception cohort of patients with recent-onset arthritis with a symptom duration <2 years that started in 1993 and is described in detail elsewhere.[6] At baseline 66-swollen and 68-tender joint counts (66-SJC and 68-TJC), laboratory investigations (including c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL) and anti-citrullinated peptide antibody (ACPA, anti-CCP2, Eurodiagnostica, the Netherlands, positive if ≥25 U/mL; from 2009 EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL)) and an MRI were performed. Follow-up visits with standard clinical assessments were performed 3 months after the first presentation and yearly thereafter. The study was approved by the Ethics Committee. Written informed consent from each patient was obtained.

MRI

From 2010 onwards an MRI was made at baseline and from June 2013 onwards not only the MCP- and wrist-joints, but also the MTP-joints were imaged after gadolinium enhancement. As contrast enhancement is beneficial for the evaluation of synovitis,[7] patients were selected from June 2013 onwards at the time contrast enhancement

of the MTP-joints was added to the protocol. Patients studied here were included between June 2013 and December 2015. A 1.5T MRI was made at the most severely affected symptomatic side or at the dominant side if symptoms were equal at both sides (see online supplementary methods). According to the protocol the MRI was made before disease modifying anti-rheumatic drug (DMARD)-initiation (including glucocorticoids) and patients were asked to stop NSAIDs 24hours before the scan. The scans were scored according to RA MRI Scoring (RAMRIS) method by two experienced readers (intraclass correlation coefficients (ICC) for synovitis 0.96). More details on the scanning and scoring method are provided supplementary *(online available)*. Mean

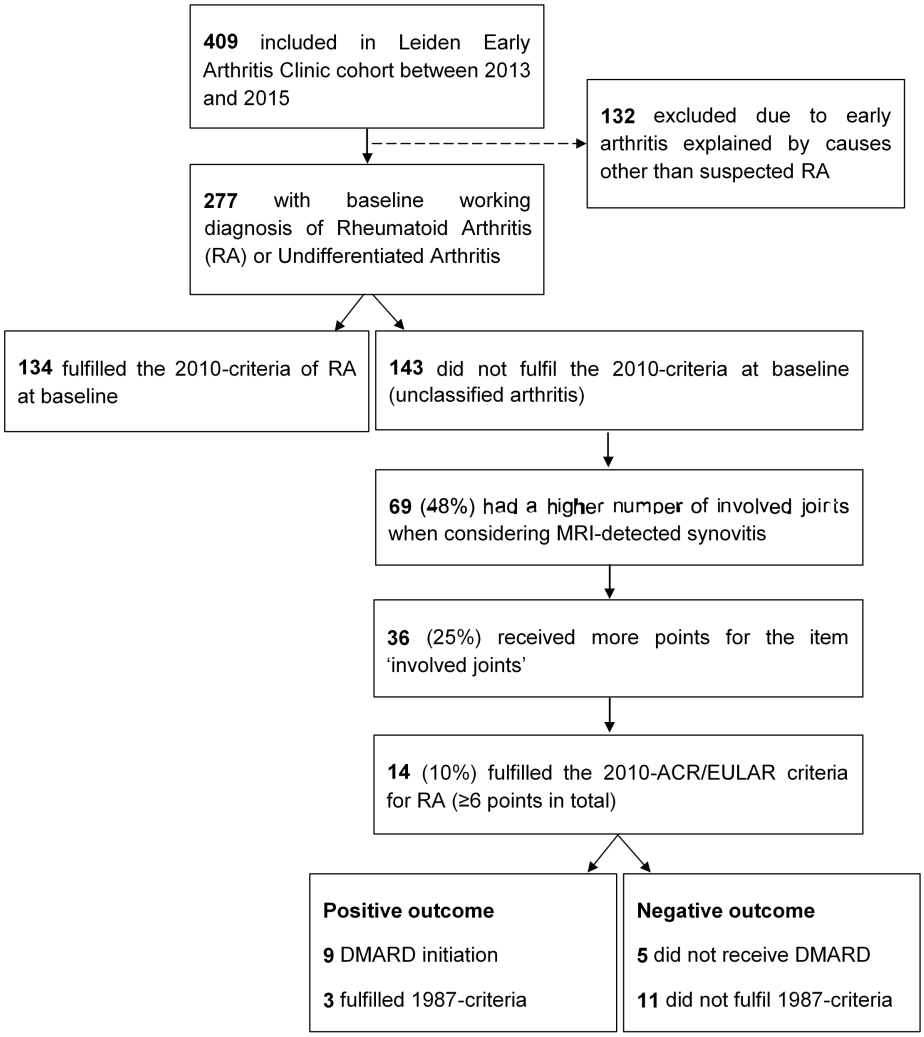

Figure 3.1: Flowchart of patient selection from the Leiden Early Arthritis Clinic cohort.

scores of two readers were calculated and in case of a mean score of ≥1, the MRI was considered positive for MRI-detected inflammation (synovitis, tenosynovitis or bone marrow oedema (BMO)). The MRI reading results were not communicated to the clinicians at any time point.[6, 8]

Incorporation of MRI-detected inflammation for the classification of RA-patients

The 2010-criteria were applied to all 277 patients with clinical synovitis of at least one joint that had no alternative explanation for their complaints and were considered as at risk for RA by their treating rheumatologist. Joint counts were performed with and without the addition of MRI-detected inflammation. For example, in case a joint was neither tender nor swollen, but was positive for MRI-detected synovitis (mean score ≥1 per joint by 2 separate independent readers) it resulted in a positive joint for the calculation of the 2010 ACR/EULAR classification criteria with MRI-detected synovitis. Although the 2010-classification criteria stated that synovitis detected by advanced imaging modalities might be assessed to determine the number of involved joints, MRI also depicts tenosynovitis and BMO. Therefore we also explored if adding information of these features increased the accuracy of the criteria. Patients that fulfilled ≥6 points of the classification criteria were considered 2010-criteria positive RA.[1]

Analyses

After 1-year follow-up patient files were assessed on two outcomes that were used as a proxy of RA. The primary outcome was the initiation of a DMARD (including the start of oral, intra-articular or intramuscular glucocorticoids); this outcome was also used in the data-driven phase of the derivation of the 2010-criteria. The secondary outcome was fulfilment of the 1987-criteria. We calculated test characteristics for the 2010-criteria without and with the addition of MRI-detected synovitis. The net reclassification index was calculated.

Results

At baseline 143 out of the total of 277 patients studied did not fulfil the 2010-criteria when the number of involved joints was determined at clinical evaluation only (Figure 3.1) and 134 did. Table 3.1 shows the baseline characteristics; in line with previous observations the patients that did not fulfil the criteria were mostly auto-antibody negative. When MRI-detected synovitis was also considered to count the number of involved joints, 69 patients had increased joint counts. Subsequently we determined the number of patients that received more points for the item 'number of involved joints'; this concerned 36 patients. Then we counted the additional number of patients in whom the total points had become 6 or higher. A total of 14 additional patients now fulfilled the 2010-criteria for RA. Thus, when data on MRI-detected synovitis were included 10% of patients that were formally classified as UA were now additionally classified as having RA.

Then the 1-year follow-up data were studied. When MRI-detected synovitis was not

considered, the sensitivity (95% CI) of the 2010-criteria was 62% (55; 69) and the specificity 90% (82; 95) for DMARD initiation as outcome (Table 3.2). Nine of the 14 additionally classified patients (64%) were started on DMARDs and were considered as true positives, whereas the other five patients (36%) were not treated with DMARDs. These five patients developed alternative clinical diagnoses during the first year (gout (n=2), inflammatory osteoarthritis (n=1), paraneoplastic inflammatory arthritis (n=1)) or had spontaneous resolution of arthritis in the first year (n=1). With the addition of MRI-detected synovitis the sensitivity increased to 67% (60; 73) and the specificity decreased to 84% (73; 90). The area under the receiver operating characteristic curve (AUC) changed from 0.76 to 0.75. The net reclassification index -2.4% (Supplementary table 3.3).

Results for the secondary outcome, fulfilment of the 1987-criteria after 1-year, were similar (Table 3.2). The sensitivity changed from 79% (71; 85) to 81% (74; 87) and the specificity from 78% (71; 84) to 71% (63; 78). The net reclassification index was -5.1% (Supplementary table 3.4).

To investigate whether the additionally classified patients with MRI-detected synovitis could be explained by the definition of MRI-detected synovitis, we also applied a cut-off based on findings from symptom-free volunteers, as previously published,[9] instead of a cut-off of mean ≥1. Then MRI-detected synovitis was considered present in a joint if this was seen in <5% of age matched healthy controls. This caused less UA-patients to fulfil the 2010-criteria and also resulted in both an increase in falsely and correctly additionally classified RA-patients (data not shown). The area under the receiver operating characteristic curve (AUC) remained 0.76.

Since MRI does not only depict synovitis, but also tenosynovitis and BMO, it was explored if incorporation of these inflammatory findings changed the results. As depicted in Table 3.2, the test characteristics and AUC were almost similar to that of

Table 3.1: Baseline characteristics of 277 patients studied and for those that did not fulfil the 2010-criteria when MRI results were not considered (Undifferentiated Arthritis, UA).

	All patients (n=277)	UA patients (n=143)
Age, mean (SD)	57 (16)	56 (17)
Female, n (%)	176 (64)	85 (59)
68-Tender joint count, median (IQR)	6 (9)	3 (5)
CRP (mg/L), median (IQR)	7 (18)	5 (11)
Symptom duration in days, median (IQR)	73 (166)	59 (156)
RF positive (≥3.5 IU/mL), n (%)	97 (36)	11 (8)
ACPA positive (≥7 U/mL), n (%)	97 (36)	22 (16)
Either RF or ACPA positive, n (%)	127 (46)	29 (20)

ACPA, anti-citrullinated peptide antibody; RF, rheumatoid factor; CRP, c-reactive protein; SD, standard deviation; IQR, Inter quartile range.

MRI-detected synovitis.

Discussion

This study provided evidence on the value of the inclusion of MRI-detected synovitis in addition to the evaluation of tender and swollen joints for the classification of RA. Our data show that the accuracy as measured by the AUC did not improve. This conclusion is similar to that reported in two abstracts that to our knowledge did not proceed to papers published in peer-reviewed journals.[10, 11] We observed that almost 50% of patients had MRI-detected synovitis in joints that were neither swollen nor tender at physical examination. However this resulted in a positive classification for the 2010-criteria in a minority of patients. Furthermore one-third of additionally classified patients did not have RA with DMARD-treatment as reference and could be considered as false-positives.

A meta-analysis on the performance of the 2010-criteria by Radner *et al* reported a

Table 3.2: Test characteristics of the 2010 EULAR/ACR criteria for RA without and with considering MRI-detected inflammation for the primary outcome (initiation with DMARDs in the first year) and secondary outcome (fulfilment of the 1987-criteria at year one).

Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
DMARD initiation in the first year as outcome					
2010-RA without considering MRI					
62 (55; 69)	90 (82; 95)	95 (90; 97)	46 (38; 54)	70 (64; 75)	0.76
2010-RA with considering MRI-detected synovitis					
67 (60; 73)	84 (73; 90)	92 (86; 95)	47 (39; 56)	71 (66; 76)	0.75
2010-RA with considering MRI-detected tenosynovitis					
66 (59; 72)	86 (77; 92)	93 (88; 96)	47 (39; 56)	71 (66; 76)	0.76
2010-RA with considering MRI-detected bone marrow oedema					
64 (57; 70)	86 (77; 92)	93 (87; 96)	46 (38; 54)	70 (64; 75)	0.75
2010-RA with considering any MRI-detected inflammation					
68 (61; 74)	82 (72; 89)	91 (86; 95)	48 (39; 57)	72 (66; 77)	0.75
1987-criteria fulfilment in the first year as outcome					
2010-RA without considering MRI					
79 (71; 85)	78 (71; 84)	76 (68; 83)	81 (74; 87)	79 (74; 83)	0.79
2010-RA with considering MRI-detected synovitis					
81 (74; 87)	71 (63; 78)	71 (63; 78)	81 (74; 87)	76 (70; 80)	0.76
2010-RA with considering MRI-detected tenosynovitis					
81 (74; 87)	74 (66; 80)	73 (65; 80)	82 (75; 88)	77 (72; 82)	0.78
2010-RA with considering MRI-detected bone marrow oedema					
81 (73; 87)	76 (68; 82)	74 (66; 81)	82 (74; 87)	78 (73; 82)	0.78
2010-RA with considering any MRI-detected inflammation					
82 (75; 88)	69 (61; 76)	70 (62; 76)	82 (74; 87)	75 (70; 80)	0.76

Test characteristics are shown in percentages with a 95% CI except for the AUC, area under the receiver operating characteristic curve. PPV, positive predictive value; NPV, negative predictive value. Any MRI-detected inflammation consists of either synovitis, tenosynovitis or bone marrow oedema.

sensitivity and specificity for DMARD initiation of 65% and 80% respectively. Our findings are in line with these data.

We also did not identify studies or trials stating that imaging modalities were used for the application of the classification criteria. Hence we are unfamiliar with how often novel imaging modalities are currently used to this end. The value of ultrasound for the classification criteria has been studies previously.[12–15] All studies were differently designed. In two studies the presence of clinically evident inflammatory arthritis was not required for inclusion.[12, 14] Another study showed associations between ultrasound-detected synovitis and fulfilment of the 2010-criteria, but test characteristics with and without the use of ultrasound were not provided.[15] One study calculated test characteristics and showed that the use of ultrasound resulted in an increased sensitivity at the cost of specificity, which is in line with our findings.[13] Also these ultrasounds studies showed, similarly to our study, an increase of both correctly and incorrectly classified RA-patients.[15]

The method how MRI-detected synovitis should be incorporated in the 2010-criteria was not thoroughly explained.[1] We used MRI additionally to clinical evaluation of joints. However, the study of Nakagomi *et al* that used ultrasound, included patients without clinical synovitis and determined the number of involved joints solely by imaging.[12] This resulted in patients fulfilling the criteria for RA without any clinically detectable synovitis.

Importantly, concerning the type of inflammation assessed, our main focus was the addition of MRI-detected synovitis, as this was explicitly stated in the table by Aletaha *et al.*[1] To further examine the impact of other types of MRI-detected inflammation, we seperately analysed the value of tenosynovitis, BMO and the presence of any type of inflammation as an addition to the criteria. These results were similar to the outcomes of MRI-detected synovitis.[8]

The definition of the presence of synovitis on imaging was not explicated in the 2010-criteria. Several previous studies showed low-grade synovitis in small joints of asymptomatic persons, especially at higher age.[16–18] Although the nature of this phenomenon remains indefinite, not considering this may possibly result in an overestimation of affected joints. Therefore we analysed an alternative definition for synovitis-positivity and investigated the effects if a joint was considered positive when this was present in <5% of age matched healthy controls. This also resulted in an increase in falsely and correctly classified RA-patients. Consequently, we think that the presence of low-grade synovitis in the general population does not explain the lack of increased accuracy when using MRI-detected synovitis in the criteria.

In this study we observed an increased sensitivity at the cost of the specificity. It could be discussed that classification criteria should be sensitive and therefore incorporation of imaging into the 2010-criteria for RA could be considered favourable. At the other hand, here this also resulted in a substantial increase of false positives.

In addition to the outcome studied here, it would also be interesting to evaluate more a long-term outcome like disease persistence. Further, the present findings require external validity in other cohorts of early RA patients to assess if these results are generalizable.

In conclusion, we did not find an increased accuracy of the 2010 ACR/EULAR classification criteria when MRI-detected synovitis was incorporated. Further research on this subject in other longitudinal cohorts is needed. At present there is no scientific proof that MRI-detected synovitis is of additional benefit for classification of RA.

Acknowledgements

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Supplementary data

Supplementary methods are online available at *Annals of the Rheumatic Diseases Online*.

Supplementary tables

Table 3.3: Reclassification of patients fulfilling the ACR/EULAR 2010-criteria for RA at baseline, without and with MRI-detected synovitis at baseline and outcome initiation with DMARDs within one year.

	Start with DMARD within 1 year		
	No DMARD	DMARD	Total
Baseline RA (2010-criteria)			
No RA	116	27	143
RA	32	102	134
Baseline RA (2010-criteria) including synovitis detected by MRI			
No RA	105	24	129
RA	43	105	148
Total	148	129	227

The net increase in correct classifications was 4.4% (9/204) and incorrect classifications with MRI-detected synovitis 6.8% (5/73), the net reclassification index was -2.4%.

Table 3.4: Reclassification of patients fulfilling the ACR/EULAR 2010-criteria for RA at baseline, without and with MRI-detected synovitis at baseline and outcome fulfilment of the 1987-criteria within one year.

	1987-criteria fulfilment		
	No RA	RA	Total
Baseline RA (2010-criteria)			
No RA	116	27	143
RA	32	102	134
Baseline RA (2010-criteria) including synovitis detected by MRI			
No RA	105	24	129
RA	43	105	148
Total	148	129	227

The net increase in correct classifications was 2.3% (3/129) and incorrect classifications with MRI-detected synovitis 7.4% (11/148), the net reclassification index was -5.1%.

4

Do musculoskeletal ultrasound and magnetic resonance imaging identify synovitis and tenosynovitis at the same joints and tendons? A comparative study in early inflammatory arthritis and clinically suspect arthralgia

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Abstract

Objective

Ultrasound (US) and magnetic resonance imaging (MRI) are recommended in the diagnostic process of rheumatoid arthritis. Research on its comparability in early disease phases is scarce. Therefore, we compared synovitis and tenosynovitis detected by US and MRI on joint/tendon level.

Methods

Eight hundred forty joints and 700 tendons of 70 consecutive patients, presenting with inflammatory arthritis or clinically suspect arthralgia, underwent US and MRI of MCP (2–5), wrist and MTP (1–5) joints at the same day. Greyscale (GS) and power Doppler (PD) synovitis were scored according to the modified Szkudlarek method (combining synovial effusion and hypertrophy) and the recently published EULAR-OMERACT method (synovial hypertrophy regardless of the presence of effusion) on static images. US-detected tenosynovitis was scored according to the OMERACT. MRI scans were scored according to the RAMRIS. Test characteristics were calculated on joint/tendon level with MRI as reference. Cut-off for US-scores were ≥1 and ≥2 and for MRI ≥1.

Results

Compared to MRI, GS synovitis according to EULAR-OMERACT (cut-off ≥1) had a sensitivity ranging from 29 to 75% for the different joint locations; specificity ranged from 80 to 98%. For the modified Szkudlarek method, the sensitivity was 68–91% and specificity 52–71%. PD synovitis had a sensitivity of 30–54% and specificity 97–99% compared to MRI. The sensitivity to detect GS tenosynovitis was 50–78% and the specificity 80–94%. For PD tenosynovitis, the sensitivity was 19–58% and specificity 98–100%.

Conclusion

Current data showed that US is less sensitive than MRI in the early detection of synovitis and tenosynovitis, but resulted in only few non-specific findings. The higher sensitivity of MRI is at the expense of less accessibility and higher costs.

Background

The value of sensitive imaging methods such as musculoskeletal ultrasound (US) and magnetic resonance imaging (MRI) for disease monitoring in rheumatoid arthritis (RA) is currently being discussed.[1] The diagnostic value of US and MRI in very early disease phases of RA is also being investigated, and there appears to be an agreement on the notion that these modalities have an added value in the diagnostic process.[1] The EULAR imaging taskforce also recommended the use of US and MRI for this purpose without distinguishing between both modalities.[2] These modalities have advantages and disadvantages. MRI is generally considered as the most valid method, yielding reproducible results in a three-dimensional view, and it has the advantage that it depicts bone marrow oedema. Its use is limited by insufficient availability in several centres and higher costs. A disadvantage of US is the machine and operator dependency. Currently available data obtained in patients at risk for RA revealed that US-detected synovitis or tenosynovitis scores (greyscale (GS) or power Doppler (PD)) and MRI-detected synovitis or tenosynovitis scores were predictive for RA development.[3–10] These studies generally used only one modality and did not directly compare findings of both modalities.

Presently, there is limited knowledge whether US and MRI identify the same lesions in the earliest phase of RA. One study compared MRI and US on joint/tendon level in patients with early classified RA; data suggested that MRI is more sensitive than US.[11] The existing studies in early arthritis or arthralgia that performed both MRI and US did not make comparisons on joint or tendon level, did not include the feet, or used low-field MRI.[12–15] In addition, only few studies included tenosynovitis,[11–13] and none of them used standardised scoring methods such as the recently published EULAR-OMERACT method for US scoring.[16]

Therefore, we aimed to evaluate to what extent both modalities can be used interchangeably in patients at risk for RA. We conducted a cross-sectional study in patients presenting with early inflammatory arthritis (IA) or clinically suspect arthralgia (CSA) and investigated on joint and tendon levels whether US and MRI detected the same inflammatory lesions (synovitis and tenosynovitis).

Methods

Patients

Patients that newly presented with early IA or CSA between May and October 2017 at the Leiden rheumatology outpatient clinic were studied. They were consecutively included in either the Early Arthritis Clinic (EAC) cohort or the CSA cohort. Requirements for inclusion in both cohorts are described in reference and supplementary.[8, 17] Both cohort studies were approved by the local Medical Ethical Committee. All patients provided informed consent.

Study protocol

All patients underwent unilateral contrast-enhanced MRI of metacarpophalangeal (MCP), wrist, and metatarsophalangeal (MTP) joints and musculoskeletal US at the same day <2 weeks after first presentation.
According to the protocol, imaging was done before disease-modifying antirheumatic drug (DMARD) initiation (including glucocorticoids) in patients with IA. DMARDs were not prescribed to patients with CSA. All patients were asked to stop NSAIDs 24 h before imaging. More details are provided supplementary.

MR imaging and scoring

All patients were scanned on the same scanner (an MSK Extreme 1.5 T extremity MR system (GE Healthcare, Wisconsin, USA)). Unilateral MRI scans of wrist, MCP (2–5) and MTP (1–5) joints were made of the most affected side, or the dominant side in case of equally severe symptoms. Sequences acquired were coronal pre-contrast T1-weighted fast spin-echo (FSE) and coronal and axial post-contrast T1-weighted FSE with frequency-selective fat suppression of MCP and wrist, and post-contrast coronal and axial sequences of the MTP joints. More details are provided in reference and supplementary.[17]
Each MRI-scan was scored according to RA MRI scoring (RAMRIS) method by two experienced readers (inter-reader intraclass correlation coefficients (ICC) > 0.94).[18, 19] MRI scores for joints (synovitis) and tendons (tenosynovitis) ranged from 0 to 3. Mean scores of two readers were calculated and lesions were considered absent in case it was scored by only one reader.

Musculoskeletal ultrasound scanning and scoring

A high-end US machine was used (GE Logiq E9, Genova, Italy) with a linear array transducer of 6–15 MHz. US examinations were performed bilaterally in GS and PD mode according to a standardised protocol. The same locations that were scanned by MRI were studied here. PD was assessed with a pulse repetition frequency of 0.8 kHz, and gain was set to a level until background signal was removed. The presence of synovitis was assessed on a semiquantitative scale (0–3) for GS/PD according to Szkudlarek *et al.*,[20] and synovial effusion and hypertrophy were combined (called 'modified Szkudlarek method').[21] Tenosynovitis was examined on a semi-quantitative scale (0–3) for GS/PD according to OMERACT.[22] A detailed US-scoring protocol is provided supplementary. All US scores per joint/tendon ranged from 0 to 3. During the study, the newly developed EULAR-OMERACT-scoring method for synovitis was published.[16] To explore if the results changed when this definition was used, the static images of US were re-scored for GS synovitis by two examiners (ICC 0.92) and mean scores were calculated. The different scoring methods are described in supplementary Table 4.4 and in the supplementary methods. Imaging results were not communicated to clinicians at any time point.

Statistical analyses

We compared semi-quantitative scores of US-detected synovitis and tenosynovitis to MRI-detected synovitis and tenosynovitis scores (each on a scale from 0 to 3),

respectively, for each location using spearman's correlation coefficients. For the primary analyses, we used the method according to the EULAR-OMERACT for GS synovitis. After analysing (semi-)quantitative data, US and MRI scores were dichotomized. For US, different cut-offs were studied: ≥1 and ≥2 for GS-synovitis, ≥1 for PD-synovitis and ≥1 for GS/PD-tenosynovitis. Additionally, GS synovitis and tenosynovitis scores ≥2 or PD ≥1 were combined. MRI-scores were dichotomized with ≥1 as cut-off and also on a cut-off based on findings from symptom-free volunteers, which has been published previously.[23] Then, an MRI was considered positive if synovitis or tenosynovitis was seen in <5% age-matched healthy controls. We calculated test characteristics for US with MRI as reference. Analyses were done on individual joint/tendon level and firstly presented on joint-group level (wrist, MCP, MTP joints) for reasons of clarity. Sub-analyses included stratification for patients presenting with IA and CSA and presentation of data at individual joint/tendon level. Finally, for GS synovitis, the 'modified Szkudlarek method' was compared to the EULAR-OMERACT method and also compared to MRI.[16, 18, 21] IBM SPSS (New York, USA) v23 was used.

Results

Study population

Seventy patients newly presenting to the rheumatology outpatient clinic (40 with recent-onset CSA, 30 with early IA) were included. Table 4.1 presents their baseline characteristics. The majority was female; mean age was 45 for patients with CSA and 57 for patients with IA (supplementary Table 4.5). In total, 840 joints and 700 tendons were examined.

Table 4.1: Baseline characteristics of 70 patients studied.

	All patients (n=70)
Age, mean (SD)	50 (15)
Female, n (%)	43 (61)
68-Tender joint count, median (IQR)	5 (2-8)
66-Swollen joint count, median (IQR)	2 (1-6)
CRP (mg/L), median (IQR)	3 (3-11)
RF positive (≥3.5 IU/mL), n (%)	20 (29)
ACPA positive (≥7 U/mL), n (%)	16 (23)
Either RF or ACPA positive, n (%)	22 (31)

*Swollen joint count based on inflammatory arthritis (IA)-patients, as all clinically suspect arthralgia (CSA)-patients per definition do not have swollen joints.
ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

Table 4.2: Test characteristics for ultrasound-detected synovitis and tenosynovitis with MRI as reference

	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Synovitis	GS ≥1 (EULAR-OMERACT)			PD ≥1			GS ≥2 (EULAR-OMERACT) or PD ≥1		
MCP joints	39 (27; 53)	98 (95; 99)	0.69	54 (41; 66)	97 (94; 99)	0.75	54 (41; 66)	97 (94; 99)	0.75
Wrist joints	29 (19; 40)	94 (89; 97)	0.61	30 (21; 41)	99 (95; 100)	0.64	30 (21; 41)	99 (95; 100)	0.64
MTP joints	75 (61; 85)	80 (75; 85)	0.78	41 (28; 56)	99 (97; 99)	0.70	68 (53; 80)	86 (81; 89)	0.77
Tenosynovitis	GS ≥1			PD ≥1			GS ≥2 or PD ≥1		
Extensor wrist tendons	78 (59; 86)	80 (74; 86)	0.78	58 (42; 73)	98 (95; 99)	0.78	67 (50; 80)	97 (93; 98)	0.82
Flexor wrist tendons	50 (31; 69)	94 (90; 97)	0.72	42 (24; 61)	99 (97; 100)	0.71	50 (31; 69)	99 (96; 100)	0.75
Flexor MCP tendons	74 (60; 84)	89 (84; 92)	0.81	19 (11; 31)	100 (98; 100)	0.59	36 (24; 49)	100 (98; 100)	0.68

Test characteristics are shown in percentages with a 95% CI except for the AUC, area under the receiver operating characteristic curve; GS: Grey-scale; PD: Power Doppler.

Synovitis detected by US versus MRI

Figure 4.1(a–c) presents the scores for GS-detected synovitis (EULAR-OMERACT method) versus MRI-detected synovitis (OMERACT-RAMRIS method). Analyses were performed on individual joints and tendons (i.e. MCP-2 of US versus MRI) and presented per joint group (MCPs, wrist, MTPs). All scores within joint groups were significantly correlated (Supplementary Table 4.6). In MTP joints, MRI scores of 0 infrequently coincided with scores of 1 for US (Figure 4.1 c); this is in contrast to findings on MCP and wrist level (Figure 4.1 a, b). In line with this observation, the corresponding test characteristics showed a high specificity (> 90%) for GS synovitis of wrist and MCP joints and a somewhat lower specificity of 80% for MTP joints. The sensitivity was poor for MCP and wrist (29–39%) and higher (75%) for MTP joints with MRI as reference (Table 4.2).

