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The Forefoot in Early Rheumatoid Arthritis

Anatomy, Imaging and Clinical Aspects



Yousra J. Dakkak

The Forefoot in Early Rheumatoid Arthritis:
Anatomy, Imaging and Clinical Aspects

Yousra J. Dakkak

The studies described in this thesis were performed at the Department of Rheumatology of the Leiden University Medical Center, Leiden, the Netherlands.

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The Forefoot in Early Rheumatoid Arthritis: Anatomy, Imaging and Clinical Aspects

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Tell me and I forget

Teach me and I remember

Involve me and I learn

*Derived from Xun Kuang,
Chinese philosopher, 312–230 BC*

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Introduction

Introduction

Synovium in joints, tendons and bursae

A joint consists of two bones that together form an articulation. In general the goal is movement and flexibility of the body. Generally joints are synovial lined, such as the large multidirectional joints of the shoulders and hips, and the unidirectional joints of the fingers. In addition there are fibrous and cartilaginous joints that are more stable, such as the sutures connecting the skull bones, and the symphysis. The synovial joints are the main focus of this thesis. There are several characteristic features to a synovial joint. First, it contains a layer of cartilage that covers the articulating surfaces. Secondly, a joint capsule is present consisting of an inner synovial membrane and an outer fibrous membrane. The synovial membrane attaches to the margins of the joint surfaces and encloses the articular cavity. It produces synovial fluid to lubricate the articulating surfaces. A synovial membrane can also be found outside the joint capsule, where closed sacs of synovial membrane form tendon sheaths and bursae (Figure 1).⁽¹⁾ The synovial tendon sheath, also referred to as tenosynovium, surrounds the tendon and serves to reduce friction by providing a smooth gliding surface, this helps to prevent tendon injury at locations where there is excessive movement or bone.^(2,3) Not all tendons have a synovial sheath, for example it is absent at the Achilles tendon.⁽⁴⁾ Other structures that can be found near joints are the bursae, that occur primary or secondary to friction. Primary bursae are native synovium-lined structures closely related to bone and tendon sheaths. They lie between tendons and overlying structures, like bone, where they serve to reduce the friction of one structure moving over the other.⁽²⁾ Secondary non-native bursa, also referred to as adventitious bursae, form at sites of friction, for example neobursa after upper leg amputation and friction with the prosthesis. Unlike the primary bursae, adventitious bursa do not have a synovial lining.⁽⁵⁾ Normally, only a small amount of fluid is present in a native bursa, but this increases in case of synovitis and can become symptomatic.

The small joints of the hands and feet are examples of synovial joints that are surrounded by tendons that may or may not have a synovial tendon sheath, depending on the location.⁽⁶⁻¹⁰⁾ At the small hand joints, the metacarpophalangeal (MCP)-joints, a sheath is present around the flexor tendons, but believed to be absent around the extensor tendons.⁽¹¹⁾ Regarding the small foot joints, the metatarsophalangeal (MTP)-joints, there is no consensus in anatomic literature