Subsequently, PD synovitis scores were compared to MRI. Also here, increased US scores were accompanied by increased MRI scores, and correlations were statistically significant (supplementary Table S3, *online available*). As presented (4.1 d–f), PD scores were only rarely ≥1 when MRI-detected synovitis scores were 0. Furthermore, we observed regularly that PD scores were 0 for joints that were scored ≥1 by MRI. These observations were reflected by the test characteristics, which showed a high specificity for PD (97–99%) for all locations (MTP, MCP, wrist) with only a low to moderate sensitivity (30–54%, Table 4.2).

Test characteristics when US positivity was defined by a combination of GS scores ≥2 or PD ≥1 are provided in Table 4.2. The combined scores showed a high specificity (> 92%) accompanied by an increased sensitivity for the MCP and wrist joints (30–54%) but not for the MTP joints (68%) in comparison to GS/PD alone.

Tenosynovitis detected by US versus MRI

Figure 4.2 (a–c) presents the data of GS-detected tenosynovitis versus MRI-detected tenosynovitis scores. MRI scores were significantly correlated to GS scores (supplementary Table S3). However, scores ≥1 for MRI were also often accompanied by US scores of 0. Test characteristics were in line with these observations, with a specificity of 80% for the extensor wrist tendons and > 89% for the other tendons (flexor wrist, flexor MCPs), and a moderate sensitivity (50–78%, Table 4.2).

Figure 4.2 (d–f) shows the data of PD tenosynovitis versus MRI. PD signals were infrequently increased. MRI detected 113 tendons with tenosynovitis (out of 700), while for PD this was only 45. The corresponding test characteristics in Table 4.2 showed a high specificity (98–100%) with a low to moderate sensitivity (19–58%).

Defining tenosynovitis as a combination of GS ≥2 or PD ≥1 slightly improved the test characteristics for the extensor and flexor tendons of the wrist, but not for the flexor tendons of the MCPs, compared to the separate ultrasound features (GS/PD) (Table 4.2).

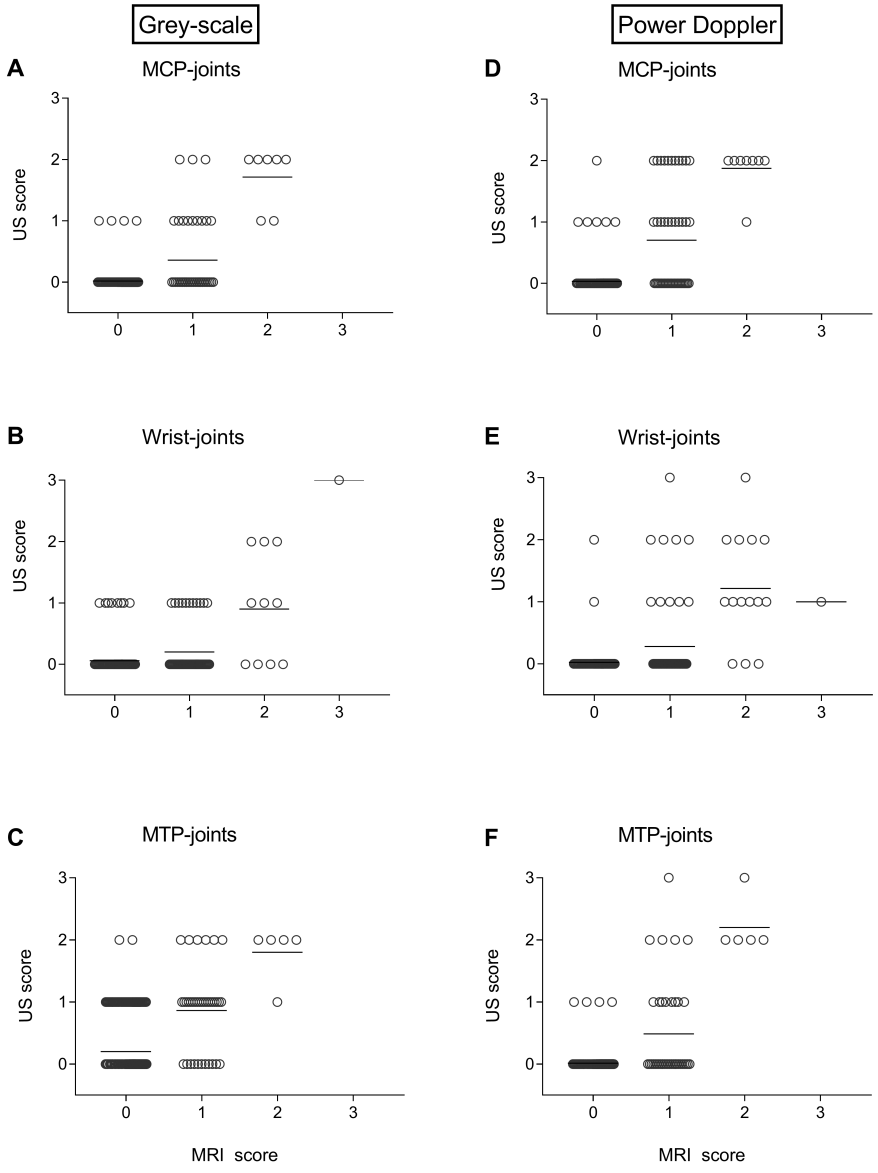

Figure 4.1: Grey-scale Ultrasound (according to EULAR-OMERACT definition, A,B,C) and power Doppler Ultrasound-detected synovitis (D,E,F) versus MRI-detected synovitis on MCP, wrist, and MTP joint level. Legend: Number of corresponding joints per MRI score was for A) 0: 222, 1: 42, 2: 7, 3: 0; B) 0: 136, 1: 55, 2: 10, 3: 1; C) 0: 285, 1: 39, 2: 5, 3: 0; D) 0: 224, 1: 48, 2: 8, 3: 0; E) 0: 137, 1: 58, 2: 14, 3: 1; F) 0: 296, 1: 39, 2: 5, 3: 0. Bars indicate the mean.

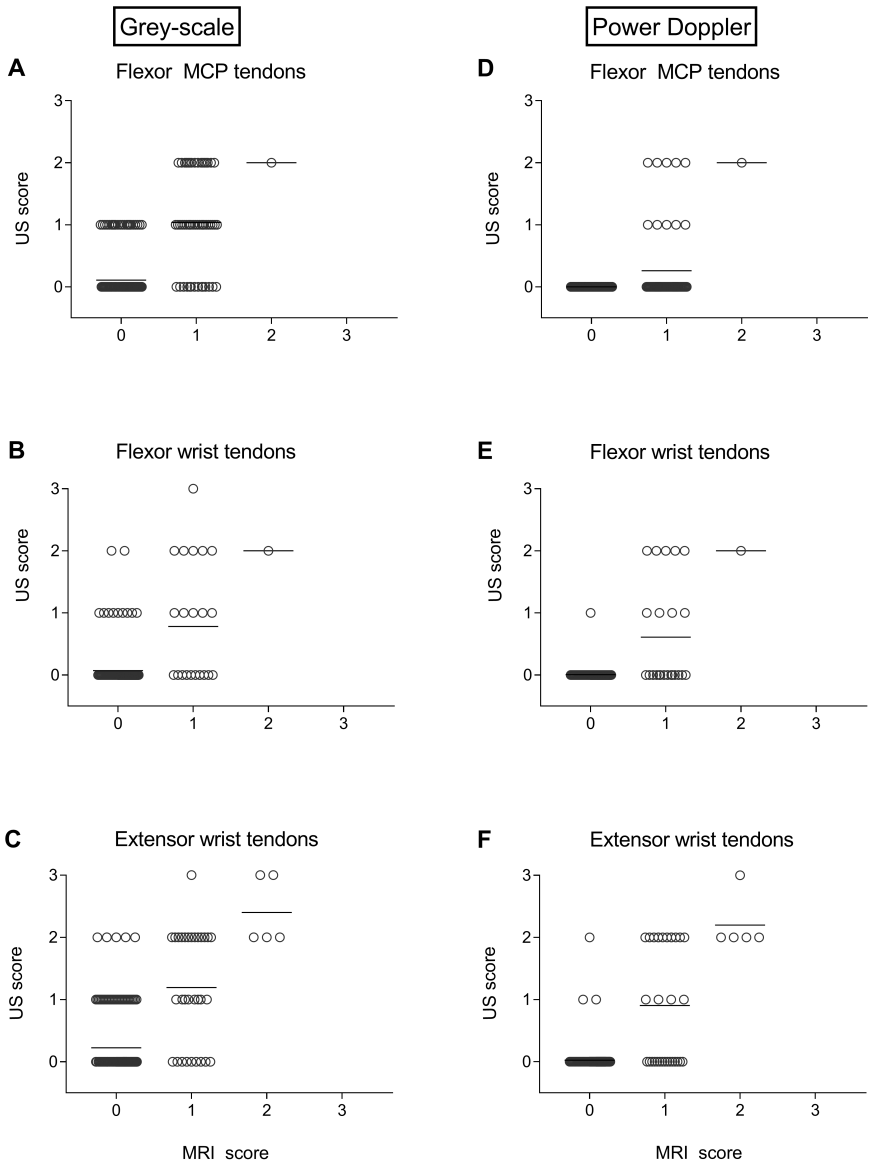

Figure 4.2: Grey-scale (A,B,C) and power Doppler Ultrasound-detected tenosynovitis (D,E,F) versus MRI-detected tenosynovitis of MCP flexor 2-5, wrist flexor and extensor tendons. Legend: Number of corresponding tendons per MRI-score was for A) 0: 226, 1: 52, 2: 1, 3: 0; B) 0: 186, 1: 23, 2: 1, 3: 0; C) 0: 173, 1: 32, 2: 5, 3: 0; D) 0: 226, 1: 52, 2: 1, 3: 0; E) 0: 185, 1: 23, 2: 1, 3: 0; F) 0: 171, 1: 32, 2: 5, 3: 0. Bars indicate the mean.

Cut-off for synovitis and tenosynovitis based on healthy volunteers

To investigate whether the excess of increased MRI-detected scores compared to US scores could be explained by the definition of positivity for MRI, we also applied a cut-off based on findings from symptom-free volunteers.[23] This resulted in a slightly increased sensitivity and AUC for GS-detected (teno)synovitis, while the specificity remained high compared to the main analyses. For PD, it only caused small differences (supplementary Table 4.7).

Sub-analyses stratified for IA and CSA

In supplementary Figure S1-S4, we provided the data of the US synovitis and tenosynovitis scores (GS and PD) versus MRI for patients with CSA and IA separately. As expected, synovitis and tenosynovitis were less frequently present and/or less severe in patients with CSA than IA. However, the pattern of concordance between MRI and US was similar. We also calculated test characteristics for patients with CSA and IA separately (supplementary Table 4.8). The sensitivity for US with MRI as reference was lower in CSA than in patients with IA. The specificity was similar in both populations.

Data presented on individual joint/tendon level

For clarity, the main results were presented on joint-group level, although analyses were performed on the joint/tendon level. However, as findings on different joints/tendons might be different and these differences cannot be seen by presentation on the joint-group level, we also provided test characteristics for each joint/tendon separately (supplementary Table 4.9, 4.10). In general, results were similar with a low to moderate sensitivity and high specificity. Remarkably, for the flexor tendons of the wrist (GS), all flexors had high specificity (88–100%). However, the sensitivity varied broadly: 71% for the FPL, 55% for the FCR and only 17% for the FDS/FDP. Also for PD, the sensitivity for tenosynovitis was generally low (17–64%). Examples of MRI-detected (teno)synovitis versus GS/PD are illustrated by 4.3.

Evaluation of two scoring methods for GS-detected synovitis

Due to recent advances in scoring methods for GS, two methods were applied and test characteristics were also determined for GS by the modified Szkudlarek method [21] with MRI as reference (Table 4.3). The modified Szkudlarek method had a higher sensitivity of 68–91% and lower specificity of 52–71% than the EULAR-OMERACT method (sensitivity 29–75%, specificity 80–98%) compared to MRI. Thereafter, we compared the scores of the two scoring methods for GS for each joint. The modified Szkudlarek method generally had higher scores than the EULAR-OMERACT method (see supplementary Table 4.11,4.12,4.13).

Discussion

This large cross-sectional study compared US and MRI findings of synovitis and tenosynovitis on the joint and tendon levels, respectively, in patients newly presenting with early IA and CSA. These are the populations where imaging modalities can have a specific role in the diagnostic process. The newly developed EULAR-OMERACT scoring

method for GS-detected synovitis for US was used. Our data showed that US findings were highly specific and rarely 'false-positive', but also less sensitive compared to MRI, resulting in 'false-negative results'. This suggests that MRI cannot be replaced by US while maintaining its sensitivity on the level of joints and tendons. How this affects the predictive accuracy needs to be investigated further in longitudinal studies.

Two different scoring methods for GS-detected synovitis were applied: the EULAR-OMERACT method and the modified Szkudlarek method, which combines synovial effusion and hypertrophy.[16, 21] Direct comparison of both scoring methods for GS synovitis showed that higher scores were obtained by the modified Szkudlarek method. In line with this and compared to MRI, the modified Szkudlarek method had more false positives which resulted in a higher sensitivity but lower specificity than the EULAR-OMERACT method. The false-positive results (MRI scores 0, GSUS > 0) obtained by the modified Szkudlarek method might be explained by the fact that it evaluates a combination of synovial effusion and hypertrophy, while in the recent EULAR-OMERACT definition hypertrophy regardless of the presence of synovial effusion was evaluated,[16] and the fact that contrast-enhanced MRI also does not visualise joint effusion. Thus, although this study did not primarily aim to compare the 'old' and 'new' GS synovitis scores, present data also showed the relationship between both GS scoring methods and revealed that the EULAR-OMERACT synovitis score for US was more concordant to the OMERACT-RAMRIS method for MRI. Unfortunately, the definition of the EULAR-OMERACT for GS synovitis was published when this study had already

Table 4.3: Test characteristics for greyscale ultrasound-detected synovitis with MRI as a reference for the 'old' synovitis definition according to the modified Szkudlarek method and for the 'new' EULAR-OMERACT synovitis definition

	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Synovitis	GS ≥1 (modified Szkudlarek)			GS ≥2 (modified Szkudlarek)		
MCP joints	73	70	0.72	39	96	0.68
	(60; 83)	(64; 76)		(28; 52)	(93; 98)	
Wrist joints	68	71	0.70	34	97	0.66
	(57; 78)	(63; 78)		(24; 46)	(93; 99)	
MTP joints	91	52	0.72	64	92	0.78
	(79; 96)	(47; 58)		(49; 76)	(88; 94)	
Synovitis	GS ≥1 (EULAR-OMERACT)			GS ≥2 (EULAR-OMERACT)		
MCP joints	39	98	0.69	17	100	0.58
	(27; 53)	(95; 99)		(9; 30)	(98; 100)	
Wrist joints	29	94	0.61	9	100	0.54
	(19; 40)	(89; 97)		(4; 17)	(97; 100)	
MTP joints	75	80	0.78	23	99	0.61
	(61; 85)	(75; 85)		(13; 37)	(97; 100)	

Test characteristics are shown in percentages with a 95% CI except for the AUC, area under the receiver operating characteristic curve. GS: Grey-scale.

started.[16] Consequently, synovitis had already been scored according to the modified Szkudlarek method. Therefore, static US images were rescored according to the EULAR-OMERACT method, which might be a potential limitation, as scoring of static images can be challenging. We used two independent readers to assess the static images; both readers showed excellent agreement between the reading results, which supports the reliability of these data.

Since the role of synovial effusion in the pathologic process of RA and other types of IA is not yet fully understood, synovial effusion was not explicitly taken into account, except within the modified Szkudlarek method.[21] Synovial effusion often has been detected in healthy persons by US, especially in the feet.[24] Unfortunately, up to now, age-related normal values for US-detected pathologies such as synovial effusion, synovial hypertrophy, tenosynovitis and erosions are still unknown and should be subject for future studies. Furthermore, it would be interesting to see the effect of findings in healthy symptom-free individuals for the definition of positivity for US. This is also subject for future research.

Importantly, there were differences between the scoring methods for US and MRI. All scoring methods consisted of semi-quantitative scales ranging from 0 to 3. However, the requirements for each grade were different for US and MRI (Additional file 1:

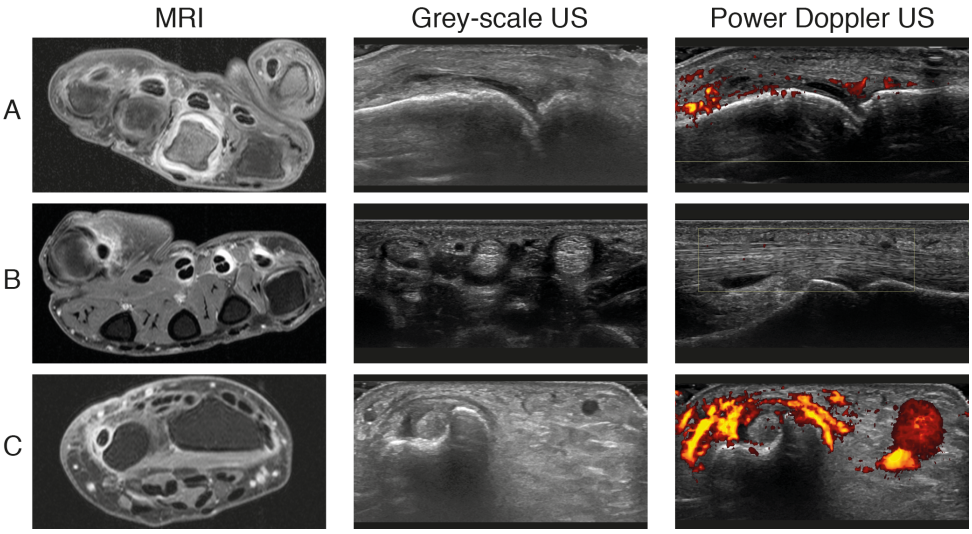

Figure 4.3: Examples of MRI-detected synovitis and tenosynovitis with corresponding Grey-scale and power Doppler ultrasound images. Legend: Examples of inflammation identified by MRI that were verified through ultrasound (US). Even though sometimes more inflammation was present on the MRI-scan we choose to show the corresponding US-images of only one joint or tendon that was present on the image. A shows an example of synovitis MCP-3 by MRI, which was confirmed by Grey-scale (GS) and Power Doppler (PD) US images of the same joint. B shows tenosynovitis of the flexor of MCP-4 which was confirmed by GS but not by PD on US. C shows inflammation of the extensor carpi ulnaris at the wrist-level which was confirmed by both GS and PD on US.

Table S1). Thus, different definitions for the different scoring methods hamper direct comparison of the different grades, though as presented by 4.1 and 4.2, increased US scores generally coincided with increased MRI scores. To assess whether this was similar in patients with CSA and IA, we also repeated the analyses for both populations separately. In both populations, higher US scores were present in patients with higher MRI scores (supplementary Figures S1-S4). However, the test characteristics were not completely similar. Although the specificity for US was similar in both populations, the sensitivity was lower in patients with CSA compared to IA. CSA patients have less severe inflammation than patients with IA and current data implied that in this setting of subclinical inflammation, US is less sensitive than MRI.

Another issue is the cut-off used for dichotomization. Our US cut-offs are frequently used in the literature. For GS, we observed that increasing the cut-off from ≥1 to ≥2 resulted in an increased specificity and a notably decreased sensitivity. This phenomenon is often observed when changing cut-offs. Based on AUCs, a cut-off ≥ 1 could be considered more favourably than ≥ 2. Also, the cut-off for MRI positivity was explored. In addition to using a cut-off of mean ≥ 1, we applied a cut-off based on healthy volunteers.[23] This caused only minor improvements in the test characteristics for US compared to MRI.

A strength of this study was that besides synovitis, also tenosynovitis was evaluated; this imaging feature is less often studied than synovitis while it is important, as tenosynovitis in IA and CSA has been shown predictive of RA development, both in studies that used MRI [9, 25] and US.[7] Furthermore, this study examined patients at risk for RA and applied the new EULAR-OMERACT score for GS-detected synovitis. We also did not only examine the wrist and MCP, but also the MTP joints. In contrast, a recent meta-analysis compared the accuracy of US-detected synovitis versus MRI in wrist, MCP, PIP, and knee joints, but not MTP joints in patients with classified RA.[26] The included studieswere also not scored according to the EULAR-OMERACT method. Despite these differences, the sensitivity and specificity for GS/PD-detected synovitis observed in this study compared to our data are roughly similar. Also GS tenosynovitis was previously studied by Wakefield *et al.* in MCP joints of classified RA-patients and were comparable to our results from patients in earlier disease phases, showing a high specificity and moderate sensitivity.[11]

In our data on tenosynovitis, the sensitivity was particularly low for the FDS/FDP tendon. A possible explanation could be that this tendon is located below the retinaculum flexorum, deeper in the wrist tissue than other tendons. Also, PDUS tenosynovitis had only a low to moderate sensitivity, despite the use of high-end US machine with a sensitive power Doppler. PD-detected tenosynovitis had only a small or no additive value to GS tenosynovitis, particularly for the MCP-flexor tendons. A reason for this could be that PD performs better from the dorsal side of the joint than from the palmar side, which may have contributed to this finding.[16, 27] Although replication in other studies is needed, the current data with MR as reference suggests that PDUS-detected tenosynovitis had no clear additive value to GSUS, which is in contrast to findings for

synovitis.

This cross-sectional study is the first that examined the concordance between synovitis detected by US and MRI in the feet of patients with (suspicion on imminent) early RA. Interestingly, GS synovitis had a higher sensitivity in the feet than in the hand joints, which was at the cost of a lower specificity (implying a higher frequency of false-positive signals in MTP joints).

MRI was the reference in this cross-sectional study on the joint/tendon level, showing false-negative findings for synovitis and tenosynovitis. For clinical purposes, analyses on patient level are also relevant, as patients often have > 1 joint affected and at least 1 joint with subclinical inflammation might be considered sufficient to indicate disease. Analyses on the patient level showed that US missed only 1/44 patients (GS) and 14/44 (PD) compared to MRI (cut-offs ≥1, data not shown). Hence, there is less discordance on the patient level than on the joint/tendon level. The comparability of US and MRI to accurately predict RA development remains an outstanding question, for which longitudinal studies with RA development as outcome are needed.

In conclusion, this is the first study that used the recently developed EULAR-OMERACT method for US in comparison to MRI, in patients consecutively presenting with early IA and CSA. These are the populations in which these imaging modalities can be used to detect (imminent) RA. US had a good specificity, but was less sensitive compared to MRI on the local tendon and joint level. However, US is more easily available, less timeconsuming and has lower costs than MRI. Longitudinal studies in 'at-risk' populations are needed to directly compare the predictive accuracy of MRI and US while using up-to-date scoring methods.

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Supplementary data

Supplementary methods are available at *Arthritis Research & Therapy Online*.

Supplementary tables

Table 4.4: Different Grey-scale ultrasound scoring methods

	GS score for joint effusion[1]	Szkudlarek GS synovitis score[1]	Modified Szkudlarek GS synovitis score[2]	EULAR-OMERACT GS synovitis score[3]
Grade 0	No effusion	No synovial thickening	No synovial hypertrophy or effusion	No synovial hypertrophy, regardless of presence of effusion
Grade 1	Minimal amount of fluid	Minimal synovial thickening: filling the angle between the peri-articular bones, without bulging over the line, linking tops of the bones	Minimal effusion and/or hypertrophy: filling the angle between the peri-articular bones, without bulging over the line, linking tops of the bones	Synovial hypertrophy with or without effusion: up to level of horizontal line that connects bone surfaces
Grade 2	Moderate amount of fluid, without distension of the joint capsule	Synovial thickening: bulging over the line linking tops of the peri-articular bones but without extension along the bone diaphysis	Moderate effusion and/or hypertrophy: bulging over the line linking tops of the peri-articular bones but without extension along the bone diaphysis	Synovial hypertrophy with or without effusion: extending beyond joint line but with upper surface convex or hypertrophy; extending beyond joint line but with upper surface flat
Grade 3	Extensive amount of fluid, with distension of the joint capsule	Synovial thickening: bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses	Extensive effusion and/or hypertrophy: bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses	Synovial hypertrophy: with or without effusion extending beyond joint line but with upper surface flat or convex

Table 4.5: Baseline characteristics of 70 patients studied

	IA patients (n=30)	CSA patients (n=40)
Age, mean (SD)	57 (16)	45 (11)
Female, n (%)	15 (50)	28 (70)
68-Tender joint count, median (IQR)	5 (2-7)	5 (3-10)
66-Swollen joint count, median (IQR)	2 (1-6)	-
CRP (mg/L), median (IQR)	8 (3-18)	3 (3-7)
RF positive (≥3.5 IU/mL), n (%)	7 (23)	13 (33)
ACPA positive (≥7 U/mL), n (%)	7 (23)	9 (23)
Either RF or ACPA positive, n (%)	8 (27)	14 (35)

IA, inflammatory arthritis; CSA, clinically suspect arthralgia; ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

Table 4.6: Correlation coefficients of US versus MRI for the different locations

	MRI vs GSUS		MRI vs PDUS	
	Spearman's ρ	p-value	Spearman's ρ	p-value
Synovitis				
MCP joints	0.57	<0.001	0.64	<0.001
MTP joints	0.43	<0.001	0.53	<0.001
Wrist joints	0.22	0.002	0.40	<0.001
Tenosynovitis				
Flexor MCP tendons	0.62	<0.001	0.43	<0.001
Flexor Wrist tendons	0.46	<0.001	0.59	<0.001
Extensor Wrist tendons	0.54	<0.001	0.70	<0.001

Correlation coefficients of two different semi-quantitative scoring methods. Obtained values are therefore not representative of the exact concordance as scores of US and MRI have different requirements. GSUS-synovitis is according to EULAR-OMERACT definition.

Table 4.7: Test characteristics for ultrasound-detected synovitis and tenosynovitis with MRI as reference, cut-off for positivity for MRI based on healthy controls

	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Synovitis	GS ≥1 (EULAR-OMERACT)			PD ≥1		
MCP joints	47	94	0.71	55	90	0.73
	(27; 68)	(90; 96)		(34; 74)	(86; 93)	
Wrist joints	52	91	0.71	64	95	0.79
	(32; 72)	(86; 94)		(43; 80)	(90; 97)	
MTP joints	72	78	0.75	38	97	0.67
	(55; 84)	(73; 82)		(23; 55)	(94; 98)	
Tenosynovitis	GS ≥1			PD ≥1		
Extensor wrist	80	79	0.79	57	96	0.76
tendons	(63; 90)	(72; 84)		(39; 73)	(92; 98)	
Flexor wrist	50	94	0.72	42	99	0.71
tendons	(31; 69)	(90; 97)		(24; 61)	(97; 100)	
Flexor MCP	54	80	0.67	19	98	0.59
tendons	(35; 71)	(75; 85)		(9; 38)	(95; 99)	

Test characteristics are shown in percentages with a 95% CI except for the AUC, area under the receiver operating characteristic curve; GS: Grey-scale Ultrasound; PD: Power Doppler.

Table 4.8: Test characteristics for US-detected synovitis and tenosynovitis with MRI as reference for CSA and IA separately

IA-patients	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Synovitis	GS ≥1 (EULAR-OMERACT)			PD ≥1		
MCP joints	57 (41; 71)	95 (88; 98)	0.76	63 (48; 76)	97 (91; 99)	0.80
Wrist joints	36 (24; 50)	90 (77; 96)	0.63	36 (24; 50)	98 (87; 100)	0.67
MTP joints	87 (71; 95)	76 (67; 83)	0.82	42 (26; 59)	99 (95; 100)	0.71
Tenosynovitis	GS ≥1 (EULAR-OMERACT)			PD ≥1		
Extensor wrist tendons	82 (64; 92)	80 (69; 88)	0.82	64 (46; 79)	98 (91; 100)	0.81
Flexor wrist tendons	55 (35; 73)	88 (78; 94)	0.72	45 (27; 65)	99 (92; 100)	0.72
Flexor MCP tendons	84 (69; 92)	89 (81; 94)	0.87	22 (11; 37)	100 (96; 100)	0.61
CSA-patients	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Synovitis	GS ≥1 (EULAR-OMERACT)			PD ≥1		
MCP joints	0 (0; 20)	100 (97; 100)	0.50	27 (11; 52)	97 (93; 99)	0.62
Wrist joints	13 (5; 32)	96 (90; 98)	0.55	17 (7; 37)	99 (94; 100)	0.58
MTP joints	46 (23; 71)	83 (77; 88)	0.65	38 (18; 64)	98 (95; 99)	0.68
Tenosynovitis	GS ≥1 (EULAR-OMERACT)			PD ≥1		
Extensor wrist tendons	50 (22; 78)	80 (72; 87)	0.65	38 (14; 69)	98 (94; 100)	0.68
Flexor wrist tendons	0 (0; 66)	97 (93; 99)	0.49	0 (0; 66)	100 (97; 100)	0.50
Flexor MCP tendons	50 (28; 72)	89 (83; 93)	0.69	13 (3; 36)	100 (97; 100)	0.56

Table 4.9: Test characteristics per joint for Grey-scale (EULAR-OMERACT definition) and power Doppler Ultrasound-detected synovitis with MRI as a reference

	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Synovitis	GS ≥1 (EULAR-OMERACT)			PD ≥1		
MCP joints						
MCP 2	50	100	0.75	63	96	0.77
	(29; 71)	(93; 100)		(41; 81)	(87; 99)	
MCP 3	40	96	0.68	56	96	0.76
	(20; 64)	(87; 99)		(33; 77)	(87; 99)	
MCP 4	20	97	0.58	36	97	0.67
	(6; 51)	(88; 99)		(15; 65)	(88; 99)	
MCP 5	38	100	0.69	50	100	0.75
	(14; 69)	(94; 100)		(24; 76)	(94; 100)	
Wrist joints						
Radio-ulnar	16	94	0.55	25	98	0.62
	(6; 38)	(84; 98)		(11; 47)	(90; 100)	
Radio-carpal	38	90	0.65	30	98	0.64
	(22; 57)	(78; 96)		(16; 48)	(88; 100)	
Inter-carpal	28	98	0.63	35	100	0.67
	(14; 48)	(88; 100)		(19; 54)	(92; 100)	
MTP joints						
MTP 1	88	62	0.75	50	98	0.74
	(64; 97)	(48; 74)		(28; 72)	(90; 100)	
MTP 2	70	66	0.68	20	100	0.60
	(40; 89)	(53; 77)		(6; 51)	(94; 100)	
MTP 3	80	82	0.81	40	100	0.70
	(38; 96)	(71; 90)		(12; 77)	(94; 100)	
MTP 4	100	93	0.97	50	100	0.75
	(51; 100)	(84; 97)		(15; 85)	(94; 100)	
MTP 5	44	95	0.70	44	95	0.70
	(19; 73)	(86; 98)		(19; 73)	(86; 98)	

Table 4.10: Test characteristics per joint for Grey-scale and power Doppler Ultrasound-detected tenosynovitis with MRI as a reference

	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Tenosynovitis	GS ≥1			Tenosynovitis PD ≥1		
MCP flexor tendons						
FD MCP 2	88	89	0.88	31	100	0.66
	(64; 97)	(78; 95)		(14; 56)	(93; 100)	
FD MCP 3	46	95	0.70	15	100	0.58
	(23; 71)	(86; 98)		(4; 42)	(94; 100)	
FD MCP 4	91	93	0.92	18	100	0.59
	(62; 98)	(84; 97)		(5; 48)	(94; 100)	
FD MCP 5	69	79	0.74	8	100	0.54
	(42; 87)	(67; 88)		(1; 33)	(94; 100)	
Flexor wrist tendons						
FDS/FDP	17	100	0.58	17	100	0.58
	(3; 56)	(94; 100)	0.58	(3; 56)	(94; 100)	
FPL	71	94	0.83	29	100	0.64
	(36; 92)	(85; 98)		(8; 64)	(94; 100)	
FCR	55	88	0.71	64	98	0.81
	(28; 79)	(77; 94)		(35; 85)	(91; 100)	
Extensor wrist tendons						
ECR	78	78	0.78	44	100	0.72
	(45; 94)	(66; 87)		(19; 73)	(94; 100)	
EDC/IP	70	83	0.77	50	100	0.75
	(40; 89)	(72; 91)		(24; 76)	(94; 100)	
ECU	76	79	0.78	71	94	0.82
	(53; 90)	(67; 88)		(47; 87)	(85; 98)	

Test characteristics are shown in percentages with a 95% CI except for the AUC, area under the receiver operating characteristic curve.
GS: Grey-scale; PD: Power Doppler; Extensor carpi radialis longus et brevis: ECR; Extensor digitorum communis and indices proprius: EDC/IP; Extensor carpi ulnaris: ECU; Flexor carpi radialis: FCR; Flexor pollicis longus: FPL; Flexor digitorum superficialis and profundus: FDS/FDP; flexor digitorum (FD) tendons 2-5 on the MCP-level.

Table 4.11: Grey-scale Ultrasound detected synovitis according to EULAR-OMERACT definition versus Szkudlarek on MCP joint level

MCP 2		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**31**	24	5	0
	1	0	**3**	5	0
	2	0	0	**0**	1
	3	0	0	0	**0**
MCP 3		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**40**	17	4	0
	1	0	**2**	1	1
	2	0	0	**2**	2
	3	0	0	0	**0**
MCP 4		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**50**	14	1	0
	1	1	**0**	1	0
	2	0	0	**1**	1
	3	0	0	0	**0**
MCP 5		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**49**	13	3	0
	1	0	**1**	1	0
	2	0	0	**0**	2
	3	0	0	0	**0**

Number of patients for each joint score according to Szkudlarek versus the EULAR/OMERACT revised score. Total number of patients was 70, but rarely a score was missing. GS: Grey-scale.

Table 4.12: Grey-scale Ultrasound detected synovitis (according to EULAR-OMERACT definition) versus Grey-scale Ultrasound detected synovitis (according to Szkudlarek) on wrist joint level

Radio-Ulnar		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**53**	10	0	0
	1	0	**3**	1	0
	2	0	0	**2**	0
	3	0	0	0	**0**
Radio-Carpal		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**21**	28	6	0
	1	0	**5**	7	0
	2	0	0	**1**	0
	3	0	0	0	**1**
Inter-Carpal		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**45**	14	2	0
	1	0	**1**	4	1
	2	0	0	**0**	2
	3	0	0	0	**0**

Table 4.13: Grey-scale Ultrasound detected synovitis according to EULAR-OMERACT definition versus Szkudlarek on MTP joint level

MTP 1		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**18**	16	0	0
	1	0	**18**	7	0
	2	0	0	**8**	0
	3	0	0	0	**0**
MTP 2		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**12**	28	1	0
	1	0	**13**	9	1
	2	0	0	**2**	1
	3	0	0	0	**0**
MTP 3		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**32**	20	0	0
	1	0	**8**	6	1
	2	0	0	**0**	0
	3	0	0	0	**0**
MTP 4		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**45**	11	2	0
	1	0	**2**	5	0
	2	0	0	**1**	0
	3	0	0	0	**0**
MTP 5		GS according to Szkudlarek			
		0	1	2	3
GS according to EULAR-OMERACT	0	**49**	8	3	0
	1	0	**2**	4	1
	2	0	0	**0**	0
	3	0	0	0	**0**

5

Improving the feasibility of MRI in clinically suspect arthralgia for prediction of rheumatoid arthritis by omitting scanning of the feet

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Abstract

Background

The use of MR-imaging is recommended for the early detection of Rheumatoid Arthritis (RA). Next to the small joints of the hands, foot-joints are often involved. Therefore, imaging inflammation of the feet in addition to hands may be informative, but prolongs scan-time and leads to additional costs. We studied the value of MRI of the feet alone and complementary to MRI of the hands in patients with Clinically Suspect Arthralgia (CSA).

Methods

357 consecutively included CSA-patients underwent contrast-enhanced 1.5T-MRI of hand (MCP2-5 and wrist) and foot (MTP1-5)-joints at baseline. Scans were scored for synovitis, osteitis and tenosynovitis. After ≥1 year follow-up, the development of clinically apparent inflammatory arthritis (IA) was studied. Cox regression was performed and test characteristics were evaluated. Sensitivity analyses were performed for the outcome RA-development (2010-criteria).

Results

MRI-detected tenosynovitis of the feet was associated with IA development, independently from synovitis and osteitis HR (95%CI) 4.75 (2.38;9.49), and independently from ACPA and CRP, HR 3.13 (1.48;6.64). From all CSA-patients, 11% had inflammation in hands and feet, 29% only in hands, and 3% only in feet. In line with this finding, the addition of MRI-feet to MRI-hands did not increase the predictive accuracy; the sensitivity remained 77%, while the specificity decreased from 66% to 62%. Sensitivity analyses with RA-development as outcome showed similar results.

Conclusion

Tenosynovitis at the forefeet in CSA predicted IA- and RA-development. Addition of foot-MRI to hand-MRI did not increase the accuracy. Foot-MRI can be omitted to reduce scan time and costs and increase the feasibility.

Introduction

In Rheumatoid Arthritis (RA), imaging is recommended to aid the diagnostic process in case of doubt on the diagnosis.[1] Although treatment recommendations generally focus on the role of imaging in patients with clinically evident arthritis, several studies have shown that imaging can also be helpful in patients with symptoms at risk for RA which are in a pre-arthritis phase due to the detection of MRI-detected subclinical joint inflammation.[2, 3] MRI in particular has shown to be sensitive and predictive in this setting, but is also costly. Thus far it is unknown if scan-time and costs can be reduced by omitting the feet and scanning the hands only in these patients.

Patients with Clinically Suspect Arthralgia (CSA) are identified based on their clinical presentation.[4, 5] Presence of CSA is associated with a risk of RA-development of 18-20% in the next year. Results of additional investigations are required to arrive at higher positive predictive values. It has been shown in CSA-patients, that presence of MRI-detected subclinical inflammation (i.e. presence of synovitis, osteitis, tenosynovitis more than observed in the general population of the same age) in hands or feet increased the risk of RA-development to ~35%.[2]

While imaging was recommended by a EULAR-taskforce in the diagnostic process of RA,[1] it was not specified which joints should be imaged. The small joints of the feet are preferential locations of early RA and also in the phase of CSA.[6] [6]. Consequently, previous MRI-studies in CSA scanned both extremities (hands and feet). However, there is no data whether scanning the feet in addition to the hands truly increases the prognostic accuracy of MRI, whilst due to repositioning it considerably increases scan time and thereby costs. Therefore this study evaluated if MRI-detected inflammation of the feet had additional value to the hands in the early detection of patients at risk for RA-development.

Methods

CSA cohort

The Leiden CSA-cohort is a population-based inception cohort with the aim of studying the symptomatic phase of RA that precedes clinical arthritis. Inclusion required presence of arthralgia of small joints for <1 year which was, because of the character of the symptoms, considered as being suspect to progress to RA by a rheumatologist.[2] Its design is described elsewhere and supplementary.[2] The CSA-cohort started before the EULAR-definition for CSA was developed.[5] The requirements for this definition were recorded but were not required to be included in the CSA-cohort.

The study was approved by the local Medical Ethical Committee. All participants signed for informed consent.

Patient selection

Consecutively included patients between April-2012 and October-2017 in the CSA-cohort that had ≥1 year follow-up (to allow time for IA-development) were selected. This

concerned 539 patients. A flowchart of the patient selection is provided (supplementary Figure 5.1). Patients without an MRI were excluded (n=32), but baseline characteristics of patients with and without MRI did not differ (Table 5.3). Furthermore, 73 patients were excluded because of participation in a placebo-controlled double-blind randomized trial (Treat Earlier (TE), trial registration number: NTR4853), because of a 50% chance on treatment with Methotrexate, as described supplementary. Finally, 357 patients were studied.

MRI and scoring

To measure MRI-detected subclinical joint inflammation, contrast-enhanced MRI-scans of MCP(2-5)-, wrist- and MTP(1-5)-joints were made of the most affected side (or dominant side in case of equally severe symptoms) on an MSK Extreme 1.5T-extremity MR-system (GE, Wisconsin). NSAIDs were stopped 24hrs before the MRI-scan. Scans were scored for MRI-detected inflammation in line with the OMERACT RAMRIS-method as described supplementary and previously published.[2, 6]

Any MRI-detected inflammation was determined by summing synovitis, bone marrow oedema (BMO or osteitis) and tenosynovitis scores. Scans were scored by two independent readers. Inter- and intra-reader intraclass correlation coefficients were ≥0.91 and ≥0.92, respectively (supplementary Table 5.4). Mean MRI-scores of both readers were calculated to obtain the total inflammation score (see supplementary methods). MRI-scores were dichotomized as described previously.[7] They were considered positive, if inflammation was scored by both readers and present in <5% of age-matched healthy volunteers.[7]

Outcomes

Patients were followed on IA-development, confirmed as joint swelling at physical examination by a rheumatologist. The secondary outcome, fulfilment of the 2010-criteria was also assessed.

Analyses

Associations were tested with Cox proportional-hazards regression using all available follow-up data. Multivariable analyses were adjusted for all types of local inflammation, and thereafter also for ACPA/RF-positivity and elevated CRP. Test characteristics, predictive accuracies with corresponding 95% confidence intervals (95%CI) were assessed at 1-year follow-up. The added value was determined by comparing these values with and without scanning of the feet and by net reclassification indices (NRI).

Several sub-analyses were performed. First, analyses were repeated with RA-development as outcome. Second, analyses were performed in the subset of CSA-patients that fulfilled the EULAR-definition; it has been shown that this is a slightly more homogeneous set of patients.[5, 8] Third, the additive value of the feet to the hand was evaluated without considering MTP1, as MTP1 is a preferential location for inflammation due to other causes such as degeneration or osteoarthritis. Although patients were included because of a clinical suspicion of imminent RA and evident

other explanations for the joints symptoms (such as evident osteoarthritis) precluded the presence of CSA and were not studied, in sub-analyses data of MTP-1 was excluded to investigate if the results obtained were driven by eventual concomitant presence of other causes of inflammation in MTP1. Finally, the analyses were repeated with a restricted inclusion period (April 2012-April 2015). In these analysis all patients that were included at the time the randomized placebo-controlled trial was running, were excluded. CSA-patients with a positive MRI for inflammation were eligible; hence in this time period part of the patients with MRI-detected subclinical inflammation were excluded from the present study. Thus, to evaluate if the results of the total group were influenced, results were compared to a subgroup of patients that were included before the trial was running.

IBM SPSS v24 was used and p-values <0.05 were considered statistically significant.

Results

Patient characteristics

Patients with CSA had a mean age of 44 years, were female in 78%; further characteristics are shown in supplementary table 5.5. Any subclinical MRI-detected inflammation in hands or feet was present in 43%. In more detail, 11% of CSA-patients had any MRI-detected inflammation in hands and feet, 29% only in hands, and 3% only in feet. Thus, sole inflammation of the feet was infrequent (supplementary Figure 5.2).

Associations between MRI-detected inflammation of feet and hands separately and IA-development

For the feet, the highest association with IA-development was observed with MRI-detected tenosynovitis (HR (95%CI) 6.64 (3.79;1.63), Table 1). This association remained present in multivariable analyses after adjustment for osteitis and synovitis, HR 4.75 (2.38;9.49) and also after additional adjustments for ACPA- and/or RF-positivity and elevated CRP, HR 3.14 (1.48;6.64).

Similar findings were obtained for the hands. The highest association was found with MRI-detected tenosynovitis (HR 6.59 (3.92;11.08) in univariable analyses. The HR was 6.16 (3.58;10.62) after adjusting for osteitis, synovitis and 5.36 (3.07;9.37) after also adjusting for ACPA/RF and CRP (Table 5.1).

Thus, in both joint-groups (hands and feet), tenosynovitis was associated with IA-development, independently of other MRI-detected inflammation features and clinical factors.

Test characteristics of MRI-detected inflammation of the feet, the hands and combined

MRI-detected tenosynovitis in the feet had a sensitivity of 29% and specificity of 95%; the AUC was 0.62. Any MRI-detected inflammation of the feet had a sensitivity of 38%, a specificity of 89% and AUC of 0.64. The moderate-low sensitivity reflects that CSA-patients that developed IA often did not present with subclinical inflammation at the

Table 5.1: Associations with inflammatory arthritis development

	All patients (n=357)		Arthritis (n=63)		No Arthritis (n=294)		HR, a (95%CI)	P-value	HR, b (95%CI)	P-value	HR, c (95%CI)	P-value
MRI features												
Feet (MTP1-5)												
Tenosynovitis, n (%)	29	(8)	17	(27)	12	(4)	6.64 (1.63; 3.79)	<0.001	4..75 (2.38; 9.49)	<0.001	3.14 (1.48; 6.64)	0.003
Synovitis, n (%)	34	(10)	16	(25)	18	(6)	4.46 (0.88; 2.53)	<0.001	2.48 (1.18; 5.23)	0.017	2.15 (0.98; 4.68)	0.06
BMO, n (%)	21	(6)	7	(11)	14	(5)	2.57 (1.17; 5.64)	0.019	0.66 (0.23; 1.69)	0.38	0.67 (0.25; 1.76)	0.41
Hands (MCP2-5 and wrist)												
Tenosynovitis, n (%)	95	(27)	41	(65)	54	(18)	6.59 (3.92; 11.08)	<0.001	6.16 (3.58; 10.62)	<0.001	5.36 (3.07; 9.37)	<0.001
Synovitis, n (%)	60	(17)	19	(30)	41	(14)	2.35 (1.37; 4.02)	0.002	1.06 (0.60; 1.87)	0.85	1.12 (0.63; 2.01)	0.69
BMO, n (%)	57	(16)	18	(29)	39	(13)	2.39 (1.39; 4.14)	0.002	1.94 (1.11; 3.38)	0.019	2.33 (1.31; 4.14)	0.004
Clinical features												
Elevated CRP, n (%)	71	(21)	21	(33)	50	(18)	2.22 (1.31; 3.75)	0.003				
ACPA and/or RF positive, n (%)	69	(21)	30	(48)	39	(14)	4.37 (2.65; 7.19)	<0.001				

a: HR of univariable analyses. b: HR of multivariable analyses; multivariable analyses were performed for the MTP, MCP and wrist separately. c: Multivariable analyses including also CRP, positivity for ACPA and/or RF.

feet-joints.

For the hands, tenosynovitis had a sensitivity of 65% and specificity of 80%, the AUC was 0.73. Any MRI-detected inflammation had a sensitivity of 77%, specificity of 66% and AUC of 0.71.

Assessing both hands and feet for tenosynovitis resulted in a sensitivity of 67%, specificity of 79% and AUC of 0.73. Thus, these test characteristics were comparable to those of MRI of the hands alone. Also when any MRI-detected inflammation was assessed, no improved test characteristics were observed. Assessing hands and feet had a sensitivity of 77% and specificity of 62% and the AUC was 0.69, which were not better than those of scanning the hands alone (Table 5.2).

Net reclassification index

The NRI when assessing tenosynovitis of hands only versus hands- and feet-MRI was 0.6%. When assessing 'any MRI-detected inflammation' the NRI was -3.9%. Thus also with this method, no benefit of adding feet-MRI to the hands was demonstrated.

Sub-analyses

Analyses were repeated with RA-development as outcome (Table 5.6). Similar findings were obtained for associations (Table 5.7) and characteristics (Table 5.8). Sensitivity analyses were also performed in CSA-patients that also fulfilled the EULAR-definition (Table S8, *online available*); these results were also similar to the main findings, for associations (Table S8, *online available*) and test characteristics (Table S9, *online available*). We repeated the analyses on the added value of foot-MRI to hand-MRI while excluding MTP1. Again, test characteristics of hands and feet were not superior to those of hand alone (Table S10, *online available*). The NRI was -2.6%.

Finally, the test characteristics were determined in the part of the cohort that was collected before the start of the placebo-controlled double-blind trial, thus before part of the patient with subclinical inflammation were excluded from the present study; similar findings were obtained (Table S11, *online available*).

Discussion

This longitudinal MRI-study in patients with CSA assessed the predictive value of MRI of the feet alone as well as the additional value of the foot-MRI to hand-MRI for predicting IA- or RA-development. We observed that tenosynovitis at the MTPs was independently predictive for RA-development. However, also for the hands tenosynovitis was predictive and adding foot- to hand-MRI did not result in an increased predictive accuracy, either when tenosynovitis or any MRI-detected inflammation was assessed. This can presumably be explained by the low percentage of patients that had inflammation of the feet but not at the hands (3%).

Previous studies in CSA scanned hands and feet and did not assess them separately.

Table 5.2: Test characteristics of subclinical inflammation and inflammatory arthritis development within 1 year

	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Feet (MTP 1-5)						
Tenosynovitis	29	95	52	89	86	0.62
	(18; 42)	(92; 97)	(34; 69)	(85; 92)	(82; 89)	
Synovitis	37	83	26	88	76	0.60
	(25; 50)	(78; 86)	(18; 38)	(84; 92)	(71; 80)	
BMO	27	85	24	87	77	0.56
	(17; 40)	(81; 89)	(15; 36)	(83; 91)	(72; 81)	
Any inflammation	38	89	38	89	82	0.64
	(26; 52)	(85; 92)	(26; 51)	(86; 92)	(77; 85)	
Hands (MCP 2-5, wrist)						
Tenosynovitis	65	80	36	93	78	0.73
	(52; 77)	(75; 84)	(27; 46)	(89; 96)	(73; 82)	
Synovitis	29	85	25	88	77	0.57
	(18; 42)	(81; 89)	(16; 37)	(83; 91)	(72; 81)	
BMO	29	86	26	88	78	0.58
	(18; 42)	(82; 90)	(17; 39)	(83; 91)	(73; 82)	
Any inflammation	77	66	28	94	68	0.71
	(64; 86)	(60; 71)	(21; 36)	(90; 97)	(62; 72)	
Hands and feet						
Tenosynovitis	67	79	35	93	77	0.73
	(54; 78)	(74; 83)	(26; 45)	(90; 96)	(72; 81)	
Synovitis	42	81	28	89	76	0.62
	(30; 56)	(77; 85)	(19; 39)	(85; 92)	(71; 80)	
BMO	48	64	18	88	61	0.56
	(35; 61)	(58; 69)	(13; 26)	(83; 91)	(56; 66)	
Any inflammation	77	62	26	94	64	0.69
	(64; 86)	(56; 67)	(19; 33)	(90; 97)	(59; 69)	

Test characteristics and their corresponding 95% intervals are shown. All values are percentages, except for the AUC.

Furthermore, in these studies synovitis and osteitis were scored in hands and feet but tenosynovitis was scored in the hands only.[2, 9, 10] Thus the previous finding that tenosynovitis in CSA was predictive for RA-development concerned only tenosynovitis of the hands.[2, 11] The current study is the first in CSA to demonstrate that tenosynovitis of the feet predicts RA-development.[2]

We did not examine the value of MRI-detected erosions, and focussed solely on MRI-detected inflammation. The value of MRI-detected erosions was studied recently, and it was shown that MRI-detected erosions in hand and feet were not predictive of RA development in patients with CSA.[12]

Several studies on MRI in arthralgia or early arthritis, scanned the hands but not the feet. Some studies did scan the feet but did not explore the value of the feet.[2, 6, 9, 10, 13–16] Therefore the (additional) value of the feet is largely unknown. One recent study did explore the added value of foot MRI to hand MRI in patients presenting with UA.[17] Also here, the predictive accuracy did not increase when data of the feet were added to the hands, which are in line with the present results obtained in the phase of CSA.

The added value was determined by comparing test characteristics and using the NRI. Similar conclusions were drawn by both methods, which illustrates the robustness of the findings. Also the fact that current results in CSA are similar to previous findings obtained in UA strengthen the notion that scanning of the feet can be omitted when the hands are imaged for the early detection of RA.[17]

In the present study, a contrast-enhanced 1.5T-MRI was used. The implications of our findings are presumably also relevant for other field-strength MRI-machines, such as 3T-MRI, as also here repositioning is required for the feet.

We are aware of the fact that the OMERACT-RAMRIS was not developed for diagnostic purposes, but for outcome measures in clinical trials. This is a limitation, but no other validated method is available. Because scoring according to OMERACT is time-consuming, other evaluation methods might be required to facilitate MRI-reading for diagnostic purposes. Based on the present results, if such methods would be developed this could restrict to hand-joints.

In conclusion, the current study showed the prognostic value of MRI-detected tenosynovitis of the feet in patients with arthralgia at risk for RA. Further, although MRI-detected tenosynovitis was associated with IA-development, addition of foot-MRI to hand-MRI did not increase the predictive accuracy. Therefore, in light of time management and cost efficiency, MRI of the feet can be omitted.

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Supplementary data

Supplementary methods and all supplementary tables are available at *Rheumatology (Oxford) Online.*

Supplementary figures

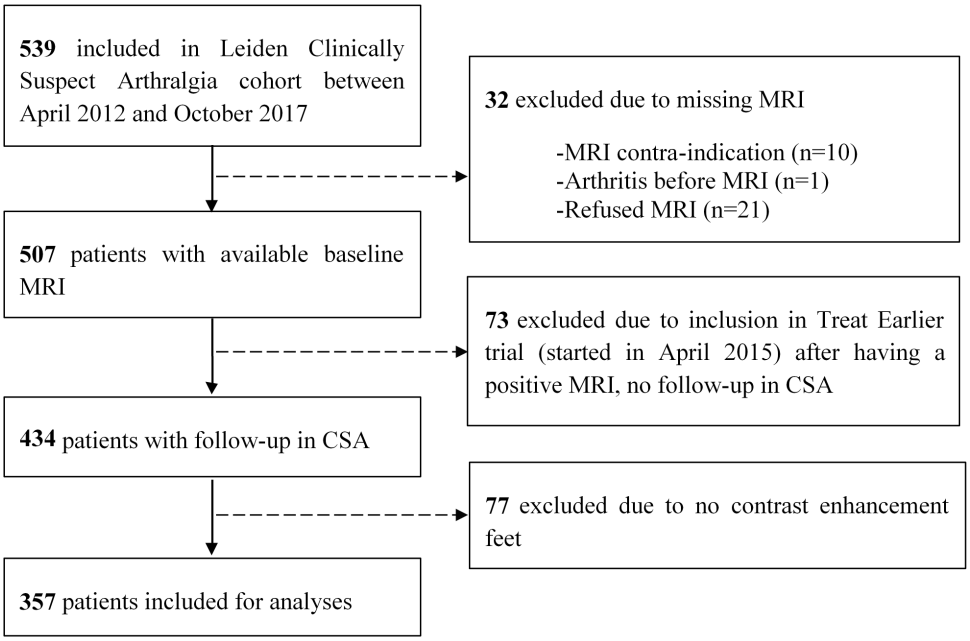

Figure 5.1: Flowchart of patient inclusion

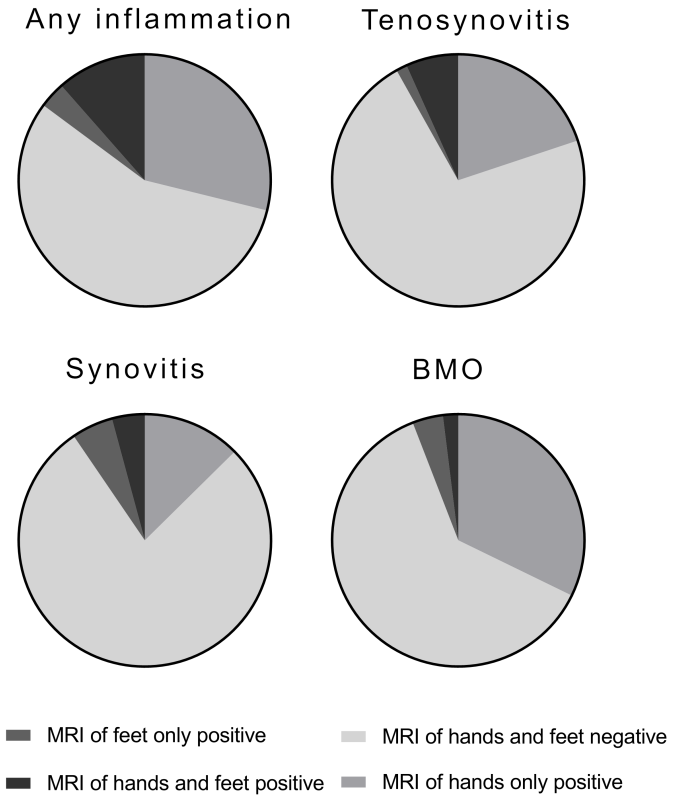

Figure 5.2: Proportions of CSA-patients with and without (A) any MRI-detected inflammation and (B) tenosynovitis (C) synovitis and (D) BMO.