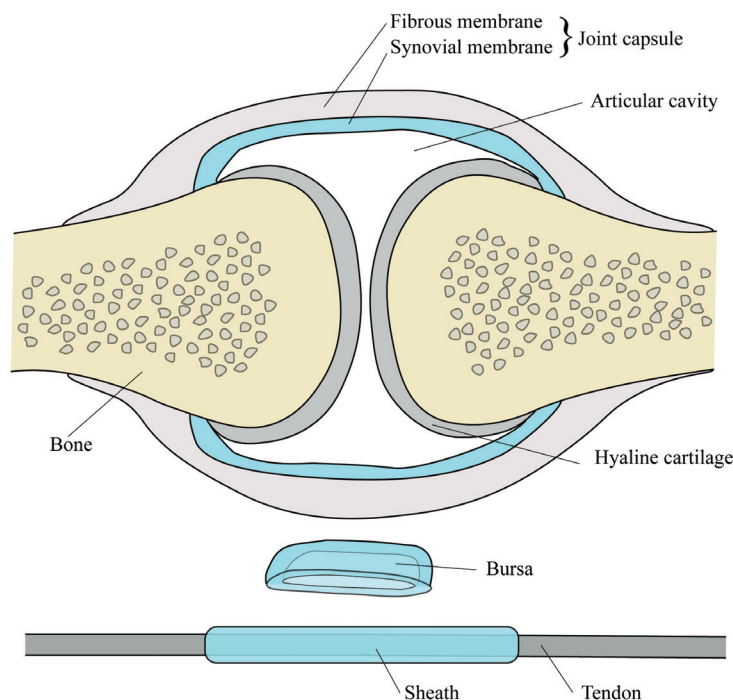


Figure 1. Example of a synovial joint with adjacent synovium-lined bursa and tendon. Synovial membranes are shown in blue. Adjusted from Gray's anatomy for students.(1)

on the presence or absence of tendon sheaths. On the extensor side of the MTP-joints, some sources portrayed extensor tendons without sheaths,(8-10) while other sources neglect to provide information on this region.(6) Regarding the flexor tendons at MTP-joints, there is controversy between sources: in some sources a sheath is described that is solely fibrous,(7) in another example it is described as both fibrous and synovial,(10) while other sources did not provide information on the matter.(8,9) The anatomical presence of tendon sheaths at the MTP-joints thus remains unclear. (Figure 2)

With regards to bursae, anatomic literature does not mention their presence at the MTP-joints, even though histopathologic studies have pointed out their presence in all intermetatarsal spaces.(12,13) Thus while the presence of synovial tendon sheaths and bursae is seen as a characteristic feature of synovial joints,(1) their presence at the MTP-joints seems overlooked. The MTP-joints will be the main focus of this thesis, synovial extra-articular structures at these joints, i.e. tendon sheaths and bursae will also be studied.

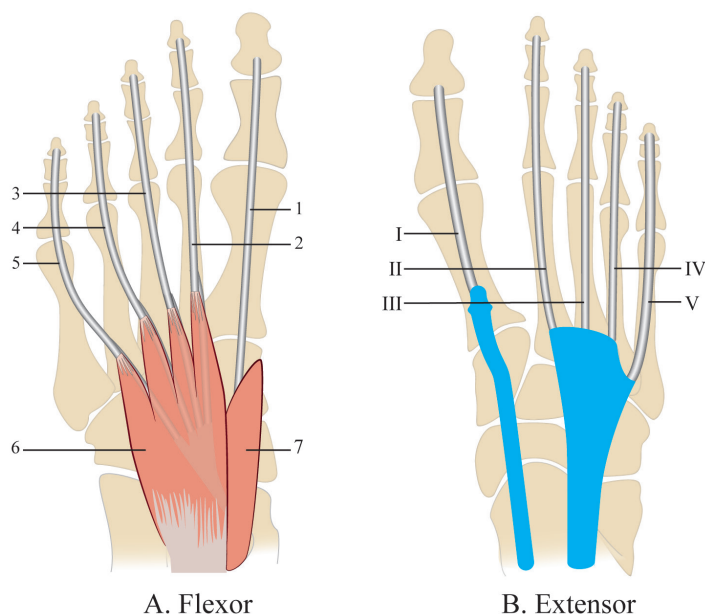


Figure 2. Anatomic absence of tendon sheaths in the forefoot according to anatomic literature. **A:** plantar view of the forefoot with flexor tendons. 1: tendon of the m. flexor hallucis longus, 2-5: tendons of the common mm. flexor digitorum longus (FDL) and common flexor digitorum brevis (FDB). Proximally the four tendons of the FDL run deep from under the FDB muscle (6) and extend distally together with the FDB tendons. The tendon of the FHL (1) proximally runs deep from under the musculus abductor hallucis (7) and the FDB. **B:** dorsal view of the forefoot with extensor tendons. The tendon sheaths are shown according to anatomic literature: the tendon sheaths of the tibialis anterior, extensor hallucis longus (I) and extensor digitorum longus tendons (II-V) end proximal of the MTP-joints. Adjusted from Netter's atlas of Human Anatomy.(8)