Supplementary tables

Table 5.3: Baseline characteristics of patients with and without an MRI

	With available MRI (n=502)	Without available MRI (n=32)	P-value
Age, mean (SD)	44 (13)	43 (12)	0.60
Female, n (%)	382 (75)	26 (81)	0.45
68-Tender joint count, median (IQR)	5 (2-10)	5 (2-8)	0.85
CRP (mg/L), median (IQR)	112 (23)	8 (26)	0.72
RF positive (≥3.5 IU/mL), n (%)	96 (20)	8 (27)	0.39
ACPA positive (≥7 U/mL), n (%)	64 (13)	5 (17)	0.61
Either RF or ACPA positive, n (%)	110 (23)	9 (30)	0.38

ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

Table 5.4: MRI scans of CSA-patients were scored by two readers according to the RAMRIS

Inter-reader intraclass correlation coefficients

	1	2	3	4	5	6	7	8	9
1	x	0.97	0.97	0.98	0.97	0.96	0.95	0.97	0.93
2	0.97	x	0.99	0.95	0.94	0.95	0.94	0.96	0.93
3	0.97	0.99	x	0.95	0.95	0.95	0.96	0.96	0.94
4	0.98	0.95	0.95	x	0.97	0.96	0.94	0.95	0.91
5	0.97	0.94	0.95	0.97	x	0.95	0.94	0.95	0.92
6	0.97	0.95	0.95	0.96	0.95	x	0.95	0.96	0.95
7	0.95	0.94	0.96	0.94	0.94	0.95	x	0.98	0.98
8	0.97	0.96	0.96	0.95	0.95	0.96	0.98	x	0.96
9	0.93	0.93	0.94	0.91	0.92	0.95	0.98	0.96	x

Intra-reader intraclass correlation coefficients

1	2	3	4	5	6	7	8	9
0.99	0.98	0.94	0.92	0.96	0.94	0.98	0.99	0.96

A total of nine readers scored MRI scans and different combinations of readers were used. All readers were trained in the same way, and inter-reader intraclass correlation coefficients (ICC) were ≥0.91. All intra-reader ICCs were ≥0.92.

Table 5.5: Baseline characteristics of CSA-patients studied

	All CSA-patients (n=357)		Arthritis (n=63)		No Arthritis (n=294)		P-value
Age, mean (SD)	44	(12)	46	(14)	43	(12)	0.11
Female, n (%)	280	(78)	44	(70)	236	(80)	0.07
68-Tender joint count, median (IQR)	5	(2-10)	5	(2-9)	5	(2-11)	0.63
Symptom duration weeks, median (IQR)	19	(9-40)	21	(8-42)	19	(10-40)	0.92
CRP increased (≥5mg/L), n (%)	71	(21)	21	(33)	50	(18)	0.007
RF positive (≥3.5 IU/mL), n (%)	61	(18)	28	(45)	33	(12)	<0.001
ACPA positive (≥7 U/mL), n (%)	41	(12)	25	(40)	16	(6)	<0.001
RF and/or ACPA positive, n(%)	69	(21)	30	(48)	39	(14)	<0.001
Presence of subclinical inflammation, n (%)	155	(43)	49	(78)	106	(36)	<0.001
MRI features							
Feet							
Tenosynovitis, mean (SD)	0.1	(0.6)	0.4	(0.8)	0.1	(0.5)	<0.001
Synovitis, mean (SD)	0.3	(0.7)	0.7	(1.2)	0.2	(0.5)	0.001
BMO, mean (SD)	0.2	(0.7)	0.4	(1.0)	0.2	(0.5)	0.14
Hands							
Tenosynovitis, mean (SD)	0.9	(1.3)	2.3	(2.8)	0.6	(1.7)	<0.001
Synovitis, mean (SD)	1.0	(1.7)	1.9	(2.3)	0.8	(1.4)	<0.001
BMO, mean (SD)	0.6	(1.3)	1.0	(2.0)	0.5	(1.0)	0.13

ACPA: anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF:immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP:c-reactive protein (positive if ≥5mg/L); SD: standard deviation; IQR: Inter quartile range.

Table 5.6: Baseline characteristics of CSA-patients that did and did not progress to RA (2010 ACR/EULAR-classification criteria)

	RA (n=38)		No RA (n=319)		P-value
Age, mean (SD)	48	(14)	43	(12)	0.030
Female, n (%)	25	(66)	255	(80)	0.045
68-Tender joint count, median (IQR)	4	(2-8)	5	(2-11)	0.13
Symptom duration in weeks, median (IQR)	23	(8-47)	19	(10-40)	0.75
CRP increased (≥5mg/L), n (%)	15	(40)	56	(19)	0.003
RF positive (≥3.5 IU/mL), n (%)	27	(73)	34	(11)	<0.001
ACPA positive (≥7 U/mL), n (%)	25	(68)	16	(5)	<0.001
RF and/or ACPA positive	29	(78)	40	(13)	<0.001
Presence of subclinical inflammation, n (%)	32	(84)	123	(39)	<0.001

ACPA: anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF:immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP:c-reactive protein (positive if ≥5mg/L); SD: standard deviation; IQR: Inter quartile range.

Table 5.7: Associations between presence of subclinical inflammation and RA-development (2010-classification criteria)

	All patients (n=357)		RA (n=38)		No RA (n=319)		HR, a (95%CI)	P-value	HR, b (95%CI)	P-value	HR, c (95%CI)	P-value
MRI features												
Feet (MTP1-5)												
Tenosynovitis, n (%)	29	(8)	13	(34)	16	(5)	8.71 (4.43; 17.12)	<0.001	5.30 (2.20; 12.78)	<0.001	2.46 (0.90; 6.77)	0.08
Synovitis, n (%)	34	(10)	12	(32)	22	(7)	5.83 (2.93; 11.59)	<0.001	2.35 (0.88; 6.26)	0.09	1.62 (0.55; 4.77)	0.38
BMO, n (%)	21	(6)	7	(18)	14	(4)	4.55 (2.00; 10.34)	<0.001	1.10 (0.38; 3.20)	0.86	1.17 (0.36; 3.75)	0.80
Hands (MCP2-5 and wrist)												
Tenosynovitis, n (%)	95	(27)	28	(74)	67	(21)	9.56 (4.64; 19.71)	<0.001	9.42 (4.45; 19.94)	<0.001	6.64 (3.03; 14.53)	<0.001
Synovitis, n (%)	60	(17)	11	(29)	49	(15)	2.20 (1.09; 4.44)	0.027	0.87 (0.42; 1.81)	0.71	1.02 (0.46; 2.26)	0.96
BMO, n (%)	57	(16)	11	(29)	46	(14)	2.43 (1.20; 4.90)	0.013	1.94 (0.95; 3.96)	0.07	2.28 (1.03; 5.08)	0.043
Clinical features												
Elevated CRP, n (%)	71	(21)	15	(39)	56	(18)	2.85 (1.49; 5.46)	0.002				
ACPA and/or RF positive, n (%)	69	(21)	29	(78)	40	(13)	16.59 (7.58; 36.33)	<0.001				

a:HR of univariable analyses. b:HR of multivariable analyses; multivariable analyses were performed for the MTP, MCP and wrist separately. c:Multivariable analyses including also CRP, positivity for ACPA and/or RF.

Table 5.8: Test characteristics of subclinical inflammation and RA-development (2010-classification criteria) within the first year as outcome

	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Feet (MTP 1-5)						
Tenosynovitis	38	95	41	94	90	0.66
	(23; 55)	(92; 97)	(26; 59)	(91; 96)	(86; 92)	
Synovitis	34	93	32	93	88	0.64
	(20; 52)	(90; 95)	(19; 49)	(90; 96)	(84; 91)	
BMO	22	96	33	93	89	0.59
	(11; 39)	(93; 97)	(17; 55)	(89; 95)	(85; 92)	
Any inflammation	47	88	28	94	85	0.68
	(31; 64)	(84; 91)	(18; 42)	(91; 96)	(80; 88)	
Hands (MCP 2-5 and wrist)						
Tenosynovitis	75	78	25	97	78	0.77
	(58; 87)	(73; 82)	(18; 35)	(94; 98)	(73; 82)	
Synovitis	28	84	15	92	79	0.56
	(16; 45)	(80; 88)	(8; 26)	(89; 95)	(75; 83)	
BMO	31	86	18	93	81	0.58
	(18; 49)	(81; 89)	(10; 29)	(89; 95)	(76; 84)	
Any inflammation	84	64	19	98	66	0.74
	(68; 93)	(59; 69)	(13; 26)	(95; 99)	(61; 71)	
Hands and feet						
Tenosynovitis	75	78	25	97	78	0.77
(58; 87)	(73; 82)	(18; 35)	(94; 98)	(73; 82)		
Synovitis	28	84	15	92	79	0.56
	(16; 45)	(80; 88)	(8; 26)	(89; 95)	(75; 83)	
BMO	31	86	18	93	81	0.58
	(18; 49)	(81; 89)	(10; 29)	(89; 95)	(76; 84)	
Any inflammation	84	60	17	98	62	0.72
	(68; 93)	(55; 65)	(12; 24)	(94; 99)	(57; 67)	

Test characteristics and their corresponding 95% intervals are shown. All values are percentages, except for the AUC.

II

Impact on daily life

6

Is ACPA-Positive Rheumatoid Arthritis Still a More Severe Disease Than ACPA-Negative Rheumatoid Arthritis? A Longitudinal Cohort Study in Rheumatoid Arthritis Patients Diagnosed From 2000 Onward

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Abstract

Objective

Because of its association with joint destruction, anti-citrullinated protein antibody (ACPA)-positive rheumatoid arthritis (RA) is considered to be more severe than ACPA-negative RA. Clinically relevant joint destruction is now infrequent thanks to adequate disease suppression. According to patients, important outcomes are pain, fatigue, and independence. We evaluated whether ACPA-positive RA patients diagnosed during or after 2000 have more severe self-reported limitations and impairments, including restrictions at work, than ACPA-negative RA patients.

Methods

A total of 492 ACPA-positive and 450 ACPA-negative RA patients who fulfilled the 2010 criteria and were included in the Leiden Early Arthritis Clinic cohort during or after 2000 were compared for self-reported pain, fatigue, disease activity, general well-being (measured by numerical rating scales), physical function (measured by the Health Assessment Questionnaire), and work restrictions, including absenteeism at baseline and during the 4-year follow-up. Linear mixed models were used.

Results

At disease presentation, ACPA-negative patients had more severe pain, fatigue, self-reported disease activity scores, and functional disability ($p<0.05$), although absolute differences were small. During follow-up, ACPA-negative patients remained somewhat more fatigued ($p=0.002$), whereas other patient-reported impairments and limitations were similar. Thirty-eight percent of ACPA-negative and 48% of ACPA-positive patients reported absenteeism ($p=0.30$), with median 4 days missed in both groups in the last 3 months. Also, restrictions at work among employed patients and restrictions with household work were not statistically different at baseline and during follow-up.

Conclusion

In current rheumatology practice, ACPA-positive RA is not more severe than ACPA-negative RA in terms of patients' relevant outcomes, including physical functioning and restrictions at work. This implies that efforts to further improve the disease course should be proportional to both disease subsets.

Introduction

Anti-citrullinated protein antibody (ACPA)-positive and ACPA-negative rheumatoid arthritis (RA) patients are considered as having different disease entities with differences in etiopathology, as both subsets have differences in genetic and environmental risk factors.[1] ACPA-positive RA has always been considered as a more severe subset of RA, as the presence of ACPA is associated with more severe joint destruction and a higher mortality rate.[2–4]

During the last decade treatment strategies have improved, and earlier treatment initiation and treat-to-target approaches have resulted in better disease outcomes.[5] Especially from the year 2000 onward, early treatment with methotrexate (MTX) has become key and, at present, clinically relevant joint destruction has become infrequent.[6–10] In addition, RA patients no longer have an evidently increased mortality rate.[11–13] Therefore, these traditional outcomes of RA have become less important. This leads to the consideration of what should be the current essential disease outcomes.

A recent study emphasized determining these outcomes, and according to patients, the important outcomes are pain, fatigue, and independence.[14] Independence strongly relates to physical functioning and the ability to perform one's tasks at home and at work.[15] It is still unknown if ACPA-positive patients in current rheumatology practice have a worse disease than ACPA-negative RA patients, as evaluated with the abovementioned patient-reported outcomes (PROs). Therefore, this study assessed, in RA patients who were diagnosed from 2000 onward and were treated with up-to-date treatment strategies, whether ACPA-positive patients have more severe PROs, including functional disability and work restrictions, than ACPA-negative RA patients.

Patients and methods

Longitudinal cohort

Patients were included in the Leiden Early Arthritis Clinic (EAC) cohort, a population-based inception cohort in The Netherlands that started in 1993. Inclusion required the presence of arthritis confirmed at physical examination and symptom duration <2 years. Baseline visit was at first presentation of arthritis at the outpatient clinic. Follow-up visits were performed yearly with questionnaires, 66 swollen (SJC66) and 68 tender joint counts (TJC68), and laboratory investigations (including C-reactive protein (CRP)-level; immunoglobulin M-rheumatoid factor (RF, positive if ≥3.5 IU/ml); and ACPA, anti-cyclic citrullinated peptide (anti-CCP2), Eurodiagnostica, positive if ≥25 U/ml; from 2009 EliA CCP, Phadia, positive if ≥7 U/ml), as described in detail elsewhere.[16] For the present study, RA patients included in the Leiden EAC cohort during or after 2000 were analyzed. Patients were treated according to routine care. According to local and national protocols, patients were treated initially with MTX; in case of failure a second conventional disease-modifying antirheumatic drug (DMARD) was started or added, and in case of subsequent failure a biologic DMARD was allowed. The strategy of treatment adjustment changed over time, as in our hospital Disease Activity Score

(DAS)-steered treatment adjustments became standard as of 2005.[17, 18]

To measure experienced pain, fatigue, disease activity, and general well-being, patients were asked by trained research nurses to indicate on single-item numerical rating scales (NRS), ranging from 0 (no symptoms) to 10 (extreme symptoms), the grade that best reflected how they felt affected by arthritis during the last 24 hours. To measure limitations in physical functioning, the multi-item Health Assessment Questionnaire (HAQ), expressed as a disability index (DI) from 0 (no disability) to 3 (severe disability), was used. A questionnaire on work ability was added to the study protocol in 2010. It contained questions from 1) the RA-specific Work Productivity Survey, addressing work status and type of work; 2) the Work Productivity and Activity Impairment Rheumatoid Arthritis questionnaire, assessing influence of disease on productivity at a paid job (presenteeism) or during nonpaid work in the past 7 days, ranging from 0 (no restrictions) to 10 (severe restrictions); and 3) additional questions on the number of days patients had worked with these restrictions in the past 7 days, as well as work days absent in the past 3 months (see Supplementary Table 6.3).

Among employed patients at baseline, we analyzed absenteeism and the number of patients that reported absenteeism; we also analyzed presenteeism (level of restrictions at work) and the number of days employed patients had worked with restrictions in the last week due to arthritis, as well as restrictions with household activities for all patients. Data were gathered at baseline and at the yearly follow-up visits. Written informed consent was obtained from all patients. The study was approved by the local medical ethics committee.

Patient selection

From all early arthritis patients included between 1993 and 2016 (n=3,722), 2,615 were included during or after 2000; of these, 982 fulfilled the 2010 classification criteria for RA at baseline [19] (see Supplementary Figure 6.5).

RA patients with missing ACPA status were excluded (n = 40); they did not differ in age, sex, SJC66, CRP level, RF positivity, or symptom duration from patients with available ACPA data (see Table S2, *online available*). In total, 450 ACPA-negative and 492 ACPA-positive patients were studied. To evaluate whether the choice of classification criteria affected the results, analyses were repeated with RA defined as fulfilling the 1987 criteria.[20] Of the 2,615 patients included from 2000 onward, 563 fulfilled the 1987 criteria at baseline (225 ACPA-negative patients, 338 ACPA-positive patients). A portion of the patients that fulfilled the 1987 criteria did not fulfill the 2010 criteria and vice versa.

Since the introduction of the questionnaire on work ability in 2010, 130 ACPA-negative and 152 ACPA-positive RA patients fulfilling the 2010 criteria were included (see Supplementary Figure 6.5). Of these 282 patients, 24 ACPA-negative and 36 ACPA-positive patients did not fill in the work ability questionnaire at baseline. These 60 patients did not differ in age, sex, symptom duration, SJC66, CRP level, or RF positivity

from those who did complete the work ability questionnaire (see Table S3, available on the Arthritis Care & Research web site). The addition of this questionnaire later in the study does not cause a bias, as missingness is completely at random.

Statistical analyses

We presented median levels and corresponding interquartile ranges. Baseline data were analyzed with a t-test, the Mann-Whitney U test, and chi-square test as appropriate.

For longitudinal analyses between ACPA-negative and ACPA-positive patients, linear mixed models were used. Although PROs were non-normally distributed, the residuals were normally distributed and thus fulfilled the requirement for linear mixed models. Patients were censored after 4 years of follow-up because the number of patients with follow-up longer than this period decreased. No random effects were added to the model.[21, 22] This model has the advantage that all patient information, including those who had missing data of PROs, was used, as it assumes that missing outcomes can be estimated using available measurements. Also, to prevent bias due to selective dropout of patients, we did not apply a minimum follow-up duration for inclusion in the analyses. To determine the best-fitting covariance matrix, the matrices available in SPSS were considered. Akaike information criterion was used to measure the goodness-of-fit, as this was best for the compound symmetry matrix. We obtained estimates of the main effect of ACPAs. Because the target variables are known to vary with age and sex, adjustments were made in all longitudinal analyses. For PROs of impairments and limitations, adjustments for the year of inclusion were also made.[23–25] In analyses, median values of estimated coefficients of the longitudinal analyses are shown. IBM SPSS, version 23, was used, and values less than 0.05 were considered significant.

Sensitivity analyses

In sensitivity analyses, it was first evaluated whether results would be different when ACPA-negative and RF-negative patients were compared to patients with positive ACPA and/or RF, as part of the ACPA-negative patients were RF positive. Second, analyses were repeated in patients that were included during or after 2005. This was done as this study aimed to evaluate patients who were treated according to current treatment strategies. Although an early start of MTX was common from 2000 onward, DAS-steered treatment adjustments became fully integrated in daily practice in our hospital from 2005 onward.[18]

Finally, as a reference showing that patients treated according to up-to-date treatment strategies were different from patients who were treated in the past, we performed similar analyses for patients who were included in the EAC between 1993 and 1999. In this era, DMARDs were initiated with delay, and/or mild DMARDs (such as hydroxychloroquine) were started as initial therapy, as described elsewhere.[5]

Results

Patient characteristics

(Table 6.1) presents baseline characteristics of included RA patients (fulfilling the 2010 criteria). ACPA-negative patients were older (mean age 63 versus 54 years; p<0.001), had more swollen joints than ACPA-positive patients (median 9 versus 5; p<0.001), more tender joints (median 16 versus 10; p<0.001), and a shorter disease duration (median 103 versus 144 days; p<0.001). Over time a similar proportion (70-80%) of patients achieved DAS-remission (44 joints assessed, DAS≤2.4) (Figure 6.1), indicating that despite differences in characteristics between both groups the disease activity was equally suppressed in both groups.

Table 6.1: Baseline characteristics of RA patients (fulfilling 2010 criteria) for analyses on patient-reported impairments and limitations, and work restrictions

	ACPA-negative (n=450)	ACPA-positive (n=492)	P-value
Age, mean (SD)	60 (16)	54 (14)	<0.001
Female, n (%)	295 (66)	333 (68)	0.49
68-Tender joint count, median (IQR)	16 (10-24)	10 (5-17)	<0.001
66-Swollen joint count, median (IQR)	9 (4-14)	5 (3-10)	<0.001
CRP (mg/L), median (IQR)	12 (3-32)	11 (4-24)	0.40
RF positive (≥3.5 IU/mL), n (%)	154 (34)	431 (88)	<0.001
Symptom duration in days, median (IQR)	103 (58-194)	144 (72-294)	<0.001
	ACPA-negative (n=130)	ACPA-positive (n=152)	P-value
Age, mean (SD)	59 (16)	54 (14)	0.009
Female, n (%)	90 (69)	99 (65)	0.47
68-Tender joint count, median (IQR)	13 (8-21)	8 (4-12)	<0.001
66-Swollen joint count, median (IQR)	7 (3-12)	5 (2-8)	0.005
CRP (mg/L), median (IQR)	11 (3-32)	8 (3-18)	0.12
RF positive (≥3.5 IU/mL), n (%)	58 (45)	129 (85)	<0.001
Symptom duration in days, median (IQR)	94 (46-210)	121 (68-280)	0.035

ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

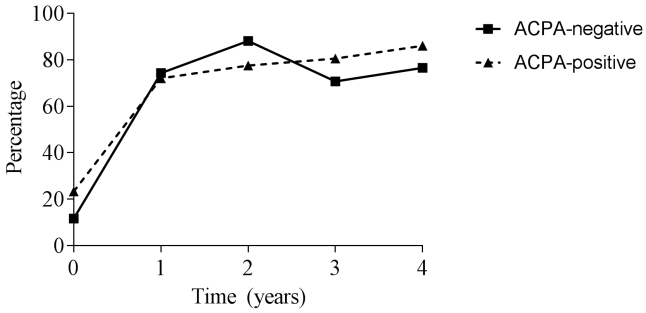

Figure 6.1: The percentages of ACPA-negative and ACPA-positive RA-patients (2010-criteria) achieving DAS-remission (DAS44<2.4) during 4-years follow-up.

Patient-reported impairments and limitations at baseline

ACPA-negative patients reported statistically significant more pain than ACPA-positive patients (median 5.8 versus 5.2, p=0.045), more severe fatigue (median 5.5 versus 5.0, p=0.003), more severe disease activity (median 6.1 versus 5.6, p=0.006) and more functional disability (1.0 versus 0.9, p=0.001), although absolute differences were small (Figure 6.2). General wellbeing was equal for both groups of patients (median 4.3 versus 4.0, p=0.25). As, due to the composition of the 2010-criteria ACPA-negative patients can only fulfill the criteria in case of >10 involved joints and ACPA-negative patients indeed had more swollen joints, we hypothesized that the patient selection by the criteria used might explain the higher PROs in ACPA-negative patients. Therefore analyses were repeated in 1987-criteria positive RA-patients. Baseline characteristics are shown in Supplementary Table 6.4. Here, no significant differences were observed between ACPA-negative and ACPA-positive RA-patients (6.2).

Course of patient-reported impairments and limitations during 4 years of disease

The 450 ACPA-negative and 492 ACPA-positive RA-patients (2010-criteria) were studied during 4-years follow-up, as shown in Figure 6.1, which shows the predicted values adjusted for age, gender and year of inclusion. For all measured variables, the largest improvement was seen during the first year. Both patient groups had equal amounts of pain over time. ACPA-negative patients remained more severely fatigued over time (p=0.002; β=0.53; this β indicates that on a NRS ranging 0-10 ACPA-negative patients were 0.5 more severely fatigued). The self-reported disease activity and the HAQ were equal between both groups. We corrected for age in all analyses and this had only a significant effect in the longitudinal analysis of the HAQ (β=0.008; p<0.001 on a scale ranging from 0-3). When the 1987-criteria positive RA-patients were studied over time, no statistically significant differences were found for all variables (Figure S2, *online available*). Repeating the analyses in RA-patients (both if defined by the 2010- or the 1987-criteria) with additional correction for RF-factor positivity, SJC and symptom duration, resulted in no significant differences between ACPA-negative and

ACPA-positive patients.

Patient-reported restrictions with work and household activities at baseline

Baseline characteristics of the 130 ACPA-negative and 152 ACPA-positive patients that completed questionnaires on work restrictions are presented in Table 6.1. Absenteeism and presenteeism among patients with paid work were not different at disease presentation as shown in Table 6.2. 38% ACPA-negative versus 48% of ACPA-positive employed patients reported absenteeism in the last 3 months (p=0.30), with median 4 days missed at work for both groups. Presenteeism due to arthritis was equal, median 3 versus 5, and the days worked with restrictions due to arthritis was median 4 versus 3

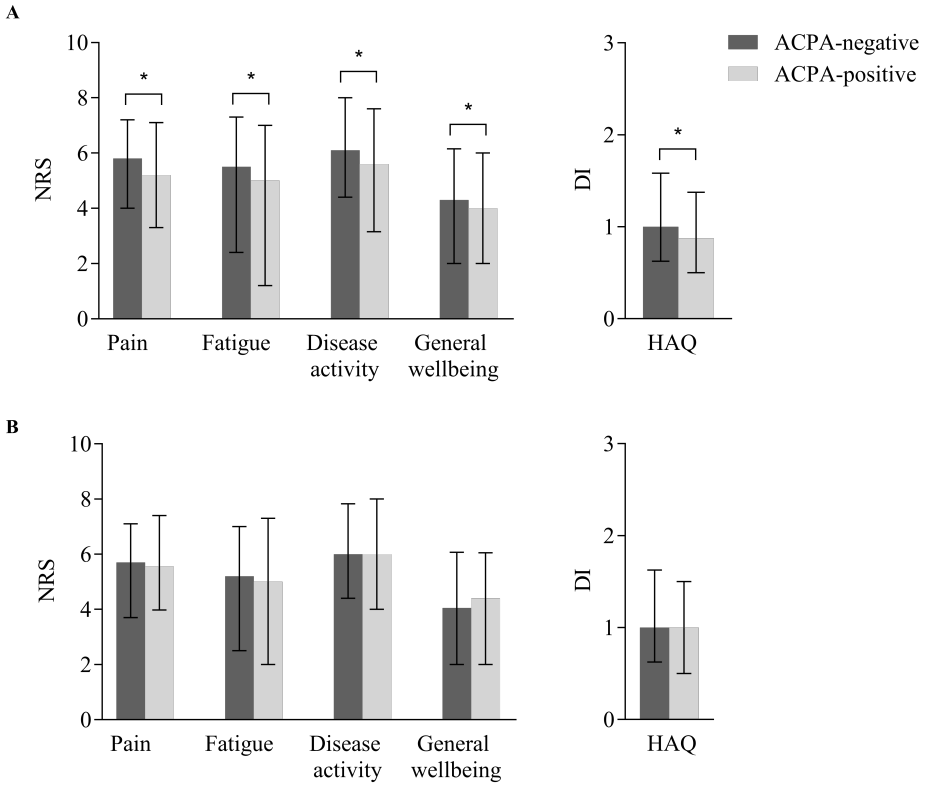

Figure 6.2: Patient-reported outcomes of impairments and limitations of ACPA-negative and ACPA-positive patients for the 2010-criteria (A) and 1987-criteria (B) at baseline.
Legend. Median values and corresponding interquartile ranges are shown for severity of self-reported pain, fatigue, disease activity and general wellbeing measured by NRS (numerical rating scale) ranging from 0-10, and physical function by the health assessment questionnaire-disability index (HAQ-DI) ranging from 0-3 in the last 24 hours. *p-values<0.05 with Mann-Whitney U test.

days for ACPA-negative and ACPA-positive patients, respectively. Also, restrictions due to arthritis at home were similar. The median level of restriction was 6 versus 7 in ACPA-negative and ACPA-positive patients and median days restrictions due to arthritis was 7 versus 6, respectively. Statistically, differences were non-significant for all analyses.