Relevance of anatomic knowledge in the interpretation of imaging

Anatomical knowledge is a fundamental component for the interpretation of medical practice and science. The general assumption is that every part of us that can be seen with the naked eye has already been discovered. However, ways of viewing the body change due to advances in imaging techniques, such as MRI.(14) Through advanced imaging we bring into view progressively finer detail within the human body that pose new questions on how to interpret what can be seen. This in turn may increase our anatomical knowledge, as advanced imaging may lead to the discovery of structures that have previously not been described in anatomic literature.

Examples of this can be found in the rheumatologic field. Historically, rheumatoid arthritis (RA) is a disease that is characterized by inflammation of the synovial lining of the joints. In addition, it is known that inflammation of the tenosynovium,

referred to as tenosynovitis, can also occur. Tenosynovitis can clinically be found in patients with active, longstanding RA, and predisposes the risk of tendon rupture. (15) Recent detailed imaging studies of the hand have revealed that subclinical tenosynovitis can also be found in the early phases of RA.(15,16) However, MRI-detected inflammation is seen around tendons with, but also around tendons that are believed to lack a tenosynovial sheath, according to anatomic literature, referred to as peritendinitis.(11) This peritendinous enhancement may be seen with or without local synovitis, and thus represents more than just a secondary peritendinitis due to synovitis.(11) Anatomic literature does not always provide references on how its images are realized. In addition, there are inconsistencies between and within anatomical reference texts.(14,17) It may thus seem justifiable to revisit previous assumptions. Regarding the MTP-joints, MRI-detected inflammation around tendons has been described at the MTP-joints in patients with RA.(18) As stated, current anatomic literature does not provide clear information on the presence or absence of tendon sheaths that is necessary for the interpretation of these MRI-findings. Therefore, anatomical studies are warranted: if these reveal the presence of a tenosynovium, these MRI-findings can be interpreted as tenosynovitis. This way, as advanced imaging gives us an increased interest in anatomy, in turn, new anatomic findings may then increase our understanding of advanced imaging, and ultimately of disease. As imaging findings may challenge anatomic research, this in turn may lead to revision of the classic textbook images.

Rheumatoid arthritis

RA is a systemic autoimmune disease that is characterized by chronic, persistent inflammation of synovial joints. In Caucasians, its prevalence is 0.5-1%. It affects women more often than men, and its incidence increases with age. Uncontrolled, it can result in erosive joint damage, disability and an increased mortality.(19)

The classic presentation of RA is a symmetrical polyarthritis that involves the small synovial joints of hand and feet, with joint pain, stiffness and swelling. A variety of symptoms can be present, and no single symptom is specific for RA. Importantly, no diagnostic criteria for RA exist. Therefore the diagnosis is made by the rheumatologist based on a combination of clinical findings and additional investigations, such as laboratory tests and imaging.(20)

For research purposes, classification criteria are used to create relatively homogeneous groups of patients. Throughout the years different classification criteria have been held for RA. Previous classification criteria such as the 1987

ACR criteria were developed for established RA, and included radiographic erosions and rheumatoid nodules. In the last decades, substantial advances in the management of RA have been made, as it has become apparent that early treatment with disease modifying anti-rheumatoid drugs (DMARDs) improves the outcome of disease. Therefore more recently, the 2010 ACR/EULAR classification criteria have been established to allow the selection of patients in an earlier disease stage.(21) In these 2010 criteria, findings of established disease such as rheumatoid nodules and radiographic erosions are no longer included, and acute phase reactants and auto-antibodies that are associated with RA are included and are weighed heavily. It is important to note that these classification criteria can only be applied to patients with a clinical diagnosis of RA.(Table 1)

In clinical practice and trials disease activity in RA is assessed by composite indices, like the Disease Activity State (DAS). The original DAS includes a 44 swollen joint count.(22) For reasons of convenience, a reduced DAS, the DAS28, has been introduced that assesses 28 joints by excluding evaluation of ankle and foot joints. And thus, even though the feet are a preferential location of involvement in early arthritis, they are excluded from this important outcome measure. Previously it was shown that the practicality of the reduced 28 joint count comes at the cost of accuracy, as the DAS28 underestimates disease activity, particularly in patients where the ankle and foot joints are affected.(23) Indeed, tenderness and swelling of foot joints was found in a substantial number of RA-patients who were considered to be in the state of remission.(24) It has been suggested that, given the high burden of foot complaints and the imminence of walking disability, a more attentive attitude to forefoot inflammation in outcome studies in RA seems justifiable.(25)

The role of imaging in RA

Imaging is used for several purposes in the management of RA, including diagnosis, prognostication, disease monitoring and also as an outcome measure in trials. (26) On conventional radiographs joint of hands and feet damage is measured by erosions and joint space narrowing. Radiographic studies have revealed that in the early phases of disease erosive change is more common in the feet than in the hands.(27,28) Traditionally, erosive change is considered an important outcome measure. However in case of prompt treatment patients have limited bone and joint damage that can be detected by radiographs. Therefore MRI and ultrasound are gaining more recognition in the management of RA, as they are more sensitive in detecting damage and in addition allow visualization of inflammation of soft tissues.(26)

Table 1. Classification criteria for Rheumatoid Arthritis

Revised ACR 1987 criteria	2010 ACR/EULAR criteria
Morning stiffness ≥ 1 hour	Joint involvement
Arthritis ≥3 joint areas	- 1 large joint (0)
Arthritis of hand joints	- 2-10 large joints (1)
Symmetric arthritis	- 1-3 small joints (2)
Rheumatoid nodules	- 4-10 small joints (3)
Presence of RF	- >10 joints, including at least 1 small joint (5)
Radiographic changes (erosions)	Serology
	- ACPA and RF negative (0)
	- Low-positive ACPA or RF (2)
	- High-positive ACPA or RF (3)
	- Acute-phase reactants
	- Normal CRP and ESR (0)
	- Abnormal CRP or ESR (0.5)
	Duration of symptoms
	- <6 weeks (0)
	- ≥6 weeks (1)
4/7 criteria must be present to fulfil criteria	6/10 points must be present to fulfil criteria

ACR: American college of rheumatology; EULAR: European league against rheumatism;
RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; CRP: c-reactive protein;
ESR: erythrocyte sedimentation rate.

MRI and ultrasound both show synovitis and tenosynovitis. A unique feature of MRI is its capability to detect change in the bone marrow described as osteitis or bone marrow edema (BME). All three features are considered to be inflammatory in nature. Both ultrasound and MRI have advantages and disadvantages. Ultrasound is easily accessible but is operator dependent, and while MRI is more expensive it is generally considered to yield more reproducible results. Finally MRI is more sensitive than ultrasound in detecting tenosynovitis and synovitis.(29,30)

Because of the advantages of MRI, is it increasingly used for research purposes. As the complexity and the amount of information provided by MRI pose a challenge, the OMERACT MRI RA Working Group has developed a scoring system: The RA MRI scoring system (RAMRIS) that scores erosions, synovitis and BME. It was developed to standardize MRI-scoring of the small joints of the hands for research purposes and is recognized as a valid outcome measure in trials.(31) Regarding the development, application and validation of this MRI-score, only the small joints of the hands were addressed. The MTP-joints, however, have been neglected.(32) In addition to the RAMRIS a score was developed by Haavardsholm that scores tenosynovitis.(33)

Regarding imaging of the feet, radiographic studies have revealed the important added value of imaging the feet to the hands.(34) Regarding MRI this has not been evaluated, although MRI findings may be as prevalent at MTP-joints as the hands.(18,35) It would therefore be of interest to study the added benefit of MRI of the foot to that of the hand.