Table 6.2: Baseline data of ACPA-negative and ACPA-positive RA-patients (1987-criteria) on restrictions with work and household activities

	ACPA-negative (n=130)	ACPA-positive (n=152)	P-value
Productivity at home			
Level of restrictions in household work productivity past 7 days, median (IQR)	6 (2-8)	7 (3-8)	0.84
Days restricted in household productivity past 7 days, median (IQR)	7 (2-7)	6 (2-7)	0.25
Employed, n (%)	40 (31)	69 (45)	0.001
Age, mean (SD) years	47 (13)	49 (11)	0.31
Type of work:			0.48
Physical, n (%)	7 (18)	16 (23)	
Physical and mental, n (%)	19 (48)	25 (36)	
Mental, n (%)	13 (33)	27 (39)	
Productivity in the work place			
Work hours per week, median (IQR)	32 (20-38)	28 (20-40)	0.80
Work days per week, median (IQR)	5 (4-5)	5 (3-5)	0.31
Missed any work in last 3 months, n (%)	15 (38)	33 (48)	0.30
Days missed at work in last 3 months (absenteeism), median (IQR)	4 (2-21)	4 (2-12)	0.92
Level of restrictions in work productivity (presenteeism) past 7 days, median (IQR)	5 (2-8)	3 (2-8)	0.41
Days restricted while at work past 7 days, median (IQR)	4 (2-7)	3 (0-5)	0.20

*Analysed in employed patients only. 0-10 scale, where 0 means no restrictions and 10 means complete restrictions. Percentages were calculated on non-missing data. There were no statistically significant differences. ACPA, anti-citrullinated peptide antibody; RA, Rheumatoid Arthritis; SD, standard deviation; IQR, Inter quartile range.

When the 1987-criteria positive RA-patients were studied, no statistically significant differences were observed for all analyses (Supplementary Table 6.5).

Course of patient-reported restrictions with work and household activities during 4 years of disease

Presenteeism was assessed during 4-years follow-up and was equal between both groups (p = 0.89). ACPA-negative 2010-criteria positive patients had more days with restrictions at work (p=0.02; β=0.89, this β indicates that ACPA-negative patients had 0.89 days more restrictions) than ACPA-positive patients. Both restrictions at home (p=0.17) and the days restrictions at home (p=0.64) were equal, as illustrated by Figure 6.4. Evaluating

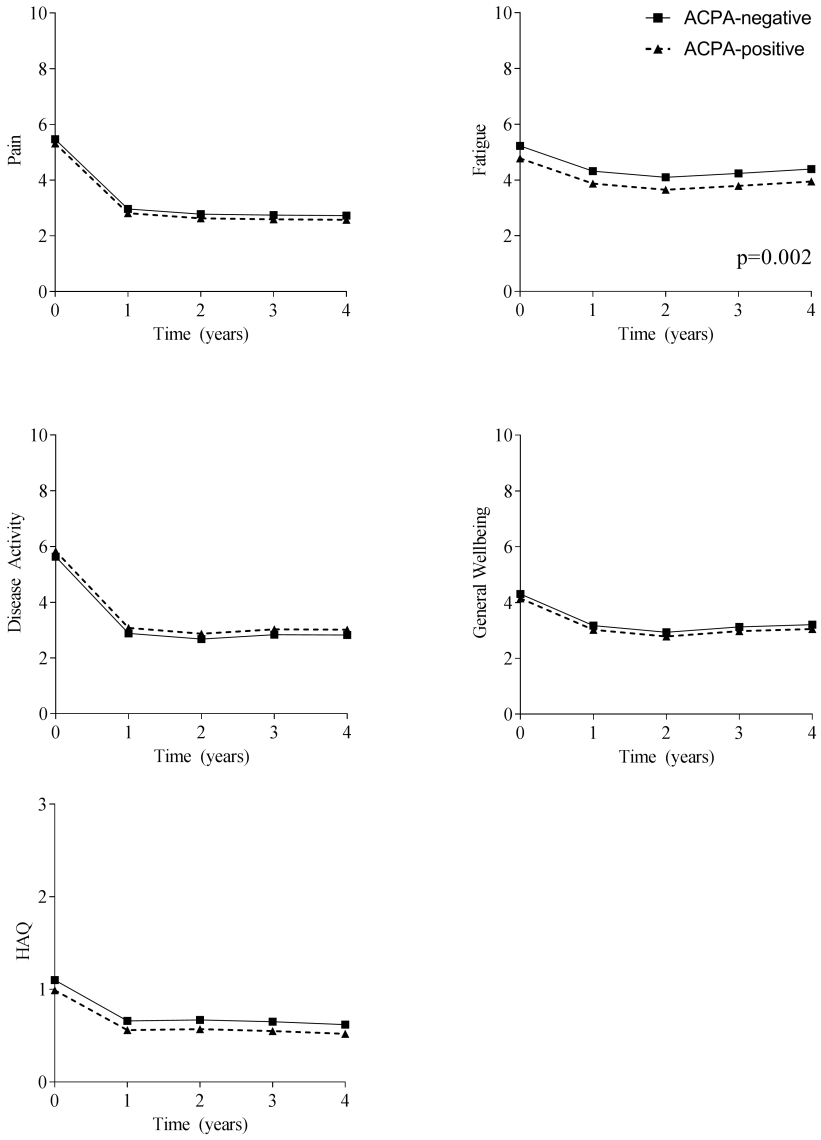

Figure 6.3: Patient-reported outcomes of impairments and limitations of ACPA-negative and ACPA-positive RA-patients for the 2010-criteria during 4-years follow-up.
Legend. Presented are median predicted values obtained by linear mixed models adjusted for age at inclusion, gender and year of inclusion. In case of significance of the interaction between ACPA and time, this was added to the modeled figures. Pain, fatigue, disease activity and general wellbeing were measured by a 0-10 NRS scale. Physical function was measured by the HAQ with a disability index from 0-3. Both groups experienced equal pain; ACPA-negative patients were more severely fatigued (p=0.002; β=0.53) than ACPA-positive patients; both groups had equal self-reported disease activity, general wellbeing and HAQ. The number of available data per follow-up year for ACPA-positive patients for pain: 457, 316, 224, 240, 209; fatigue: 447, 276, 187, 202, 176; disease activity: 457, 315, 224, 239, 209; general wellbeing: 449, 316, 223, 242, 210; HAQ: 430, 268, 140, 221, 197. For ACPA-negative patients for pain: 404, 257, 177, 165, 138; fatigue: 400, 232, 150, 143, 114; disease activity: 403, 257, 177, 166, 138; general wellbeing: 401, 257, 175, 166, 139; HAQ: 382, 224, 105, 147, 120.

the 1987-positive RA-patients over time revealed no significant differences in all these analyses (Figure S3, *online available*).

Sensitivity analyses

Because 33% of the ACPA-negative 2010-criteria positive RA-patients were RF-positive, patients without ACPA or RF (n=296) were compared to patients with ACPA and/or RF (n=646). At baseline, patients without ACPA and/or RF had more self-reported pain (p=0.003), were more severely fatigued (p=0.045), had a more severe disease activity (p<0.001) and more severe functional disability (p=0.001). General wellbeing was equal (p=0.17). Thus, these findings were similar to the results of the main analyses. Over 4-years follow-up patients without ACPA and/or RF had more severe pain (p=0.007; β=0.37), were more severely fatigued (p=0.001; β=0.60), had more severe disease activity (p=0.001; β=0.44) and more severe general wellbeing (p=0.026; β=0.29). The HAQ over time was not statistically different between both groups (p=0.08). RA-patients (2010-criteria) without ACPA or RF (n=72) and patients with ACPA and/or RF (n=210) were evaluated for restrictions at work and at home. At baseline patients with and without ACPA and/or RF had equal absenteeism (p=0.21), presenteeism (p=0.75), number of days restrictions at work (p=0.31), level of restrictions at home (p=0.91) and number of days restrictions at home (p=0.97). Over 4-years follow-up both groups had equal presenteeism (p=0.78). ACPA- and RF-negative patients had more days restrictions at work due to arthritis (p=0.043; β=1.2). The level of restrictions at home (p=0.77) and days restrictions at home (p=0.50) were equal between the groups. Because DAS-steered treatment became regular as of 2005, analyses were repeated for 2010-RA-patients included ≥2005. This showed similar results as that of the total group. At baseline ACPA-negative patients reported more severe pain than ACPA-positive patients (p=0.016; β=0.20), more severe fatigue (p=0.003; β=0.45), more severe disease activity (p<0.001; β=0.39), more severe general wellbeing (p=0.029; β=0.14) and more functional disability (p=0.001; β=0.08 on a scale ranging from 0-3). Also follow-up data showed similar results as that of the total group, as shown in Figure S4 (*online available*). Finally, to compare the main findings with those obtained on RA-patients that were treated in earlier time periods and thus with different treatment strategies, the analyses of patient-reported impairments and limitations in ACPA-positive and ACPA-negative patients were also performed on RA-patients included in the EAC between 1993 and 1999 (n=335). As shown in Figure S5 (*online available*), several PROs were more severe in ACPA-positive RA-patients during 4-years follow-up; statistical significance was reached for general wellbeing (p=0.020; β=0.10) and a tendency towards significance for patient-reported disease activity (p = 0.06; β=0.05).

Discussion

This large longitudinal study assessed if at present ACPA-positive RA-patients are still more severely affected than ACPA-negative RA-patients, using self-reported impairments and limitations including functional disability and restrictions at work as outcomes. The current availability of treatment strategies to suppress inflammation

drastically reduced the frequency and degree of joint damage, which makes that prospects of RA-patients have changed substantially.[10] Consequently, other disease outcomes have become central and patients have rated pain, fatigue, wellbeing and independence, items which have been studied here, as most important.[14] In addition, physical functioning and work ability, the key component of independence in RA are important from a socio-economic perspective. We did not observe a more severe disease patient burden in ACPA-positive RA. Evidently, the present data require validation in an independent cohort. Nonetheless, the assumption that ACPA-positive RA is a

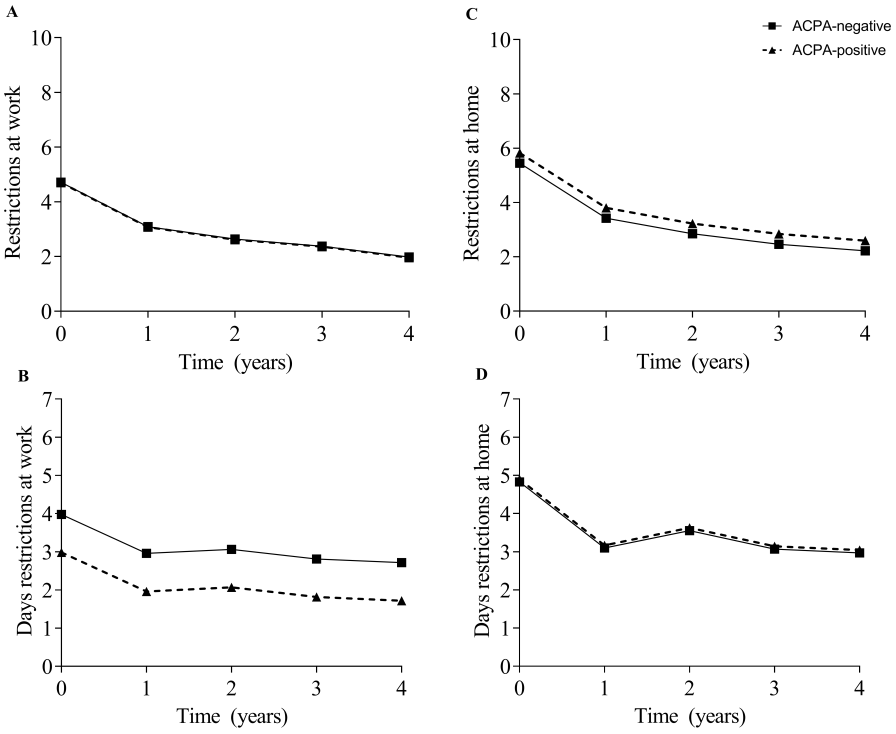

Figure 6.4: Presented are median predicted values obtained by linear mixed models adjusted for age at inclusion and gender of ACPA-negative and ACPA-positive RA-patients according to the 2010-criteria. Presenteeism (level of restrictions at work) (A), number of days restrictions at work (B) and level of restrictions (C) and days restrictions with household activities (at home) (D) over 4-years follow-up. Level of restrictions was measured on a scale of 0-10. Days restrictions due to arthritis ranged from 0-7 days. Presenteeism was equal (p=0.89). ACPA-negative patients had a significantly higher number of days restrictions at work due to arthritis (p=0.02; β=0.89). Level of restrictions (p=0.17) and number of days they had restrictions at home (p=0.64) were equal.
The number of available data per follow-up year for ACPA-positive patients for level of restrictions at work: 63, 52, 44, 31, 19; for days restrictions at work: 53, 50, 36, 27, 17; level of restrictions at home: 103, 83, 75, 59, 37; for days restrictions at home: 89, 69, 63, 51, 28. For ACPA-negative patients for level of restrictions at work: 38, 20, 12, 9, 5; for days restrictions at work: 36, 17, 10, 9, 4; for level of restrictions at home: 82, 58, 39, 24, 12; for days restrictions at home: 71, 44, 26, 16, 8.

more severe disease seems no longer true in current rheumatology practice when the mentioned patient-reported outcomes are considered.

Contrary to the hypothesis tested, we actually observed some differences to the detriment of ACPA-negative patients. However, these differences were small and clinically irrelevant. As ACPA-negative patients were older, which was also shown in previously performed studies, we corrected for age in all longitudinal analyses.[26] Also when analyses were additionally adjusted for comorbidities, similar results were obtained (data not shown). We hypothesized that the small differences found were most likely caused by the fact that RA-patients without ACPA or RF need > 10 joints involved to fulfill the criteria and ACPA-negative patients with positive RF required 4-10 joints involved as reflected by the patient characteristics which showed that ACPA-negative RA-patients (according to the 2010-criteria) had a higher tender- and swollen joint count than ACPA-positive patients. This effect has been observed before.[27, 28] For this reason we repeated the analyses in patients classified according to the 1987-criteria, with a more similar joint count between ACPA-negative and ACPA-positive patients. Then, we did not observe the somewhat higher disease burden for ACPA-negative RA, when treated with current treatment strategies and considering patient-reported impairments and limitations. Thus, although this study was not set up to compare the 2010- and 1987-criteria, the presented data do confirm previously reported observations that ACPA-positive 2010-RA consists of a less severe subset of patients than ACPA-positive 1987-RA and that ACPA-negative 2010-RA consist of a more severe subset of patients compared to ACPA-negative 1978-RA.[27, 28]

In current research, there is a tendency to concentrate more on ACPA-positive than on ACPA-negative RA. For example, much more whole genome genetic studies were performed on ACPA-positive RA.[29] This focus in etiopathologic studies is possibly explained by the paradigm that ACPA-negative RA might represent a more heterogeneous subset of patients, and that current research has revealed fewer clues on the possible causes or mediators of ACPA-negative RA. This could have resulted in ACPA having conquered a more prominent position in the identification of RA within the 2010-criteria. This study however does not intend to address the issue on the classification criteria. The data presented clearly demonstrate that at present ACPA-negative RA is equally severe as ACPA-positive RA when patient-reported impairments and limitations are studied as outcomes. This has implications for future research, both for etiopathophysiological and clinical studies. The present data highlights the importance of keeping the scope set on ACPA-negative RA as well, because it has become an equally severe disease. Moreover the prevalence of ACPA-negative RA like measured in early arthritis cohorts, concerns up to half of the total RA-population.[26, 30]

The risk of misdiagnosis is often estimated higher for ACPA-negative RA than for ACPA-positive RA. In this study, patients were diagnosed with RA according to the treating rheumatologist and this clinical diagnosis was verified after 1 year of disease in the medical files of all patients. Hence, patients that evolved to have other diseases were no longer in the data set. Thereafter patients were checked on fulfilling the 2010-criteria

(or 1987-criteria for sub-analyses). When all these conditions were met, patients were included. Because of this stringent selection, we think that the risk of misdiagnosis of ACPA-negative RA is low.

Secondary comorbidities like fibromyalgia (FM) could also influence the PROs, like pain and fatigue.[31] Data on secondary FM was not collected in our cohort. However, we have no reason to believe that secondary FM would have influenced our comparisons between autoantibody-positive and autoantibody-negative patients, as previous studies have demonstrated that RA-patients with and without concomitant FM have an equal prevalence of RF-positivity.[31–34]

Measuring patients' perceptions of health is a standard approach in observational studies and epidemiological research. Measurements of PROs have proven to be valid and responsive and are sensitive to detect differences between patient groups.[28, 35–38] This is the first study to extensively compare several PROs and work ability among ACPA-positive and ACPA-negative RA-patients during 4-years follow-up. Other studies have included the HAQ or DAS in their analyses and sometimes other patient-reported outcomes.[28, 36–39] However, these measurements were mainly performed at baseline and were not conducted to find differences between ACPA-positive and negative patients over time. Further, it was shown that patients with RA in countries with higher welfare score worse on PROs despite lower levels of objectively measured disease outcomes.[8, 25, 40] However, this study is conducted in only one country.

PROs may be influenced by secular trends.[23–25] Patients studied were included between 2000 and 2014. To prevent confounding effects we did correct the analyses for the year of inclusion. There is no reason to believe that personal contextual factors such as education or self-efficacy are different between ACPA-positive and ACPA-negative patients.

A limitation of PROs could be that reproducibility is sometimes not very satisfactory [41] and the difficulty of any study using self-reported outcomes can be that they may be susceptible to non-response and recall bias. We do not expect this to cause a difference for the comparison made. Also, we are aware that absenteeism is calculated with a recall period of 3 months and some patients present with symptom durations shorter than this. However, if this had any effect, it would have led only to an underestimation of absenteeism in ACPA-negative patients, as they more often had a shorter symptom duration at presentation.

Our frequencies of employment, absenteeism and presenteeism are in accordance with previous studies in RA that also showed that RA-patients are interfered considerably by means of work restrictions even despite improved treatment strategies.[42–44] Data of the Dutch reference population was obtained from the Dutch 'Centraal Bureau voor Statistiek'.[45] Here 45% of the persons aged 45-55 years (this was the most prevalent age category in the patients' cohort) had missed days at work due to sickness during 12 months of the year 2016. The average sick leave was 8 days per year. In comparison,

38-48% of the employed ACPA-negative and ACPA-positive RA-patients missed days at work during 3 months period. In both ACPA-groups the median days missed at work were 4 per 3-months, extrapolation to a 12 months period would result in an estimated sick leave of 16 days per year. This is evidently more than the sick leave in the reference population and these data confirm that RA patients currently still have increased work restrictions. Furthermore, this study adds that no differences were found between ACPA-positive and ACPA-negative patients. Notably the number of working patients was relatively small in our data-set, but findings that the results on restrictions at work were similar to those of the patient-reported impairments and limitations show face-validity.

This study was conducted to evaluate patients that were diagnosed early and were treated according to up-to-date treatment strategies, consisting of early initiation of methotrexate and DAS-steered treatment adjustments. We cannot compare the actual DMARDs used over time in both groups as these data were not collected sufficiently accurate. According to local guidelines initial treatment of ACPA-positive and ACPA-negative RA was similar: treatment regimen consisted of initial treatment with a DMARD (preferably MTX), in case of failure a second conventional DMARD was started and in case of failure a biologic DMARD was allowed. From 2005 onwards, in our hospital DAS-steered treatment became standard,[18] meaning that treatment regimens were adjusted based on the individuals' disease activity. Analysis of biologic DMARDs used after 2-years follow-up revealed that these were used by 9% of ACPA-positive patients and 1% for ACPA-negative patients. Furthermore, the disease activity measured during follow-up was similar in both groups. Hence it is possible that the ACPA-positive patients required more, or more aggressive DMARDs to achieve a similar DAS. Our results could therefore be considered as the consequence of improved treatment strategies.

In line with this notion, we evaluated if PROs were different between ACPA-positive and ACPA-negative patients that were treated in earlier periods with treatment strategies that are now considered outdated. Although the number of patients in this group was smaller, ACPA-positive patients indeed had some PROs that were worse than those of ACPA-negative patients. Results of the present study therefore imply that thanks to improved treatment strategies, not only differences between ACPA-positive and ACPA-negative RA in outcomes such as joint damage severity diminished or disappeared, but that this applied for differences in patient-reported outcomes.

In conclusion, this study thoroughly compared various PROs and restrictions with work during follow-up in ACPA-positive and ACPA-negative RA-patients. It demonstrated that ACPA-positive and ACPA-negative RA managed with nowadays treatment strategy represent an equally severe subset of disease. We do not know if rheumatologists take PROs into account when making treatment decisions. However, as joint damage becomes less relevant as outcome, in the future we should explore if PROs can be considered. Further research is required, but the important personal health impact as well as the socio-economic burden highlighted by the present study imply that effort to further improve the disease course should be proportional to ACPA-positive and ACPA-negative RA.

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Supplementary data

Supplementary data are available at *Arthritis Care & Research Online*.

Supplementary figure

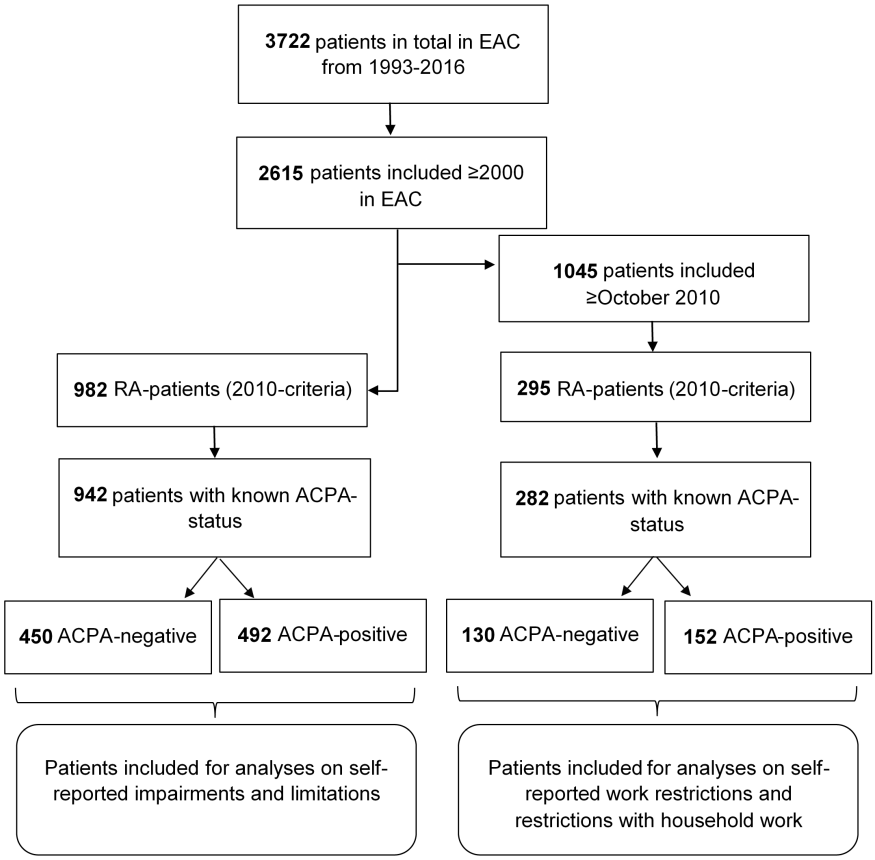

Figure 6.5: Flowchart of patient selection. Legend. Flowchart of patient selection from the Leiden Early Arthritis Clinic (EAC) cohort. The questionnaire on work ability was added to the protocol in 2010. All patients studied for analyses on self-reported work restrictions are part of the patients included for analyses on self-reported impairments and limitations. Analyses were also done in RA-patients included ≥2000 that met 1987-criteria. For self-reported impairments and limitations there were 225 were ACPA-negative and 338 ACPA-positive RA-patients; for work restrictions there were 57 ACPA-negative and 125 ACPA-positive RA-patients.

Supplementary tables

Table 6.3: Work ability questionnaire.

From WPS-RA
Is the patient currently employed outside of home: yes/no *If employed:* What is your occupation: Which box describes their job function best: non-manual, mixed, manual. *If unemployed:* Please check the box that describes their status best: homemaker (voluntary), retired, student, unable to work (due to arthritis or not), jobless.
Other questions
If employed: Absence from work during the last 3 months: yes/no. If yes, how many days have you missed during the last 3 months. How many days did rheumatic complaints affect your productivity during the past 7 days while you were working (0-7). *All patients:* How many days did your rheumatoid arthritis affect your productivity of your normal daily activities, other than work at a job during the past 7 days (0-7).
From WPAI-RA:
If employed: How much did your rheumatic complaints restrict your productivity during the past 7 days while you were working (0-10; 10 unable to work). *All patients:* How much did your rheumatic complaints restrict your productivity of your normal daily activities, other than work at a job during the past 7 days (0-10; 10 unable to work).

Table 6.4: Baseline characteristics of ACPA-negative and ACPA-positive RA-patients (according to the 1987-criteria) for analyses on patient-reported impairments and limitations

	ACPA-negative (n=225)	ACPA-positive (n=338)	P-value
Age, mean (SD)	62 (15)	55 (14)	<0.001
Female, n (%)	142 (63)	226 (67)	0.36
68-Tender joint count, median (IQR)	14 (7-23)	10 (6-17)	0.002
66-Swollen joint count, median (IQR)	8 (4-15)	7 (3-11)	0.001
CRP (mg/L), median (IQR)	15 (5-33)	12 (5-27)	0.34
RF positive (≥3.5 IU/mL), n (%)	66 (29)	296 (88)	<0.001
Symptom duration in days, median (IQR)	86 (49-155)	136 (70-263)	<0.001

ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

Table 6.5: Baseline data of ACPA-negative and ACPA-positive RA-patients (1987-criteria) on restrictions with work and household activities

	ACPA-negative (n=57)	ACPA-positive (n=125)	P-value
Productivity at home			
Level of restrictions in household work productivity past 7 days, median (IQR)	7 (3-8)	7 (3-8)	0.63
Days restricted in household productivity past 7 days, median (IQR)	7 (2-7)	5 (3-7)	0.29
Employed, n (%)	19	55	0.016
Age, mean (SD) years	50 (13)	49 (11)	0.90
Type of work:			
Physical, n (%)	5 (26)	11 (20)	
Physical and mental, n (%)	11 (58)	18 (33)	
Mental, n (%)	3 (17)	25 (45)	
Productivity in the work place			
Work hours per week, median (IQR)	36 (28-40)	26 (20-40)	0.86
Work days per week, median (IQR)	5 (5-5)	4 (3-5)	0.19
Missed any work in last 3 months, n (%)	9 (47)	28 (51)	0.79
Days missed at work in last 3 months (absenteeism), median (IQR)	9 (2-31)	5 (2-12)	0.32
Level of restrictions in work productivity (presenteeism) past 7 days, median (IQR)	6 (3-10)	4 (2-8)	0.38
Days restricted while at work past 7 days, median (IQR)	3 (1-7)	3 (0-5)	0.53

*Analysed in employed patients only. 0-10 scale, where 0 means no restrictions and 10 means complete restrictions. Percentages were calculated on non-missing data. There were no statistically significant differences. ACPA, anti-citrullinated peptide antibody; RA, Rheumatoid Arthritis; SD, standard deviation; IQR, Inter quartile range.

7

Does psychological stress in patients with Clinically Suspect Arthralgia associate with subclinical inflammation and progression to Inflammatory Arthritis?

Aleid Boer
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Abstract

Background

Within established rheumatoid arthritis (RA), stress can have pro-inflammatory effects by activating the immune system via the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. It is unknown if stress levels also promote inflammation during RA development. We studied whether the psychological stress response was increased in clinically suspect arthralgia (CSA) and if this associated with inflammation at presentation with arthralgia and with progression to clinical arthritis.

Methods

In 241 CSA patients, psychological stress was measured by the Mental Health Inventory (MHI-5) and the Perceived Stress Scale (PSS-10) at first presentation and during follow-up. Systemic inflammation was measured by C-reactive protein (CRP) and joint inflammation by 1.5 T-MRI of wrist, MCP, and MTP joints.

Results

At baseline, 12% (24/197) of CSA patients had a high psychological stress response according to the MHI-5. This was not different for patients presenting with or without an elevated CRP, with or without subclinical MRI-detected inflammation and for patients who did or did not develop arthritis. Similar findings were obtained with the PSS-10. When developing clinical arthritis, the percentage of patients with 'high psychological stress' increased to 31% (p=0.025); during the first year of treatment this decreased to 8% (p=0.020). 'High psychological stress' in non-progressors remained infrequent over time (range 7–13%). Stress was associated with fatigue (p=0.003) and wellbeing ($p < 0.001$).

Conclusion

Psychological stress was not increased in the phase of arthralgia, raised at the time of diagnoses and decreased thereafter. The lack of an association with inflammation in arthralgia and this temporal relationship, argue against psychological stress having a significant contribution to progression from CSA to inflammatory arthritis.