Aims and outline of this thesis

RA is an evolving disease, where patients nowadays are treated early in the disease course. Because of the shift to treat early disease phases, MRI has gained increased recognition and is increasingly utilized. And while RA is a disease where the small joints of both the hands and feet are involved, the focus in research has primarily been on involvement of the hands, as the DAS28 excludes the feet and the RAMRIS is not even validated for the MTP-joints. Perhaps most surprisingly, even anatomic literature seems to be incomplete when it comes to the description of the normal anatomy of the feet.

Therefore, this thesis has three general aims:

- To validate the use of the RAMRIS for MRI of MTP-joints
- To increase understanding of the anatomy of soft tissues in the forefoot and to study its involvement in RA by MRI
- To study the association of MRI-detected inflammation at the MTP-joints to clinical outcomes

All studies in this thesis were performed using the Leiden Early Arthritis Clinic (EAC). This is a longitudinal inception cohort that contains consecutive included patients that present to the rheumatology outpatient clinic of the Leiden University Medical Center with clinically confirmed arthritis and a symptom duration of <2 years.(36) At baseline, swollen joint counts were performed, serum samples were obtained, and an MRI of a unilateral hand and foot was performed. All patients were naïve to DMARDs at the moment of inclusion in the cohort, and patients received regular rheumatologic care. It is important to note that the results of the MRI were blind for the treating physician.

To provide an overview of studies available on the application of the RAMRIS on MRI of the MTP-joints, a systematic literature review was performed in **chapter 2**. The aim of this review was to summarize studies evaluating the validity of the RAMRIS applied to MRI of the MTP-joints according to the OMERACT Filter criteria:

Truth, Discrimination and Feasibility. Truth is further subdivided into Face, Content and Construct validity. Discrimination is divided into test-retest reliability, ability to discriminate in trials, longitudinal construct validity and thresholds of meaning. Finally a research agenda was set. In subsequent chapters of this thesis, we aimed to resolve some of the items from this research agenda.

An important aspect of Discrimination is the reliability of scoring.(37) Therefore, in **chapter 3** we studied whether applying the RAMRIS to the MTP-joints is reliable. As the focus in rheumatology is shifting from established erosive RA to early arthritis and even to patients with arthralgia that are suspect to progress to arthritis,(38) this study was performed in patients with early arthritis and also in patients with clinically suspect arthralgia without apparent arthritis upon physical examination.

As part of Face and Content validity it is important that MRI is able to capture the intended pathophysiological feature.(39) In the case of tenosynovitis, the pathophysiological feature is the synovial sheath surrounding the tendons. Besides that anatomic literature leaves it undetermined if tendons at the MTP-joints have a synovial sheath,(6-10) it is also unknown whether tenosynovitis at the MTP-joints is associated with RA. In **chapter 4** we therefore studied the anatomical presence of a tenosynovium of the tendons at the MTP-joints in an anatomical study. The main goal of this was clarify whether MRI-detected contrast-enhancement around the tendons can be interpreted as tenosynovitis. Subsequently the association of these MRI-lesions with RA was studied in a large cross-sectional study in patients with early RA.

Besides classic MRI-inflammation defined by synovitis, tenosynovitis and BME, other MRI findings have gained little attention. Intermetatarsal and submetatarsal areas may be involved in RA and reveal abnormalities on MRI such as intermetatarsal bursitis, Morton's neuroma and submetatarsal bursitis.(40) In **chapter 5** we therefore studied the occurrence of these lesions in early RA.

Next, Construct validity was assessed by studying MRI with physical examination and disability as clinical outcomes. Physical joint examination for swelling is a crucial element in the assessment of the clinical status of RA-patients. However, physical examination of the MTP-joints is generally considered difficult.(41) Therefore in **chapter 6** the association of arthritis upon physical joint examination and MRI-detected inflammation at the MTP-joints was assessed. In addition, in RA-patients walking disabilities are common,(42) therefore in **chapter 7** we studied whether walking difficulties were associated with MRI-detected inflammation.