Introduction

In chronic inflammatory diseases like rheumatoid arthritis (RA), psychological stress is considered to negatively affect the disease course. It activates the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, which associate with the release of neurotransmitters (i.e. norepinephrine), hormones (i.e. cortisol) and activation of immune cells.[1–3] During stress, the normal downregulation of the inflammatory response is hindered, possibly causing pro-inflammatory effects. Despite these effects, it is presently unknown if stress mediates the development of early inflammatory arthritis or RA.

The prevalence and the effects of psychological stress have been thoroughly investigated within patients with established RA. Compared to the general population, RA patients experience more stress.[4] Moreover the stress response is deranged, especially in patients with increased disease activity scores and disease exacerbations.[5–8] Patients have increased stress-induced inflammatory cytokine levels (i.e., interleukin (IL)-6, IL-1b, IL-2) and impairments in the capacity of glucocorticoids to inhibit this inflammatory response.[9–11] Likewise, psychological stress has been associated with increased C-reactive protein (CRP) levels.[1, 12] Furthermore, research in patients with established RA has indicated that pre-existing inflammation can facilitate stress-induced inflammation,[2, 12] potentially inducing a vicious circle between psychological stress and inflammation. Notably, the pro-inflammatory effects observed in these studies were independent of the disease duration.[6, 13, 14]

The developmental course of RA is incompletely understood, though it is recognized that it consists of several phases. [15] The phase preceding that of clinically apparent (chronic) arthritis is a symptomatic one, called clinically suspect arthralgia (CSA). CSA patients have a combination of clinical characteristics that are recognizable by rheumatologists, and are at risk to develop RA.[16] These characteristics were also recently described by a EULAR taskforce.[17] Part of the CSA patients have subclinical joint inflammation that is detectable by MRI at first presentation to a rheumatologist,[18] and subclinical inflammation is present in the vast majority of those CSA patients that progress to RA.[16]

It is presumed that biologic mechanisms evolving in this symptomatic pre-arthritis phase of RA are important for the future course of the disease. Whether psychological stress is associated with inflammation in the phase of CSA or with progression to clinically apparent arthritis or RA is presently unknown and subject of this study. Based on the abovementioned observations in patients with established RA, stress might contribute to the development of subclinical inflammation and subsequently mediate progression to RA. The recent observation that life events pose a (small) risk at development of RA fits into this hypothesis.[5] However alternatively, stress can also be a consequence of symptoms and physical limitations without having exacerbating effects on inflammation in the phase of CSA. To increase the comprehension of the effects of the perceived psychological stress response in a symptomatic pre-arthritis phase, this study aimed to determine associations and time-relationships between stress

and inflammation in patients presenting with CSA and during progression to early clinical arthritis. The psychological stress response was measured by two validated questionnaires, the five-item Mental Health Inventory (MHI-5) and Cohen's perceived stress scale (PSS-10).[19–21] Inflammation was measured by systemic inflammation assessed using C-reactive protein (CRP) levels and subclinical joint inflammation determined using magnetic resonance imaging (MRI) of hand and foot joints.

Methods

Patient population

Patients included in the Leiden Clinically Suspect Arthralgia (CSA) cohort between April 2012 and March 2015 were studied. The CSA cohort is a population-based inception cohort that started at the rheumatology outpatient clinic in Leiden, The Netherlands, with the aim of studying the symptomatic phase of RA that precedes clinical arthritis. Inclusion required the presence of arthralgia of small joints for <1 year which was because of the character of the symptoms, considered as being suspect to progress to RA by a rheumatologist. A detailed description is provided elsewhere,[16] but identification of CSA occurred mainly by the clinical expertise of the rheumatologist. Furthermore, CSA was identified at the first visit, before the results of routine laboratory investigations were known. Notably, general practitioners in our region are discouraged to perform anti-citrullinated protein antibodies (ACPA) testing themselves but are encouraged to refer in a case of any suspicion on imminent RA. After inclusion in the CSA cohort, routine visits were performed after 4 months, 1 year and 2 years. At the request of patients (e.g. in case they experienced more symptoms) patients were also seen in between the scheduled visits. All patients were followed for development of clinically apparent arthritis for 2 years. Follow-up in the CSA cohort ended earlier when clinical synovitis had developed, confirmed with joint swelling at physical examination by the treating rheumatologist. CSA patients were not treated with disease-modifying anti-rheumatic drugs (DMARDs) or corticosteroids in the phase of CSA. For the patients that developed clinical synovitis, further data was obtained as they were subsequently included in the Leiden Early Arthritis Clinic (EAC) cohort.[22] Data collected at clinical arthritis onset and 1 year thereafter were used. Patients who were diagnosed with RA were treated in conformance with national guidelines, which consists of early initiation with a DMARD (preferably methotrexate), in case of failure a second conventional DMARD (either switching or adding) and disease activity score (DAS)-steered treatment adjustments. Biologics were allowed if ≥2 conventional DMARDs failed but that this did not occur in the studied period of 1 year after clinical arthritis onset. A flowchart of the study protocol is available in Supplementary Figure 7.3. Written informed consent was obtained from all patients. The study was approved by the local medical ethics committee.

Study protocol

At each visit physical examinations, including 66-swollen and 68-tender joint counts (66-SJC and 68-TJC) were performed and blood samples were taken to measure CRP (positive if ≥5 mg/L); immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5

IU/mL); and ACPA (anti-CCP2, EliA CCP, Phadia, The Netherlands, positive if ≥7 U/mL). Questionnaires were completed, including the health assessment questionnaire (HAQ)-disability index (DI), 36-item Short Form Health Survey (SF-36) and self-reported wellbeing, pain and fatigue on numerical rating scales ranging from 0 (no complaints) to 10 (extreme complaints). The PSS-10 was added later to the protocol in 2013 and was gathered only at baseline. Further, to measure subclinical joint inflammation, MRI scans of metacarpophalangeal (MCP), wrist and metatarsophalangeal (MTP joints were made of the most affected side (or the dominant side in case of equally severe symptoms) on an MSK Extreme 1.5 T extremity MR-system (GE, Milwaukee, WI, USA). MRI scans were made of the same side at baseline and at arthritis onset (before the start of disease-modifying drugs including corticosteroids) and 1 year thereafter. Non-steroidal anti-inflammatory drugs (NSAIDs) were stopped 24 h before the MRI scan. The scans were scored for MRI-detected inflammation according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA MRI scoring (RAMRIS) method as described supplementary and previously published.[16] Total inflammation scores consisted of the sum of synovitis, bone marrow edema (BMO) and tenosynovitis scores. All scans were scored by two independent readers and mean scores of both readers were calculated to obtain the total inflammation score (see Supplementary Methods). The cut-off of MRI positivity was based on healthy controls as described previously.[23] An MRI was considered positive for subclinical inflammation (tenosynovitis, synovitis or BMO) if this was present in <5% of healthy volunteers (an example is provided in the supplementary methods).

Psychological stress questionnaires

The psychological stress response was measured by two questionnaires. First, for the main analyses we used the MHI-5 which is a component of the SF-36 questionnaire.[19, 24] Baseline MHI-5 was missing in 18% of the CSA-patient and no differences were found in baseline characteristics between patients with an available and missing MHI-5 (Additional file 1: Table S1). The MHI-5 is a brief self-administered questionnaire which includes scales to screen for anxiety and depression.[20, 25] It is well-validated with good psychometric properties for detecting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) type I axis diagnoses,[26] these disorders include clinical mental disorders like anxiety and depression.[27] The MHI-5 has a Cronbach's α between 0.74 and 0.90.[19, 26] The items were scored on a six-point frequency rating scale and questions are provided in the Additional file 1: Supplementary Methods.After linear conversion, possible scores on the MHI-5 range from 0 to 100, with lower scores reflecting a higher stress response. As the score has been considered as a dichotomous variable (absence or presence of a psychological stress response), a score ≥52 indicated minimal psychological stress (anxiety or depression) and <52 high psychological stress; here simply called 'high stress'. The application of this questionnaire to screen for stress by means of depression and anxiety has been examined thoroughly, as illustrated by several studies.[25, 26, 28]

Second, to investigate the main results on stress further we analysed the PSS-10. As this questionnaire was added to the protocol at a later time point, the PSS-10

data was missing in 44% of CSA patients. No differences were found in baseline characteristics between patients with an available and missing PSS-10 (Additional file 1: Table S2). Patients filled in a Dutch translation which consisted of ten items regarding predictability, controllability and life overload as perceived by the individual during the last month.[21] Questions are provided in the Additional file 1: Supplementary Methods and each item of the questionnaire was rated on a five-point Likert-type scale (0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often) how they felt with a maximum score of 40. Total scores were calculated after reversing positive items' scores (questions 4, 5, 7, 8) and then summing up these scores with the negative items' scores.[21] A higher total score indicates a greater perceived stress response. As there is no predetermined cut-off of high psychological stress, results on this questionnaire were not dichotomized. As reference, the mean score of PSS-10 obtained in 2387 respondents in the United States was 12.1 for males and 13.7 for females.[29]

Statistics

We tested dichotomous outcomes of markers of inflammation (CRP positivity, MRI positivity and arthritis onset). Associations at baseline were tested with logistic regression with MHI-5 as dependent variable and with linear regression with PSS-10 as dependent variable. Longitudinal data of the MHI-5 were assessed with logistic regression with a generalized estimating equation (GEE) model with an unstructured matrix and a logit link function. Longitudinal data on CRP levels and MRI-detected inflammation scores were analysed with a GEE model with an unstructured matrix. In all analyses, (at baseline and follow-up) we corrected for age and gender. Further, as sub-analysis, we repeated analyses in CSA patients that also fulfilled the EULAR definition of arthralgia suspicious for progression to RA. To fulfil the definition patients should have ≥3 of these characteristics: joint symptoms of recent onset (duration <1 year), symptoms of MCP joints, morning stiffness ≥60 min, most severe symptoms in early morning, presence of a first-degree relative with RA, difficulty with making a fist and a positive squeeze test of MCP joints.[17] IBM SPSS v23 (IBM Corp, Armonk, NY, USA) was used. The significance level was set at 0.05. To adjust for multiple testing for the ten different comparisons made at baseline, we applied Bonferroni correction and then p values <0.005 were considered significant.

RESULTS

Patient characteristics

Table 7.1 presents the baseline characteristics of the 241 CSA patients. The mean age was 44 and the majority was female. Forty-five patients developed clinical synovitis after a median follow-up of 17 weeks; 65% of these patients fulfilled the 2010 criteria and 91% started DMARD therapy.

Stress measured at presentation with CSA

At presentation with CSA, 10% (4/39) of patients with arthritis during follow-up and 12% (24/197) of the total group of CSA patients had a high psychological stress response ('high stress') according to the MHI-5 (score <52). This was not different for patients

presenting with or without an elevated CRP (16 versus 11%, p=0.36), or with or without subclinical MRI-detected inflammation (11 versus 13%, p=0.56, Figure 7.1). Also for the continuous values of CRP and MRI-detected inflammation scores with stress we did not find any significant relationships (p=0.89 and p=0.90, respectively). Further, we did not find associations between stress and age, gender, 68-TJC, self-reported pain, or HAQ-DI. Significant associations were observed between stress and self-reported fatigue (odds ratio (OR)=1.5, (95% confidence interval (95% CI) 1.1; 1.9); p=0.003) and wellbeing (OR=1.6, (95% CI 1.3; 2.1); p<0.001). This means that patients with a high stress response had 1.5 times more severe fatigue and they felt 1.6 times more severely affected in their general wellbeing compared to patients without 'high stress'.
When analysing the continuous values of the MHI-5, instead of dichotomized, this showed similar results. We found no association for patients presenting with or without an elevated CRP (p=0.15), or with or without subclinical MRI-detected inflammation (p=0.60) and also not between stress and age, gender, 68-TJC and self-reported pain. The association between self-reported fatigue (β=-2.5 (95% CI -3.4; -1.5); p<0.001) and wellbeing (β=-3.4 (95% CI -4.5; -2.3); p<0.001) were also found here and additionally we identified associations between stress and HAQ-DI (β=-9.2 (95% CI -14.6; -3.8); p=0.001). The latter means that per point increase in functional disability patients experienced more severe stress, reflected by a 9.2 lower MHI-5 score (on a range 0–100).

When analysing the outcome arthritis-onset during follow-up, there was no association between the percentage of patients with a high stress response at baseline and the number of patients who did and did not develop clinical arthritis (10% versus 13%, p=0.68, Figure 7.1). Also for the continuous MHI-5 score this relationship was non-significant (p=0.71).

Stress measured during progression to clinical arthritis

At the time of arthritis-onset, the percentage of patients with a high psychological stress response increased to 31% (p=0.025). One year later this had decreased to 8% (p=0.020,

Table 7.1: Baseline characteristics of all 241 CSA-patients studied and of the 186 patients that also completed the PSS-10.

	MHI-5 (n=241)	PSS-10 (n=186)
Age, mean (SD)	44 (9)	44 (13)
Female, n (%)	187 (78)	147 (79)
68-Tender joint count, median (IQR)	6 (3-11)	5 (3-10)
CRP (mg/L), median (IQR)	3 (3-5)	3 (3-5)
RF positive (≥3.5 IU/mL), n (%)	51 (21)	37 (20)
ACPA positive (≥7 U/mL), n (%)	32 (13)	21 (11)
Symptom duration in weeks, median (IQR)	17 (9-31)	18 (10-31)

ACPA, anti-citrullinated peptide antibody; RF, rheumatoid factor; CRP, c-reactive protein; SD, standard deviation; IQR, Inter quartile range.

Figure 7.2).
Also, inflammation was measured over time in patients that progressed to clinical arthritis. The CRP levels were stable while progressing from CSA to clinical arthritis (mean 9.8 and 9.1 mg/L respectively, p=0.83) and decreased during the first year of treatment (mean 5.5 mg/L; p=0.056). Total MRI-detected joint inflammation -scores increased between presentation with CSA and arthritis-onset, though this did not reach statistical significance (mean score 7.1 and 8.5 respectively, p=0.066). One year after presentation with clinical arthritis the scores had decreased (mean score 6.3).

Then we investigated whether baseline stress associated with the MRI-detected total inflammation score or CRP at arthritis onset and this revealed non-significant relationships (p=0.11 and p=0.92).

Stress measured in patients that did not progress to clinical arthritis

The percentage of patients with a high psychological stress response among the CSA patients that did not progress to clinical arthritis during 2-years of follow-up (n=196)

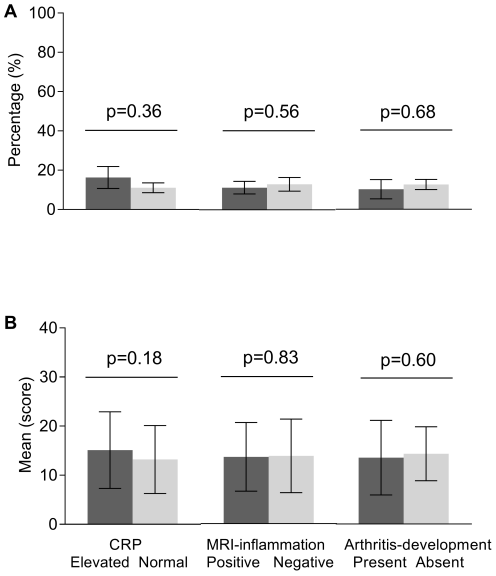

Figure 7.1: Percentages of patients with high psychological stress measured by MHI-5 (A) and obtained mean PSS-10 scores (B) in patients who at presentation with CSA had elevated versus normal CRP levels, did or did not have MRI-detected subclinical joint inflammation and patients who did and did not progress to clinical arthritis over time. In A the percentage of patients with high perceived psychological stress by MHI-5 (score <52) are shown. These were not significantly different between patients with elevated versus normal CRP (7/43 versus 17/154), with or without MRI-detected inflammation (11/97 versus 12/92) and between patients who did and did not progress to clinical arthritis over time (4/39 versus 20/158)). In B the values of psychological stress by PSS-10 are shown. These results were similar. In A whiskers indicate standard error and in B whiskers indicate standard deviation.

was stable and ranged between 7 and 13% (p=0.42, Figure 7.2).

Sub-analyses

To verify the main findings done on psychological stress present at presentation with CSA, we also analysed stress responses measured by the PSS-10. The mean PSS-10 score in all patients was 13.5 (SD 7.6). Patients that presented with or without an elevated CRP, with or without subclinical MRI-detected inflammation or who did and did not develop arthritis did not have higher stress levels (p=0.18, p=0.83 and p=0.60 respectively, Figure 7.1). We observed significant positive associations at baseline between stress and self-reported fatigue (β=0.94; p<0.001), wellbeing (β=1.20; p<0.001).

Additionally, analyses were repeated in patients that were identified as CSA by their

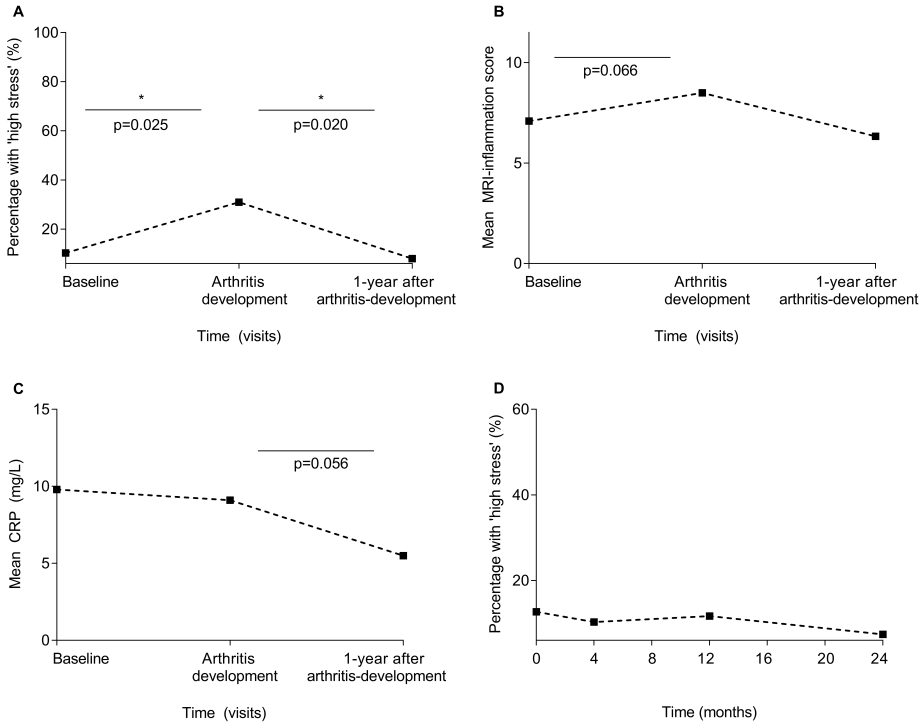

Figure 7.2: Longitudinal data of: percentages of patients with high psychological stress by MHI-5 (A), CRP levels (B), and total MRI-inflammation scores (C) in patients presenting with CSA, and during and after the development of clinical synovitis (A, B, C) and frequency of patients with 'high stress' over time in CSA-patients that did not progress to clinical synovitis (D). In A the percentages of patients with high stress, with all patients that progressed to clinical arthritis as reference (n=45). In B the MRI-detected inflammation scores increased during progression to clinical arthritis p=0.066; the number of MRI scans at the final time point is limited, hence these data were not incorporated in statistical analyses. In D the percentages of patients with high stress, among all CSA-patients that did not develop clinical arthritis during 2 years follow-up (n=196) are shown; this percentage remained rather stable (p=0.42).

rheumatologist and also fulfilled the EULAR definition for CSA (cut-off ≥3 items present), which was fulfilled by 75% of the CSA patients. The main findings were similar here too. Measuring the stress response by MHI-5 revealed that the percentage of patients with 'high stress' was not statistically different between patients presenting with or without an elevated CRP (16 versus 12%, p=0.53), with or without MRI-detected inflammation (14 versus 12%, p=0.92) or for patients who did and did not develop arthritis (13 versus 13%, p=0.92). Also when measuring stress levels with the PSS-10 no differences were observed for patients with elevated versus normal CRP, positive or negative MRI-detected inflammation and between patients with and without clinical arthritis during follow-up (p=0.34, p=0.91 and p=0.61, respectively, supplementary Figure S2, *online available*). Also in this subgroup of patients, association between stress (according to both questionnaires) and wellbeing was statistically significant (p<0.001). Repeating the longitudinal analyses on stress in the subgroup of patients that fulfilled the EULAR definition revealed similar findings as in the total group; both for the patients that progressed to clinical arthritis as in those that did not progress (supplementary Figure S3).

DISCUSSION

This longitudinal study assessed associations and time relations between the psychological stress response and inflammation in an early symptomatic phase of development of RA. We found no relationship between stress and either local or systemic inflammation in patients with clinically suspect arthralgia and also no association between stress and future clinical arthritis development. However, levels of psychological stress were increased at the visit when clinical arthritis was identified and decreased during the first year of treatment. This is the first study that evaluated stress in a symptomatic pre-arthritis phase. Although association studies cannot prove causality, the present data on the time-relationship suggest that stress may be more a consequence of symptoms and physical limitations related to the occurrence of early clinical arthritis, or of concerns related to the diagnosis that has just been made by a rheumatologist, rather than a cause for the development of inflammatory arthritis or RA.

At presentation with CSA 10% of the patients with arthritis during follow-up had high stress-levels; this percentage is similar to that of the general population.[24, 30, 31] Also, the mean PSS-10 levels that we observed (13.5) were in line with those previously reported in the USA.[21, 29]

Previously, we observed that patients with CSA had increased pain levels and that levels of functional disability already equalled those at the phase of clinically apparent arthritis. Hence, even though patients with CSA do experience significant pain and physical limitations,[32] stress levels were not evidently increased. Thus, although studies in established RA revealed associations between pain and stress, in the pre-RA stage of CSA the symptoms themselves apparently did not result in higher stress levels.

Our longitudinal analyses revealed that at the time of presentation with clinical arthritis, which generally is the time when a diagnosis is established, 31% of the patients

experienced a high stress response. This prevalence is similar to that observed in studies on (established) RA.[24, 31, 33]

Multiple studies performed in established RA showed associations between stress (both short-lived stress induced in an experimental setting and stress experienced in real life) and inflammation.[1, 2, 6, 9–14] Clear associations were observed for different markers of systemic inflammation (CRP and pro-inflammatory cytokines). Associations with DAS were also observed; interestingly these associations were stronger with the subjective parameters of the DAS, specifically patient's global assessment, evaluator's global assessment and TJC, whereas they found no clear associations with SJC and acute phase reactants.[34] MRI-detected joint inflammation has never been studied before in relation to the psychological stress response, neither in patients with CSA nor in patients with clinically apparent arthritis or RA. Thus the current observations on inflammation and stress in CSA are different from that previously reported in patients with established RA.

The stress response was assessed using two questionnaires. The main analyses were performed using data obtained by the MHI-5 and results were verified by the PSS-10. Both questionnaires are brief and have been shown to have good concordance with larger questionnaires.[24] In our study, results were similar for both questionnaires, which shows validity of the results. Furthermore, by using both questionnaires we observed associations between the psychological stress response and fatigue and general wellbeing. These associations have previously been observed in patients with RA. Thus, although the main results of this study were negative, other known associations were also present in patients with CSA.

Patients with CSA were identified by their rheumatologists using their clinical expertise. Recently, a EULAR definition for arthralgia suspicious for progression to RA was developed to be used on top of the clinical suspicion of imminent RA. This serves to reduce heterogeneity in patient groups, which is highly relevant for the execution of scientific studies and clinical trials in particular.[17, 35] In this study, we repeated the analyses in CSA patients that fulfilled this EULAR definition and similar results were obtained.

Not only stress, but also inflammation was measured over time. Joint inflammation was evaluated using MRI. As expected, the MRI inflammation score increased during progression to clinical arthritis and decreased during the first year of treatment. Despite a strong tendency in the data, statistical significance was not obtained. This is partly explained by a relatively small number of progressors. In addition, MR imaging was made unilaterally of hand and foot joints and consequently other joints that developed clinical arthritis were not imaged. Third, the serial MRIs were scored without information on time order; this decreased the sensitivity to detect changes over time and may have resulted in lower scores compared to chronological reading.[36] Importantly, serial MRIs were not primary evaluated to determine statistical significant changes in the course of MRI-detected inflammation, but rather to compare the time course of stress to

that of the course of inflammation.

This study had some limitations. As for the presence of missing data, 82% of patients completed the MHI-5 and patients with missing data did not differ from patients who completed this questionnaire. Data on the PSS-10 was missing in the oldest part of the cohort, hence missingness was completely at random. Second, the role of acute and chronic stress on inflammation may be complex,[3] here we measured the psychological stress experienced by patients during the last month. We did not collect data on other psychological factors (e.g. coping mechanisms, social support, psychiatric comorbidities) or life events to account for in measurements that could have played a role in arthritis commencement. Also the occurrence of major life events in childhood or more recently in adulthood was not specifically investigated and effects of such major stressors were not evaluated in this study. In addition, regarding systemic inflammation, we only determined CRP levels and did not evaluate other markers, like cytokines. In addition, cortisol or other hormones were not assessed. Further, an important remark could be that CRP values can be increased by diseases not related to the joints. Only 27 of 241 patients had CRP values >10; one of these patients had a comorbidity that may have influenced the CRP level (benign prostate hypertrophy with chronic inflammation). Exclusion of this patient did not change the results (data not shown). Finally, early identification of CSA is difficult, and therefore the size of the current study (241 CSA patients with longitudinal follow-up) is considerable. However, power to detect associations with stress with very small effect sizes may have been insufficient. The previously observed association between life events and risk for RA reported an OR of 1.1 and effects of this size will remain undetected in the present data.

CONCLUSIONS

In conclusion, this study is the first that evaluated the stress response in a symptomatic pre-arthritis phase and also contained longitudinal data. In the phase of arthralgia, high stress levels were infrequent. The proportion of patients with a high stress response increased at the time of clinical arthritis development and diagnosis. Hence, the course of stress levels paralleled or followed, but not preceded, the course of inflammation in this study. This temporal relationship as well as the lack of an association of stress with local or systemic inflammation in the phase of arthralgia may suggest that in this very early disease phase when disease chronicity has not yet been established, stress may have little influence on the inflammatory response, and therefore this implies that it does not mediate the progression from arthralgia to clinical arthritis. Although further studies on the association of stress and inflammation in pre-RA are required, the vicious circle of stress and inflammation as observed in patients with established RA was not yet observed in the phase of CSA.

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Supplementary data

All supplementary methods and data are available at *Arthritis Research & Therapy Online*.

Stress questionnaires

MHI-5 This questionnaire is a part of the SF-36 and contains a Dutch translation of the following questions: Over the last month, how often have you: (9b) been a very nervous person? (9f) felt downhearted and blue? (9d) felt calm and peaceful? (9c) felt so down in the dumps that nothing could cheer you up? (9h) been a happy person?

PSS-10 This questionnaire contains a Dutch translation of the following questions: In the last month, (1) how often have you been upset because of something that happened unexpectedly? (2) how often have you felt that you were unable to control the important things in your life? (3) how often have you felt nervous and 'stressed'? (4) how often have you felt confident about your ability to handle your personal problems? (5) how often have you felt that things were going your way? (6) how often have you found that you could not cope with all the things that you had to do? (7) how often have you been able to control irritations in your life? (8) how often have you felt that you were on top of things? (9) how often have you been angered because of things that were outside of your control? (10) how often have you felt difficulties were piling up so high that you could not overcome them?

Supplementary figure

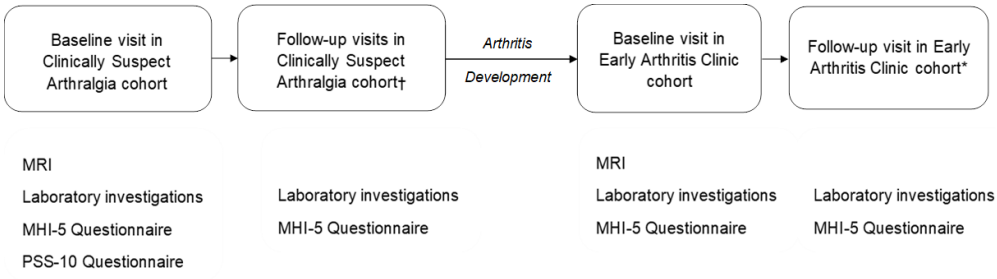

Figure 7.3: Study protocol. Inclusion in Clinically Suspect Arthralgia (CSA) cohort at first presentation to outpatient clinic after onset of arthralgia complaints (n=241). Follow-up visits in CSA-cohort at 4 months, 1 year and 2 years. Patients that developed arthritis (n=45) during follow-up were included in the Early Arthritis Clinic (EAC) cohort (n=39). CSA: In case of no arthritis development follow-up ends after 2 years; *Only 1 year visit was studied here.

8

Depression and anxiety associate with less remission after 1 year in rheumatoid arthritis

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Depression and anxiety have been considered to influence disease activity, and with great interest we read the recently published report by Michelsen *et al.*[1] In this large, prospective, multicentre observational study, depression and anxiety reduced the likelihood of joint remission based on composite scores, in rheumatoid arthritis (RA) after 3 and 6 months. Differences were predominantly caused by subjective markers of disease activity rather than by C reactive protein or erythrocyte sedimentation rate. The study cannot prove causality; however, their findings imply that baseline depression/anxiety can impair the fulfilment of remission criteria during follow-up, influencing important treatment decisions.

As replication is a keystone in research, we aimed to validate their findings in an independent cohort, the Leiden Early Arthritis Clinic (EAC), to assess generalisability of the results. The EAC is a population-based inception cohort of patients with newly diagnosed arthritis that started in 1993; from 2010 onwards patients completed the Short Form-36 (SF-36) at baseline.[2]

We studied patients included between 2010 and 2014 who fulfilled the 2010 criteria for RA (n=343) and selected patients who completed the SF-36 (n=293). Patients with RA were treated according to the insight of the treating rheumatologist: standard therapy regimen consists of early initiation with methotrexate; in case of failure a second

Table 8.1: Baseline characteristics of patients with rheumatoid arthritis with versus without baseline depression/anxiety according to the MCS ≤38 or MH ≤56

	All patients (n=293)	Depressed/ anxious (n=81)	Not depressed/ anxious (n=212)	P value
Age, mean (SD)	57 (15)	54 (15)	58 (14)	0.02
Female, n (%)	193 (66)	58 (72)	135 (64)	0.20
Symptom duration in months, median (IQR)	3 (1-8)	3 (1-7)	3 (1-8)	0.72
Currently smoking, n (%)	65 (23)	25 (33)	40 (20)	0.08
ACPA positive, n (%)	162 (55)	43 (53)	119 (56)	0.64
ESR (mm/h) median (IQR)	28 (14-41)	28 (14-42)	28 (14-41)	0.85
CRP (mg/L), median (IQR)	10 (3-22)	7 (3-26)	10 (3-20)	0.76
EGA, mean (SD)	49 (20)	49 (24)	49 (19)	0.44
PGA, mean (SD)	45 (27)	54 (27)	42 (26)	0.001
Pain, mean (SD)	60 (25)	63 (24)	58 (25)	0.92
68-TJC, median (IQR)	10 (5-17)	11 (6-19)	10 (5-16)	0.18
66-SJC, median (IQR)	5 (2-11)	5 (2-10)	6 (2-11)	0.14
DAS44, mean (SD)	2.9 (0.8)	3.0 (0.8)	2.9 (0.8)	0.45

Pain measured by a 0-100 Visual Analogue Scale (VAS). 68-TJC, 68 tender joint counts; 66-SJC, 66 swollen joint counts; ACPA, anticitrullinated peptide antibody; CRP, C reactive protein; DAS44, 44-joint Disease Activity Score; EGA, evaluator's global assessment by a 0–100 VAS; ESR, erythrocyte sedimentation rate; MCS, mental component summary; MH, mental health subscale; PGA, patient's global assessment by a 0–100 VAS; VAS, Visual Analogue Scale.

synthetic disease-modifying antirheumatic drug (DMARD) was prescribed and in case of failure a biologic DMARD was allowed.[3] Outcome of joint remission was 44-joint Disease Activity Score (DAS44 ≤2.4) after 1-year.[4, 5] Similar as Michelsen *et al.* we identified depression/anxiety by the SF-36 mental health subscale (MH ≤56) and SF-36 Mental Component Summary (MCS ≤38).

Baseline characteristics are shown in Table 8.1. The percentage of depressed/anxious RA-patients was 20% according to the SF-36MCS ≤ 38, and 23% according to the SF-36MH ≤56. Anxious/depressed patients were significantly younger and had a higher patient global assessment (Table 18.1). Anxiety and depression were negatively associated with achieving DAS remission after 1 year, analysed with logistic regression models corrected for age, gender and symptom duration (OR=0.21, 95% CI 0.09 to 0.46 for MCS; OR=0.24, 95% CI 0.11 to 0.51 for MH; p<0.001; Figure 8.1). Analyses with additional correction for baseline DAS showed similar results (MCS p<0.001; MH p=0.001). Further analyses on features of disease activity at year 1 showed that anxiety/depression was associated with more pain (β=12.1, p< 0.001 for MCS; β=11.1, p=0.03 for MH) and a trend for a higher patient's global assessment (β=9.0, p=0.07 for MCS).

Thus, our study on the association of baseline anxiety and depression with remission after 1 year validated the findings from Michelsen *et al.*. We observed higher percentages of patients with RA in DAS remission, which could be caused by the longer duration of treatment (evaluation of remission at 1 year, instead of 3 and 6 months by Michelsen *et al.*).

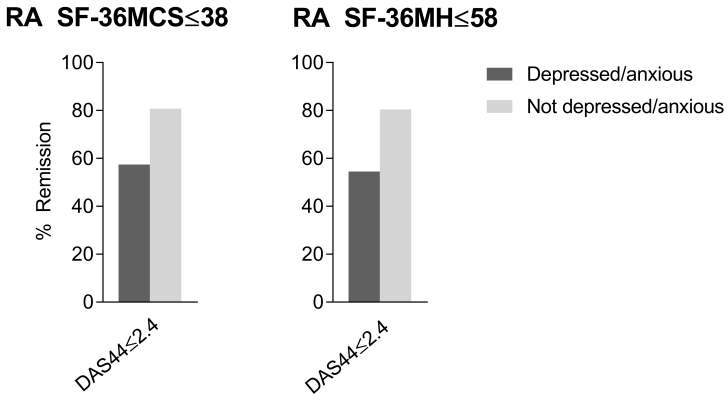

Figure 8.1: Percentages of patients with RA in remission at 1 year (DAS44 ≤2.4) for RA patients that did or did not have depression/anxiety at the time of diagnosis. DAS44, 44-joint Disease Activity Score; RA, rheumatoid arthritis; SF-36 MCS, Medical Outcomes Survey Short Form-36 mental component summary; SF-36 MH, Medical Outcomes Survey Short Form-36 mental health subscale.

Concluding, baseline depression and anxiety are associated with a lower chance to achieve DAS remission, which was mostly reflected by associations with subjective features of disease activity. Also our study cannot prove causality, although the association between the mental state and DAS components suggests that efforts to improve the psychological well-being early in the disease course may prevent higher DAS scores later on. This could potentially prevent increased medical costs due to more intensified treatment strategies.

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9

The contribution of tenosynovitis of small joints to the symptom morning stiffness in patients presenting with Undifferentiated and Rheumatoid Arthritis

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Abstract

Objective

Morning stiffness (MS) is characteristic of Rheumatoid Arthritis (RA). Despite its association with functional disability, it is insufficiently known to what extent local inflammatory processes contribute to this symptom. MRI-detected tenosynovitis of small joints is increasingly recognized as an early feature of RA, which also associates with functional impairments. Recently it was proposed that tenosynovitis may contribute to MS. Therefore, we assessed the relationship between MS and MRI-detected inflammation and in particular tenosynovitis.

Methods

286 consecutive patients newly presenting with undifferentiated arthritis and RA underwent contrast-enhanced 1.5T MRI of (2-5)MCP-, wrist- and (1-5)MTP-joints. Scans were scored for tenosynovitis according to Haavardsholm and for synovitis, conform the RAMRIS-method. MS was dichotomized as >60 minutes or not. Associations between MS and tenosynovitis/synovitis were tested with logistic regression, data were categorized (solitary or simultaneous presence of synovitis / tenosynovitis) and the presence of an additive interaction was assessed.

Results

MS was present in 40% of patients. Tenosynovitis was more often present in patients with MS than without MS (80% versus 65%), OR 2.11 (95%CI 1.21; 3.69). Also synovitis was more often present in patients with MS (58% versus 44%), OR 1.79 (1.11; 2.91). In categorized analyses, concurrent synovitis and tenosynovitis had the largest association OR 2.43 (1.30; 4.54); in contrast to the sole presence of synovitis (OR 0.85 (0.21; 3.47). The additive interaction was non-significant. The variance explained in all analyses was small, ranging 4-5%.

Conclusion

Tenosynovitis, combined with synovitis, at small joints associated with MS and contributes to the pathophysiology of MS.

Introduction

Morning stiffness (MS) is characteristic of Rheumatoid Arthritis (RA) and prevalent in 40-50% of patients.[1] MS has been a component of classification- and remission-criteria for RA, illustrating it is considered a key symptom. Its presence contributes to patients' perceived disease burden as it is consistently associated with functional disability.[1–3] Although MS is prevalent and causes functional limitations, its pathophysiology is still poorly understood.[1]

It is presumed that both systemic inflammation and local inflammation underlie MS.[4] Most studies focussed on systemic factors, which is intuitive as the circadian rhythm of symptoms parallels late night and early morning rises of pro-inflammatory markers.[5] The time-relationship and the observation that MS could be relieved by the application of low-dose prednisone during the night makes it likely that systemic inflammatory markers contribute to MS.[6]

MS is generally most pronounced in the hands. Therefore it is presumable that next to systemic inflammation, also local inflammation is important for the occurrence of MS. However, in proportion to the number of studies focussing on systemic markers, the association with local inflammation is less well studied. An association with swollen joints has been described,[1] and some studies showed correlations with ultrasound-detected synovitis.[3, 7–9]

Recently, it has been shown that, next to synovitis, tenosynovitis of small-joints is characteristic of RA . Tenosynovitis associated with functional limitations in patients with early inflammatory arthritis.[10] In this light, it has been suggested that tenosynovitis contributes directly to MS.[11] Some suggestive evidence was obtained but analyses included small patient populations and other features of local inflammation, like concomitant synovitis, were not considered.

The fact that MS is a hallmark symptom of RA of which we do not fully understand the pathophysiology prompted us to perform this large cross-sectional MRI-study in which we aimed to determine if tenosynovitis, also in relation to synovitis, at small-joints associated with MS in patients presenting with undifferentiated arthritis (UA) and RA.

Methods

Patient population

We studied cross-sectional data of 286 consecutive patients from the Leiden Early Arthritis Clinic (EAC)-cohort included between June 2013-February 2016. The EAC is a population-based inception-cohort of patients with recent-onset arthritis and symptom duration <2 years, as described previously.[12] Patients, diagnosed with RA (2010- or 1987-criteria) or UA (not fulfilling these criteria, and no other diagnosis) that underwent baseline gadolinium-enhanced MRI were selected (supplementary Figure 9.2). The clinical diagnosis was made by the treating rheumatologist. RA was further verified by

fulfilling the classification-criteria during the first-year. Patients with missing MRI-scans were excluded (n=65); they were not different from included patients (Table S1).

Baseline questionnaires, 66-swollen and 68-tender joint counts (66-SJC,68-TJC), and laboratory investigations were performed. Written informed consent was obtained from all patients. The study was approved by the local Medical-Ethics-Committee-Leiden, Approval number P17.261.

Morning stiffness measurements

Two questions on MS were filled out. The first concerned presence of MS ('joints stiff in the morning: yes/no') and the second its duration ('stiffness of the joints <30 minutes; 30-60 minutes; 1-2 hours; 2-4 hours; whole day'). Scores were dichotomized for presence (≥60 minutes) and absence of MS (either 'no' or duration <60 minutes), because this cut-off has been shown sensitive and specific for RA.[12] Additionally, we explored a cut-off of ≥30 minutes.[12]

MRI scanning and scoring

Baseline 1.5T MRI were made (before any DMARD-initiation), of MCP(2-5)-, wrist- and MTP(1-5)-joints of the most affected side (or dominant side in case of equal symptoms). NSAIDs were stopped 24hrs before MRI. Scans were performed between 9am-16pm. and scored in line with the OMERACT-RAMRIS-method by two independent readers; mean scores of both readers were calculated. Semi-quantitative scores ranged from 0-3 per location and were summed for total synovitis- and tenosynovitis-scores. MRI-scans were considered positive for MRI-detected tenosynovitis/synovitis if this was present in ≥1 joint, which was present in <5% of age-matched healthy controls (described supplementary) .

Statistics

Associations between MS and MRI-detected synovitis and tenosynovitis were tested with logistic-regression (MS entered as dependent; clinical-, imaging-findings as independent variables). The explained variance was assessed by the Nagelkerke R^2. As synovitis/tenosynovitis often co-occur , to prevent collinearity, we did not perform multivariable analyses but examined associations of isolated and simultaneous presence of synovitis and tenosynovitis by categorizing data. An additive interaction was examined,[13] by the relative risk excess (RERI), synergy index (SI) and attributive proportion (AP). In the absence of an interaction, RERI, AP equal 0 and SI equals 1,[13] and described supplementary.
Sensitivity analyses were performed, firstly in RA-patients (excluding UA-patients), secondly for MS-duration ≥30 minutes. Thirdly, as MS is often experienced at the hands, MRI-detected inflammation was assessed in hand-joints(excluding MTP-joints).
IBM SPSS v23 was used. P-values <0.05 were considered significant.

Results

Patient characteristics

Baseline characteristics are shown in Table 1. 40% experienced MS. They had higher 66-SJC and CRP (Table 9.1).

Associations between tenosynovitis and synovitis with morning stiffness

The median tenosynovitis-score was 7 in patients with and 3 in patients without MS (p=0.001). The median score for synovitis was 5 in patients with and 3 in patients without MS (p=0.001) (Figure 9.1).

Tenosynovitis was present in 70% and more often in patients with MS (80% versus 65%); OR 2.11 (1.21;3.68). Synovitis was present in 49% and more often in patients with MS (58% versus 44%; OR 1.79 (1.11;2.91)) (Table 9.2). The explained variance (R^2) ranged between 4-5% (Table 9.2).

Assessment of interaction of concurrent tenosynovitis and synovitis in categorized data

Synovitis and tenosynovitis often occurred simultaneously: combined synovitis and tenosynovitis was present in 127 patients (45%), solitary tenosynovitis in 72 (25%), solitary synovitis in 12 (4%) and 71 (25%) patients had no synovitis or tenosynovitis in imaged joints. Presence of simultaneous synovitis/tenosynovitis had the strongest association with MS (OR 2.43 (1.30;4.54)), while synovitis without tenosynovitis was not

Table 9.1: Baseline characteristics of RA and UA-patients studied and odds ratios with morning stiffness

	All patients (n=286)		MS present (n=113)		MS absent (n=173)		OR* (95%CI)
Age, mean (SD)	57	(16)	56	(15)	57	(15)	0.99 (0.98; 1.01)
Female, n (%)	178	(62)	65	(58)	113	(65)	1.39) (0.86; 2.26)
66-Swollen joint count, median (IQR)	3	(1-8)	6	(1-6)	2	(1-6)	1.08 (1.03; 1.13)
Symptom duration in weeks, median (IQR)	10	(5-27)	9	(4-27)	11	(5-27)	1.00 (0.99; 1.01)
CRP increased (≥5mg/L), n (%)	165	(58)	76	(52)	89	(52)	1.95 (1.18; 3.20)
RF positive (≥3.5 IU/mL), n (%)	104	(37)	47	(33)	57	(33)	1.36 (0.88; 2.12)
ACPA positive (≥7 U/mL), n (%)	77	(27)	33	(26)	44	(26)	1.22 (0.72; 2.08)

Positive associations with MS were found for CRP-positivity, OR 1.95 indicates that patients with an increased CRP had a 1.95 higher odds on having MS than patients with a normal CRP, and for 66-SJC 1.08, meaning that per increase in swollen joint the patient had a 1.08 higher odds on MS. *OR, odds ratio with MS, morning stiffness. ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

associated in categorized analyses (OR 0.85 (0.21;3.47) (Table 9.2, Figure 9.1).
The presence of an additive interaction between synovitis and tenosynovitis was explored; although the largest effect was obtained for concomitant synovitis/tenosynovitis, the RERI was 1.05 (–0.52;2.62), AP 0.43 (–0.18;1.05) and SI 3.78 (0.05;270.0), suggesting a small non-significant additive effect of combined synovitis/tenosynovitis (Table 9.2, Figure 9.1)

Sensitivity analyses

Analyses in RA-patients (n=168, Table 9.3), showed similar results for tenosynovitis and synovitis with MS (OR 1.82 (0.75;4.42), (Table 9.4)).
Analyses of MS ≥30 minutes, were also similar. Simultaneous presence of tenosynovitis/synovitis associated with MS (OR 2.65 (1.45;4.84), (Table 9.5)).

Discussion

This cross-sectional study provided evidence for the relationship between MRI-detected tenosynovitis and MS in RA and UA. The largest effect was obtained for simultaneous tenosynovitis/synovitis, while solitary presence of synovitis, was not associated with MS. Importantly, all effect sizes were relatively small and the proportion of variance of MS explained by tenosynovitis was minor. This suggests that local inflammation contributed to a small extent, and implies that other factors may have a greater contribution to the symptomatology of MS.
Most previous studies that investigated associations between inflammation and MS focussed on systemic inflammatory-markers such as cytokines. Very few studies addressed the issue of local inflammation. One study related MS to SJC,[1] and a few to ultrasound-detected synovitis.[3, 7–9] Our results on SJC were concordant with these studies.[1, 2] For example, an OR of 1.05 for MS with swollen joint counts was

Table 9.2: Baseline characteristics of RA and UA-patients studied and odds ratios with morning stiffness

Presence of feature		OR (95% CI)	R^2
	Synovitis	1.79 (1.11; 2.91)	0.04
	Tenosynovitis	2.11 (1.21; 3.68)	0.04
Categorized features			
Synovitis	Tenosynovitis	OR (95% CI)	
-	-	1.0 (ref)	0.05
+	-	0.85 (0.21; 3.47)	
-	+	1.53 (0.76; 3.09)	
+	+	2.43 (1.30; 4.54)	

Associations of morning stiffness with presence of MRI-detected tenosynovitis and synovitis and categorized analyses.
*OR (95% CI): Odds ratios with 95% confidence intervals.

reported,[1] which was 1.08 here. To the best of our knowledge, this was the first study that examined the effect of MRI-detected tenosynovitis in relation to MS, also taking simultaneous presence of synovitis into account. The association between MRI-detected inflammation and MS were similar in RA or the total group.

Previous studies have shown that a duration >60 minutes was specific for RA but >30 minutes also had good sensitivity and specificity.[12] In our data, findings were similar for both durations.

This study had some limitations. First, a uniformly accepted definition of MS does

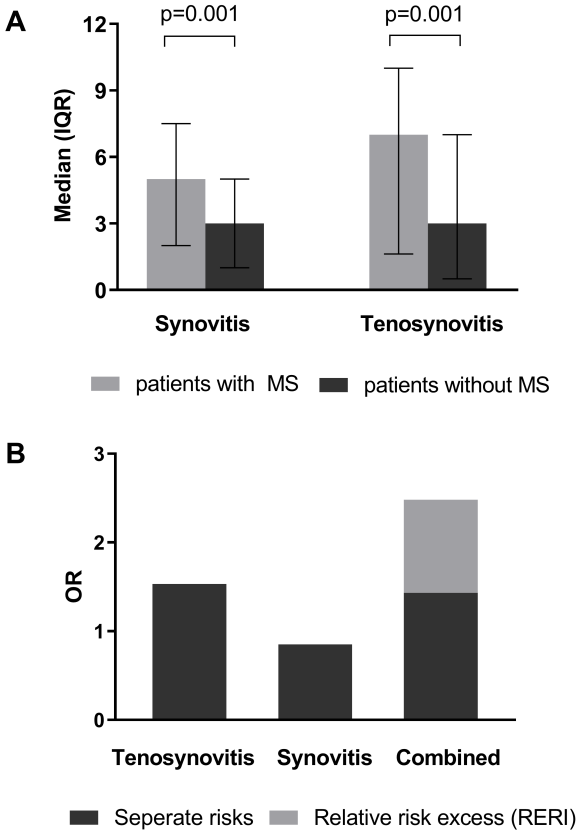

Figure 9.1: Associations of morning stiffness with (A) MRI-detected tenosynovitis and synovitis-scores and (B) evaluation of the presence of an additive interaction.
Legend. A shows median (interquartile range, IQR) synovitis and tenosynovitis-scores in patients with and without MS. B illustrates the additive effect of the combined presence of synovitis and tenosynovitis. RERI was 1.05 (–0.52;2.62), AP 0.43 (–0.18;1.05), SI 3.78 (0.05;270.0).

not exist. We collected data of MS-duration but not of MS-severity. Previous reviews concluded that there is insufficient evidence to prioritise a measure for MS.[4, 14] Whether the association of MRI-detected inflammation with MS-severity is stronger than that of MS-presence is subject for further studies.

Second, MRI-scans were performed anytime during the day. Ideally they would have been performed in the early morning when MS is most severe, but this was not feasible. Previous data showed that MRI-detected inflammation does not change during the day,[15] but we cannot rule out that this has resulted in underestimated effect-sizes.

It is surprising that the biologic mechanisms underlying MS are still poorly understood. An association with local inflammation is presumable since (infiltrated) immune cells, and also fibroblast-like synoviocytes that are resident in the joint at the synovium/surrounding synovial compartment follow the circadian rhythm. As synovitis/tenosynovitis often occur simultaneously, we hypothesized that this co-occurrence might engrave MS. Indeed we observed the highest association for the simultaneous synovitis/tenosynovitis. However, we found no additive interaction in relation to MS. Thus, concomitant synovitis/tenosynovitis had the strongest association with MS, without an additional effect.

In conclusion, particularly the simultaneous presence of tenosynovitis and synovitis, associated with MS. However, the effect sizes and percentages of explained variance suggested that the contribution of local inflammation as detected by MRI to this symptom is rather limited.

Acknowledgements

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Supplementary data

Supplementary data are online available.

Supplementary figure

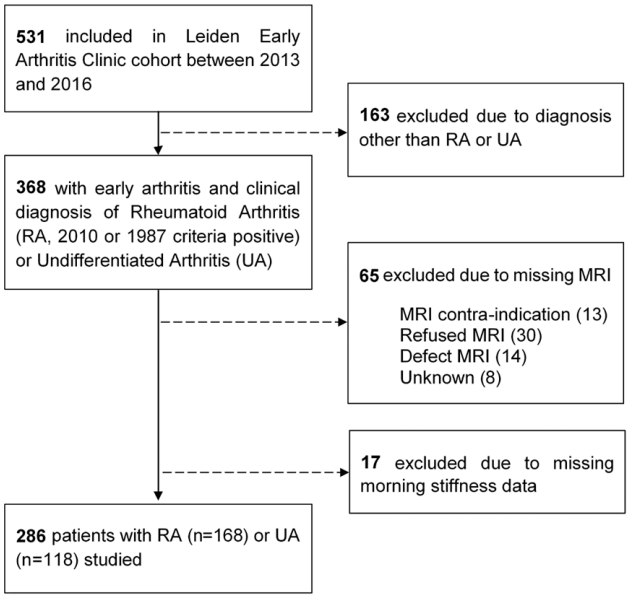

Figure 9.2: Flowchart of patient selection

Supplementary tables

Table 9.3: Sensitivity analyses: baseline characteristics of patients with RA (fulfilling 2010- and/or 1987-classification criteria) and odds ratios for presence of morning stiffness

	All patients (n=168)		MS present (n=86)		MS absent (n=82)		OR* (95%CI)
Age, mean (SD)	59	(14)	61	(13)	57	(16)	0.99 (0.96; 1.01)
Female, n (%)	111	(67)	60	(70)	51	(62)	1.40 (0.74; 2.66)
66-Swollen joint count, median (IQR)	6	(3-11)	5	(2-9)	8	(4-12)	1.04 (0.99; 1.09)
Symptom duration in weeks, median (IQR)	13	(6-29)	16	(7-33)	11	(6-29)	0.99 (0.98; 1.00)
CRP increased (≥5mg/L), n (%)	110	(67)	52	(61)	58	(72)	1.60 (0.84; 3.07)
RF positive (≥3.5 IU/mL), n (%)	94	(57)	49	(58)	45	(55)	1.02 (0.58; 1.79)
ACPA positive (≥7 U/mL), n (%)	74	(45)	42	(49)	32	(40)	0.67 (0.36; 1.24)

Positive associations with MS were found for CRP-positivity, OR 1.95 indicates that patients with an increased CRP had a 1.95 higher odds on having MS than patients with a normal CRP, and for 66-SJC 1.08, meaning that per increase in swollen joint the patient had a 1.08 higher odds on MS. *OR, odds ratio with MS, morning stiffness. ACPA, anti-citrullinated peptide antibody (anti-CCP2, EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL); RF, immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL); CRP, c-reactive protein (positive if ≥5mg/L); SD, standard deviation; IQR, Inter quartile range.

Table 9.4: Sensitivity analyses in patients with RA (fulfilling 2010- and/or 1987-classification criteria) for odds ratios for presence of morning stiffness (>60 minutes) and categorized analyses.

Presence of feature		OR (95% CI)	R^2
	Synovitis	1.38 (0.74; 2.58)	0.01
	Tenosynovitis	1.77 (0.80; 3.91)	0.02
Categorized features			
Synovitis	Tenosynovitis	OR (95% CI)	
-	-	1.0 (ref)	0.02
+	-	0.80 (0.12; 5.20)	
-	+	1.45 (0.54; 3.95)	
+	+	1.82 (0.75; 4.42)	

*OR (95% CI): Odds ratios with 95% confidence intervals.

Table 9.5: Sensitivity analyses for when MS was defined as a duration >30 minutes; odds ratios and categorized analyses

Presence of feature		OR (95% CI)	R^2
	Synovitis	1.96 (1.21; 3.18)	0.04
	Tenosynovitis	2.17 (1.29; 3.66)	0.04
Categorized features			
Synovitis	Tenosynovitis	OR (95% CI)	
-	-	1.0 (ref)	0.06
+	-	0.77 (0.23; 2.68)	
-	+	1.44 (0.75; 2.78)	
+	+	2.65 (1.45; 4.84)	

*OR (95% CI): Odds ratios with 95% confidence intervals.

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.

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11

Nederlandse samenvatting

In deze thesis, bespreken we in **deel I** de rol en implicaties van inflammatie gedetecteerd door beeldvormende technieken, in het specifiek door MRI maar tevens middels echografie om Reumatoïde Artritis (RA) vroeg op te kunnen sporen. Voor dit doel maken we gebruik van data van twee cohorten: het Clinically Suspect Arthralgia (CSA) cohort en de Leiden Early Arthritis Clinic (EAC) cohort. Verder nemen we ook MRI data van symptoom vrije controles mee. In **deel II**, kijken we meer naar de door patiënten zelf gerapporteerde uitkomsten in de fase van een klinisch voor RA verdachte artralgie en in de vroege ziekte fase van RA. We analyseren de prevalentie en het verloop van symptomen en we trachten het begrip van verschillende symptomen te verbeteren door de relatie met lokale (MRI gedetecteerde) gewrichtsontsteking te onderzoeken.

DEEL I: Vooruitgang in beeldvormende technieken voor de vroege detectie van RA

In **Hoofdstuk 2**, onderzoeken we de toepassing van een referentie gebaseerd op symptoom vrije controle personen om een MRI op aanwezigheid van ontsteking te definiëren in patiënten met een klinisch voor RA verdachte artralgie voor de ontwikkeling van een klinisch detecteerbare inflammatoire artritis en ook in patiënten met ongedifferentieerde artritis voor de ontwikkeling van RA. In deze patiënt populaties is de waarde van gewrichtsontsteking gedetecteerd door MRI (synovitis, tenosynovitis en beenmerg oedeem) eerder gedemonstreerd en de aanwezigheid van inflammatie was geassocieerd met een verhoogd risico op RA. MRI is een gevoelige methode, derhalve is er een risico 'vals positieve MRI resultaten' te verkrijgen. Daarom kwam de vraag op of de gewrichtsontsteking gedetecteerd door MRI ook aanwezig zou kunnen zijn in een gezonde controle populatie. Dit was slechts beperkt onderzocht, en daarom heeft Mangnus et al voor dit doel 193 symptoom vrije personen uit de algemene populatie onderzocht. Deze studie wees inderdaad uit dat bepaalde vormen van laaggradige inflammatie op MRI ook aanwezig zijn in symptoom vrije controle personen, op bepaalde voorkeurs locaties en toenemend met leeftijd. Bijvoorbeeld, beenmerg oedeem in het lunatum was aanwezig in 19% van de personen tussen 40-59 jaar en ook graag 1 synovitis in de pols kwam vaak voor, 35% van de personen ouder dan 60 had synovitis in het radiacarpale gewricht. Tenosynovitis kwam niet vaak voor in de gezonde controles. In dit hoofdstuk onderzochten we de implicaties van de bevindingen in de gezonde controles door te analyseren of het meenemen van de prevalentie van de afwijkingen in gezonde vrijwilligers de voorspellende waarde van MRI zou kunnen verbeteren. Voor dit doel hebben we twee verschillende afkap punten onderzocht en hebben we de bevindingen vergelijken met de waarde van MRI zonder het meenemen van de afkappunten. De afkapwaarden welke we hebben onderzocht werden de '1% gecorrigeerde definitie' en de '5% gecorrigeerde definitie' genoemd. Dit hield in dat bijvoorbeeld voor de '5% gecorrigeerde definitie' een bepaald type inflammatie op een bepaalde locatie binnen een bepaalde leeftijdscategorie (<40, 40-59, ≥60) aanwezig was in minder dan 5% van de gezonde controles binnen dezelfde leeftijdscategorie, dan was het gezien als 'positief' voor door MRI gedetecteerde inflammatie, maar als het aanwezig was in 5% of meer dan werd het beoordeeld als 'negatief'. De toepassing van deze afkapwaarde was voordelig. Het leidde tot een afname in het aantal vals positieve resultaten, dit ging dus samen met een toename in specificiteit terwijl de

sensitiviteit stabiel bleef en de accuraatheid van MRI steeg ook. Derhalve suggereert dit overtuigend dat een afkap voor de bepaling van een positieve MRI gebaseerd op gezonde controles voordelig is voor de bepaling van een positieve MRI in patiënten met vroege of pre-RA. We onderzochten naast de afkap van 5% ook een afkapwaarde van 1%. Hier werd een MRI gezien als positief indien het aanwezig was in minder dan 1% van de gezonde controles. Echter lied deze afkapwaarde zien dat de specificiteit wederom wel steeg, maar nu ten koste van een daling in sensitiviteit. Dit betekend dat er dus patiënten worden gemist, als het gaat om de vroege detectie van RA. Concluderend laten de bevindingen dus zien dat inflammatie in gezonde controles leiden tot een valide afkapwaarde, met name de afkapwaarde van 5%, daar deze leidde tot een verbetering in test karakteristieken. Dit werd weerspiegeld door een afname in vals positieve resultaten, zonder een aanzienlijke verandering van de sensitiviteit en dus de detectie van terecht positieve resultaten.

In het volgende hoofdstuk, in **Hoofdstuk 3**, onderzochten we de toegevoegde waarde van beeldvorming in een andere toepassing. We onderzochten het voor het bepalen van het aantal betrokken gewrichten voor de classificatie van patiënten als RA. Omdat vroege classificatie van RA belangrijk is, met name voor het zo vroeg mogelijk includeren van patiënten met RA, zijn de 2010 ACR/EULAR classificatie criteria ontwikkeld. Tijdens de ontwikkeling van deze criteria was het gesuggereerd dat beeldvormende methoden, in aanvulling tot pijnlijke en gezwollen gewrichten, gebruikt zouden kunnen worden om het aantal betrokken gewrichten te bepalen. Hoe deze aanvulling toegepast zou moeten worden, was niet duidelijk gespecificeerd. Derhalve hebben wij de aanvullende waarde van inflammatie gedetecteerd door MRI, in het bijzonder voor synovitis, bepaald om het aantal betrokken gewrichten te bepalen voor de 2010 ACR/EULAR classificatie criteria. Deze aanvulling lijkt zinvol, omdat uit eerder onderzoek is gebleken dat inflammatie op MRI is geassocieerd met ontwikkeling van RA en tevens dat inflammatie in patiënten met vroege inflammatoire artritis aanwezig kan zijn in een aanzienlijke hoeveelheid gewrichten die niet gezwollen of pijnlijk waren bij lichamelijk onderzoek. We hebben patiënten met een klinische diagnose met UA of RA geselecteerd en hen gevolgd gedurende 1 jaar voor de uitkomst DMARD start. DMARD start impliceert dat de behandelend reumatoloog overtuigd is dat de patiënt persisterende klachten zal hebben van de artritis. Deze uitkomst was gebruikt als proxy voor RA, gelijk aan uitkomsten gebruikt voor andere studies. We lieten zien dat de toevoeging van synovitis gedetecteerd door beeldvorming resulteerde in een toename in het aantal betrokken gewrichten van 48%, welke daarop leidde tot een toename in het aantal punten voor het item 'involved joints' in 25% en dus een additie van 10% toename in patiënten die nu voldeden aan de 2010 ACR/EULAR criteria. Deze toename betrof zowel vals positieven als terecht positieve resultaten. De AUC steeg tevens ook niet. Wanneer we de afkap voor een positieve MRI op basis van gezonde vrijwilligers gebruikten, bleef de toevoeging van MRI niet voordelig. Dit suggereert dat er tot op heden geen overtuigend bewijs is dat de toevoeging van beeldvorming om het aantal betrokken gewrichten te bepalen voor de 2010 classificatie criteria van toegevoegde waarde is. Derhalve moet men voorzichtig zijn met het toepassen van deze notie omdat het leidt tot een a specifieke toename van patiënten die voldoen aan de 2010 ACR/EULAR classificatie criteria voor RA.

In **Hoofdstuk 4**, is het huidige MRI protocol dat wordt toegepast voor de detectie van RA kritisch geëvalueerd. Het protocol bevat naast beeldvorming van de handgewrichten (MCP 2-5 en pols) ook de gewrichten van de voeten (MTP 1-5). Hoewel MRI van de voeten waardevol kan zijn, leidt het tot een toename in scan tijd en kosten. Daarom hebben we de toegevoegde waarde van MRI van de voeten in 357 patiënten met CSA onderzocht. Alle patiënten ondergingen een met contrast versterkte 1.5T MRI op baseline en werden gevolgd tot de ontwikkeling van klinisch evidente inflammatoire artritis (IA). Eerst hebben we de voorspellende waarde van ontsteking aan de voetgewrichten bepaald. We vonden dat, gelijk als voor de handen, dat ook voor de voeten, tenosynovitis de meest voorspellende waarde had van de verschillende typen van door MRI gedetecteerde inflammatie. Deze associatie was onafhankelijk van ACPA en CRP, de HR was 3.13 (1.48; 6.64). De volgende stap bestond uit het evalueren van de toegevoegde waarde van MRI van de handen. We observeerden dat de toevoeging van MRI van de voeten tot MRI van de handen niet leidde tot een toename in de voorspellende waarde en accuraatheid van de MRI. De sensitiviteit bleef tevens stabiel 77% (64%-86%), terwijl de specificiteit tevens niet verbeterde daar deze veranderde van 66% (60%-71%) naar 62% (56%-67%) voor de uitkomst IA ontwikkeling binnen het eerste jaar. Sensitiviteitsanalyses met RA ontwikkeling als uitkomst liet vergelijkbare resultaten zien. Tevens werd er een net re classificatie index berekend, welke -3.9% was voor MRI-gedetecteerde inflammatie. Deze liet dus tevens geen voordelige effecten zien voor de additie van MRI van de voeten. We verwachten dat de afwezigheid van een additief effect meest waarschijnlijk verklaard kan worden door het feit dat er slechts weinig patiënten waren die klinische IA ontwikkelden, die enkel inflammatie van de voet gewrichten hadden, dus zonder enige inflammatie aan de handen. Daarop hebben we de prevalentie van inflammatie van de gewrichten in alle CSA patiënten bekeken, 11% had inflammatie in de handen en de voeten, 29% alleen in de handen, 3% alleen in de voeten. Derhalve concludeerde we dat, tenosynovitis in de voorvoeten in paténten met CSA de ontwikkeling van IA en RA voorspelde. Desalniettemin, een MRI van de voeten in aanvulling tot een MRI van de handen zorgde niet voor een toename van de waarde van MRI. Dit werd waarschijnlijk veroorzaakt doordat patiënten zelden inflammatie hadden aan de voet gewrichten alleen, zonder inflammatie aan de hand gewrichten. Deze uitkomst werd ondersteund door de test karakteristieken, de net re classificatie index en onze uitkomsten waren tevens in lijn met een eerder gepubliceerde studie in patiënten met UA, welke tevens onze observatie ondersteunt. Daarom concludeerden wij dat een voet MRI achterwege gelaten kan worden om scan tijd en kosten te beperken en hiermee de haalbaarheid van een MRI te verbeteren.

In **Hoofdstuk 5**, adresseren we het probleem van de voor de vroege detectie van RA frequent gebruikte beeldvormende technieken, MRI en echografie. Beiden worden momenteel aangeraden voor de vroege detectie van RA, zonder onderscheid te maken welke modaliteit het best gebruikt kan worden. Daar het voor beide beeldvormende modaliteiten is gebleken dat tenosynovitis en synovitis voorspellende waarde heeft, kan het worden verwacht dat beiden dezelfde laesies detecteren, maar dit is nooit onderzocht op gewrichtsniveau. Daarom hebben we onderzocht of echo en MRI

dezelfde inflammatoïre laesies detecteerd in 70 opeenvolgende patiënten met vroege IA of CSA op een gewrichts/pees-niveau. MRI wordt in het algemeen gezien als een zeer sensitieve en valide methode om lokale gewrichtsinflammatie. Je kunt de drie dimensionale opname maken van het gewricht en de resultaten zijn reproduceerbaar. Daarnaast is echografie een makkelijker beschikaar in verschillende centra door lagere kosten en doordat het minder tijdsrovend is. Echo heeft ook nadelen, namelijk dat de resultaten soms moeilijk zijn te reproduceren doordat het operator en machine afhankelijk is. In deze thesis werden de beeldvormende technieken vergeleken door middel van gevalideerde semi kwanitatieve scorings methoden. Deze methoden verschillen voor echo en MRI. Elke graad heeft verschillende voorwaarden voor beide modaliteiten. Voor MRI hebben we gebruik gemaakt van de OMERACT-RAMRIS methode voor synovitis en tenosynovitis. Voor echo hebben we twee scoringsmethoden gebruikt, de methode volgens Szkudlarek et al, voor grey scale (GS) en Power doppler (PD) synovitis en tenosynovitis, en de recentelijke ontwikkelde EULAR-OMERACT methode voor GS synovitis. Dit was de eerste studie welke de recent ontwikkelde EULAR-OMERACT methode voor echografie heeft gebruikt in vergelijking tot MRI in patiënten met vroege IA en CSA. Directe vergelijking van de beide echografie scoringsmethoden wees aan dat de 'modified Szkudlarek' methode de hoogste scores genereerde ten opzichte van de EULAR-OMERACT methode. De 'modified Szkudlarek' methode combineert synoviale effusie en hypertrofie. Derhalve genereerde deze methode meer vals positieve resultaten. Daar de scoringsmethode verschillen voor echografie en MRI, hadden we ook niet verwacht dat de scores 1 op 1 zouden correleren. Daarom was het vergeleken of toenemende scores voor MRI werden samengegaan door toenemende scores van echo en ook of de aanwezigheid van synovitis of tenosynovitis, met behulp van verschillende afkapwaarden, gedetecteerd door MRI, tevens werden geïdentificeerd door echografie op gewrichts- en peesniveau. In het algemeen liet onze data inderdaad zien dat een toename van scores voor MRI parallel liep met toenemende scores voor echografie. Na dichotomisering van de scores, had echografie een goede specificiteit, maar het was minder sensitief wanneer MRI als referentie werd genomen op een gewrichts- en pees-niveau. Desalniettemin liet echo soms ook inflammatie zien op locaties welke negatief waren voor inflammatie op MRI (tenosynovitis of synovitis). Het is wel van belang om op te merken dat de verschillende semi-kwantitatieve scoringsmethoden directe vergelijking van echo en MRI in de weg staan. Toch suggereren de huidige bevindingen overtuigend dat MRI niet simpelweg kan worden verplaatst door echo met behoud van sensitiviteit op gewrichts- en peesniveau. Desalniettemin was dit een cross-sectionele analyse en longitudinaal onderzoek is beter geschikt om uit te wijzen welke modaliteit met de meeste voorkeur aanbevolen dient te worden. Daarnaast is replicatie van de huidige bevindingen ook nodig.

PART II: Impact van RA op het dagelijks leven

Het tweede deel van deze thesis richt zich meer op het meten van de impact van RA middels andere uitkomst maten dan de traditionele uitkomsten, welke van belang zijn vanuit het perspectief van de patiënt. De traditionele uitkomsten zoals schade zijn minder belangrijk geworden wegens een afname van de prevalentie van structurele schade, als consequentie van de verbeterede therapeutische behandelstrategieën in RA.

Hoofdstuk 6 behandelt patient reported outcomes (PROs) inclusief fysiek functioneren en werkuitval in 982 patiënten met RA, recent gediagnosticeerd en behandeld conform huidige behandelstrategieën. Ons doel was om de twee verschillende subsets van RA te vergelijken, namelijk patiënten met anticitrullinated protein antibodies (ACPA-positief) en zonder (ACPA-negatief). ACPA-positieve RA wordt in het algemeen gezien als de meest ernstige subset van RA omdat het geassocieerd is met ernstige gewrichtsschade en een hogere mortaliteit. Echter, door hedendaagse verbeterde therapeutische strategieën, bestaand uit vroege initiatie van metotrexaat en ziekte activiteit (DAS)-gestuurde behandelstrategieën, is gewrichtsschade minder frequent aanwezig. Desalniettemin heeft hedendaags onderzoek nog steeds de neiging om zich meer op ACPA-positieve, dan ACPA-negatieve RA te focussen. Daar gewrichtsschade infrequent is geworden, zijn andere uitkomsten meer relevant geworden. Voor deze reden hebben we getracht te onderzoeken of de focus op ACPA-positieve RA tevens kan worden gerechtvaardigd wanneer andere uitkomsten worden onderzocht. Een studie heeft bepaald welke parameters belangrijk zijn voor patiënten zelf. Pijn, moeheid en onafhankelijkheid warden gezien als de belangrijkste parameters vanuit het perspectief van de patiënt, om de ziekte impact te meten. Onafhankelijkheid is sterk gerelateerd aan fysiek functioneren en ook de mogelijkheid om te werken en dagelijkse activiteiten te vervullen. In deze studie hebben we pijn, moeheid en algemeen welzijn gemeten, maar ook vragen over productiviteit op het werk en thuis. Onze data liet zien dat de PROs op baseline iets ernstiger waren voor ACPA-negatieve, in vergelijking tot ACPA-positieve patiënten. Dit in tegenstelling tot de huidige verwachting. De verschillen waren echter klein en mogelijk warden ze veroorzaakt door de manier waarop de 2010-criteria zijn opgesteld. Namelijk binnen de 2010-criteria hebben ACPA-negatieve patiënten >10 gewrichten nodig om aan de 2010-criteria voor RA te voldoen en dit zou de ernst van de klachten kunnen verklaren. We hebben daarop tevens patiënten met RA geselecteerd middels de 1987-criteria in plaats van de 2010-criteria. Met deze selectie methode zagen we inderdaad geen verschillen meer tussen ACPA-negatieve en ACPA-positieve patiënten. De longitudinale data van 4 jaar follow up, liet zien dat ACPA-negatieve en ACPA-positieve patiënten beiden op dezelfde wijze verbeterden gedurende follow up. De grootste verbetering van PROs werd gezien gedurende het eerste jaar na diagnose. We zagen enkel een klein verschil voor moeheid, welke iets ernstiger was voor ACPA-negatieve patiënten. Dit was 0.5 op een schaal van 0-10. Naast deze uitkomsten hebben we in een deel van de patiënten andere uitkomsten bekeken. Vanaf 2010 hebben patiënten tevens een vragenijst over arbeidsparticipatie ingevuld. De baseline resultaten waren vergelijkbaar voor ACPA-positieve en ACPA-negatieve patiënten. Longitudinaal onderzoek wees uit dat de beide subsets tevens voor deze uitkomsten een vergelijkbaar verloop hadden over de eerste 4 jaar na diagnose. We zagen echter voor deze uitkomsten ook wat kleine verschillen ten nadele van ACPA-negatieve RA patiënten (2010-criteria). Na het toepassen van additionele correcties voor baseline verschillen tussen ACPA-negatieve en ACPA-positieve RA (bijvoorbeeld het aantal gezwollen gewrichten), lieten multivariabele analyses geen verschillen meer zien. Analyse van data van eerdere tijdsperioden (1993-1999) liet zien dat ACPA-positieve RA wel een ernstigere ziekte was in vergelijking tot ACPA-negatieve RA, wanneer deze

gemeten werden door PROs en werkverlies. In conclusie zagen we geen ernstigere ziekteverloop voor ACPA-positieve, in vergelijking tot ACPA-negatieve RA patiënten, wanneer ze volgens huidige behandelstrategie, bestaand uit vroege initiatie van een DMARD (bij voorkeur methotrexaat) en DAS-gestuurde behandelstrategieën werden behandeld, wanneer deze werd vergeleken met de betreffende PROs, inclusief restricties op het werk en thuis. Daarom zou huidig onderzoek zich evenveel moeten richten op het verbeteren van ACPA-positieve en ACPA-negatieve RA, daar beiden een even ernstige ziektelast laten zien.

Een ander frequent geobserveerd fenomeen in RA is ochtendstijfheid (OS). Dit symptoom omvat de sensatie van stijfheid van het gewricht, welke meestal optreedt in de vroege ochtend of na langere perioden van rust. Ondanks dat het symptoom prevalent is, is de patofysiologie nog steeds slecht begrepen. In **Hoofdstuk 7**, wordt de relatie tussen OS en lokale MRI-gedetecteerde inflammatie onderzocht in 286 patiënten met RA (2010-criteria) en UA (verdacht voor RA maar voldoet niet aan 2010-criteria) van het EAC cohort. OS is onderdeel geweest van klassificatie en remissie criteria, wat illustreert dat het wordt gezien als een belangrijk symptoom. Het symptoom werd gerelateerd aan het circadiaanse ritme en de centrale regulatie van cytokines via de hypothalamus-hypofyse-bijnier (HPA)-as en het autonome zenuwstelsel. Het is zelfs aangetoond dat de toediening van laaggedoseerde prednison gedurende de nacht, de ernst van OS zou kunnen verminderen. Maar omdat OS een lokaal symptoom is, welke in essentie het meest wordt ondervonden aan de gewrichten van de hand, kan het worden gehypothetiseerd dat lokale ontsteking ook sterk gerelateerd aan OS zou kunnen zijn. Ondanks de relatie met circulerende inflammatoire factoren, de relatie met lokale inflammatoire factoren is slechts minimaal onderzocht. Derhalve hebben we deze studie uitgevoerd met als doel om te onderzoeken of de aanwezigheid van OS was gerelateerd aan lokale inflammatie welke sensitief middels MRI werd gemeten, in patiënten met RA of UA. We onderzochten synovitis en tenosynovitis, welke zijn gescoord volgens de gevalideerde OMERACT-RAMRIS scoringsmethode. MRI is sensitiever dan lichamelijk onderzoek. Ondanks deze sensitieve meet methode, vonden we alleen kleine associaties met OS. De hoogste associatie werd gevonden voor het tegelijkertijd optreden van synovitis en tenosynovitis, terwijl de alleenstaande aanwezigheid van synovitis niet was gerelateerd aan OS. De gevonden effect maat was verrassend klein, wat impliceert dat andere onbekende lokale factoren mogelijk een belangrijke rol spelen voor de symptomatologie van OS.

In **Hoofdstuk 8**, werd een frequent gestelde vraag uit de klinische praktijk besproken. Is er een rol voor in het dagelijkse leven ondervonden psychologische stress, op het ontstaan van RA? Ondanks dat dit een observationele studie was, streefden we ernaar om te onderzoeken wat de rol en tijdsrelatie was van dagelijkse stress op het ontstaan van RA in patiënten met CSA. We konden geen causaliteit onderzoeken omdat di teen observationele studie was, maar de analyses werden uitgevoerd om de aanwezigheid van een associatie tussen ondervonden psychologische stress en inflammatie gemeten op verschillende manieren, namelijk lokaal door een MRI van de gewrichten, systemisch door CRP in het serum en ook door IA ontwikkeling tijdens follow up. Deel van de

patienten met CSA ontwikkelen IA tijdens follow up en het merendeel zal dan voldoen aan de 2010-criteria. Deel van de patiënten zullen nooit klinisch detecteerbare IA ontwikkelen en de symptomen verdwijnen vaak geleidelijk weer. We onderzochten het verloop van de ondervonden stress op baseline en gedurende follow up. Dit was gemeten op baseline door middel van twee vragenlijsten. Patiënten vulden de 'Cohen's perceived stress scale' in, bestaand uit 10 vragen (PSS-10), daarnaast vulden zij ook de 'Short Form 36' (SF-36) in, vanwaar we de scores van de 'Mental Health Index' (MHI-5) hebben geëxtrapoleerd. Op baseline en het begin van de symptomen, konden we geen relatie aantonen tussen psychologische stress en lokale door MRI gedetecteerde gewrichtsinflammatie of systemische inflammatie gemeten door CRP. Ook voor de uitkomst artritis ontwikkeling, konden we geen associatie aantonen. We observeerden dat psychologische stress op het moment van de start van de klachten ongeveer gelijk was ten opzichte van de algemene populatie. Ten tijde van het optreden van artritis, en het moment van de diagnose van RA, steeg de ondervonden stress significant. Het jaar daarna daalde het weer tot het baseline niveau. In patiënten die nooit klinische artritis ontwikkelden, bleef de prevalentie van stress ongeveer stabiel gedurende follow up. Een associatie tussen baseline stress en inflammatie 1 jaar later werd tevens niet aangetoond. Daarom concludeerden we dat de huidige data geen duidelijke associatie tussen inflammatie of IA ontwikkeling en dagelijkse psychologische stress liet zien. Het verloop van stress en inflammatie liepen parallel in plaats van dat de een aan de ander vooraf ging. We kunnen niet uitsluiten dat ernstige psychologische stress een impact zou kunnen hebben op het ontstaan van RA omdat we bijvoorbeeld geen 'life events' hebben gemeten, maar ons enkel hebben gericht op psychologisch stress ondervonden in het dagelijks leven. Daarnaast is het mogelijk dat kleine effecten gemist kunnen zijn in deze subset van 241 CSA patiënten. Desalniettemin laten de data overtuigend zien dat, ondanks dat patiënten met CSA al sinificante pijn en fysieke klachten ondervinden als gemeten door de HAQ, er geen duidelijke relatie was van dagelijkse stress op de ontwikkeling van RA. Dit was een uniek onderzoek daar het beloof van stress nooit eerder op deze manier was onderzocht, in een cohort met patiënten met CSA, welke een verhoogd risico hebben op RA ontwikkeling.

Hoofdstuk 9 gaat door met het onderzoek naar de effecten van psychologische stress in een ander cohort bestaand uit patiënten met vroege RA. We hebben getracht de recente bevindingen van Michelsen et al. Welke lieten zien dat de ziekte activiteit als gemeten door de DAS gedurende follow up, was gerelateerd aan depressie/angst op baseline, bij aanvang van de ziekte RA. De bevindingen impliceren dat baseline depressie of angst zou kunnen leiden tot een minder grote verbetering in DAS. In onze studie werd baseline depressive/angst gemeten door de 'mental component summary' en de 'mental health index', welke beide onderdeel zijn van de SF-36. We konden de bevindingen van Michelsen et al. bevestigen omdat het tevens in ons cohort met patiënten met vroege RA, baseline depressie en angst gerelateerd waren aan een lagere kans op het verkrijgen van DAS-remissie (gedefinieerd als een DAS ≤2.4). De hoogste associaties warden gezien voor depressive/angst en de meer subjectieve componenten van de DAS, zoals de 'patient global assessment', wat impliceert dat verdere inspanning om het psychologische welbevinden van RA patiënten ook een positieve impact zou

kunnen hebben op de ziekte activiteit en daarmee ook (onnodige) behandelingsstrategie wijzigingen zou kunnen voorkomen als gevolg van een hogere DAS.

CONCLUSIES

Een substantieel deel van deze thesis concentreerde zich op de toegevoegde waarde van MRI voor de vroege detectie van RA. In tegenstelling tot de toegevoegde waarde, zagen we ook dat MRI te gevoelig kan zijn en ook patiënten kan aanwijzen met MRI-gedetecteerde inflammatie zonder dat ze chronische RA zullen ontwikkelen. In de klinische praktijk moet de exacte rol van beeldvorming in de vroege detectie van RA nog worden vastgesteld. Tevens zijn de oorzaken van inflammatie op MRI in patiënten met een klinisch voor RA verdachte artralgie of inflammatoire artritis nog niet volledig begrepen. Toekomstig onderzoek zal moeten uitwijzen in welke individuele patiënten de MRI de meeste toegevoegde waarde heeft en in combinatie met welke klinische karakteristieken. Daarnaast zal ook de kosten effectiviteit onderzocht moeten worden. Het tweede deel van deze thesis onderzocht de meer subjectieve componenten van de ziekte, welke ook erg belangrijk zijn voor patiënten zelf. Daarnaast wordt het perspectief van de patiënt tegenwoordig ook steeds meer meegenomen in de beslissing van behandel strategieën. Ondanks dat huidige behandelopties hebben geresulteerd in verbeterde ziekte uitkomsten en chronische schade in veel patiënten kan worden voorkomen, hebben patiënten nog steeds problemen in het dagelijks leven en op het werk. Uitkomsten als pijn en moeheid blijven vaak aanwezig en deze zouden in toekomstige behandelstrategieën meegenomen moeten worden omdat ze een grote last veroorzaken voor zowel de patiënt als voor de maatschappij.

Curriculum Vitae

Aleid Boer werd op 27 november 1987 geboren in Den Hout. In 2006 behaalde zij haar gymnasium diploma aan het Sint-Oelbertgymnasium te Oosterhout.

Zij vervolgende haar opleiding aan de Universiteit van Utrecht waar zij een jaar Scheikunde studeerde. In 2007 startte zij met de opleiding Geneeskunde aan het Erasmus Medisch Centrum te Rotterdam. Hier volgde zij naast de studie Geneeskunde ook de Master of Science Neuroscience. Tijdens de coschappen was zij actief lid van de Co-Raad en tijdens het laatste jaar van de coschappen fungeerde zij nog als voorzitter van de Co-Raad Rotterdam. Zij sloot haar studie af met het oudste coschap op de afdeling interne geneeskunde van het Reinier de Graaf Gasthuis te Delft. In september 2014 werd het artsexamen behaald.

Direct hierop startte zij met haar eerste baan als arts-assitent interne geneeskunde in het TweeSteden Ziekenhuis te Tilburg en een jaar later ging zij aan het werk als arts-assistent interne geneeskunde in het Maasstad Ziekenhuis te Rotterdam.

In september 2017 startte zij haar promotie onderzoek op de afdeling Reumatologie aan het Leids Universitair Medisch Centrum onder begeleiding van professor dr. A.H.M. van der Helm-van Mil, met als afdelingshoofd professor dr. T.W.J. Huizinga.

Momenteel is zij werkzaam als arts in opleiding tot Reumatoloog aan het Erasmus Medisch Centrum te Rotterdam. In dit kader is zij sinds september 2019 gestart met de vooropleiding interne geneeskunde in het Sint-Fransiscus Gasthuis.

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1. **Boer AC**, Burgers LE, Mangnus L, Brinck RM, Nieuwenhuis WP, Steenbergen HW, Reinierse M, Huizinga TWJ, van der Helm- van Mil AHM *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 (Oxford). Oct 1;56 (10): 1700-1706 (2017). doi:10.1093/rheumatology/kex235.

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