The value of MRI-detected inflammation of the MTP-joints to recognize patients that will develop RA is still unknown. In addition, in clinical practice, radiographs of both hands and feet are obtained as previous studies have shown that this combined assessment provides better sensitivity and specificity than the hands and feet alone.⁽⁴³⁾ In analogy to conventional radiography, a combined hand and foot MRI score might state an important advancement to the present RAMRIS that only images the hand. For Feasibility, it is important to know whether imaging of the foot is of additional value to the hand, as it prolongs the scan time and thereby costs. Therefore in **chapter 8** we aimed to answer both questions: first we studied whether MRI-detected inflammation of the foot is predictive for RA-development. Secondly we studied whether combining MRI-detected inflammation of the foot to that of the hand is of additional value.

Chapter 9 consists of a summary and general conclusions of the studies performed in this thesis. In **chapter 10** the summary and general conclusions are provided in Dutch.

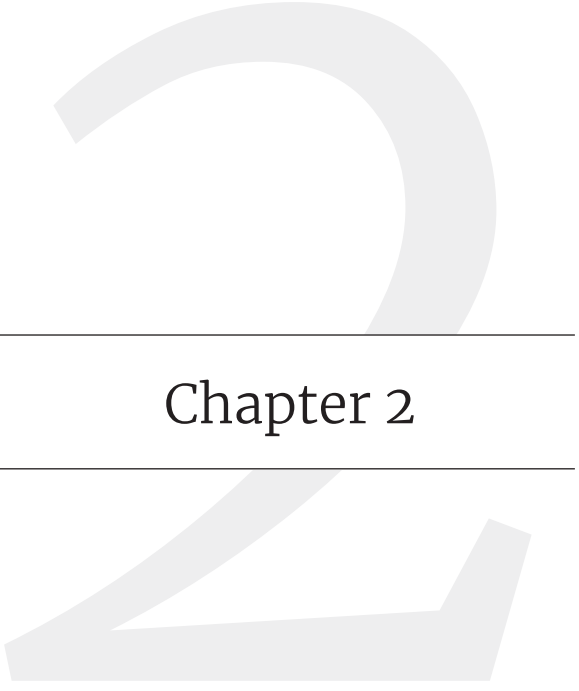
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Chapter 2

*Validity of the Rheumatoid Arthritis
Magnetic Resonance Imaging Score applied
to the forefeet using the OMERACT Filter:
a systematic literature review*

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Abstract

Objective: Magnetic Resonance Imaging(MRI) depicts inflammation and structural damage in Rheumatoid Arthritis(RA). The validity of MRI-scoring of wrist- and metacarpophalangeal-joints according to the RA MRI score(RAMRIS) has been demonstrated. The Outcomes in Rheumatology Clinical Trials(OMERACT) RAMRIS Working Group recently called for validation of the RAMRIS of the metatarsophalangeal(MTP)-joints. Therefore, a systematic literature review was performed to test if the RAMRIS applied to the MTP-joints meets the OMERACT Filter of Truth, Discrimination and Feasibility.

Methods: Medical literature databases up to January 2018 were systematically reviewed for studies reporting on RAMRIS applied to MRI of the MTP-joints in RA. To be included, an article had to contain at least one MRI-feature (synovitis, bone marrow edema (BME), tenosynovitis, erosion, joint space narrowing (JSN)) and one item from the OMERACT Filter: Truth (face, content and construct validity), Discrimination (test-retest reliability, ability to discriminate in trials, longitudinal construct validity, and thresholds of meaning) and Feasibility.

Results: Of the 749 retrieved studies, 13 were included, of which 9 provided data on construct validity, 4 on discrimination (3 on reliability, 2 on longitudinal construct validity and 1 on ability to discriminate in trials) and none on feasibility. Construct validity was suggested for BME and erosions, but lacking for synovitis, tenosynovitis and JSN. Data for discrimination remain to be developed for all outcomes.

Conclusion: According to the OMERACT Filter, the validity of the RAMRIS of the forefeet is insufficient in different aspects. A research agenda was determined.

Introduction

In rheumatoid arthritis (RA), conventional radiographs are traditionally used to assess structural damage as an outcome measure for the efficacy of treatment in trials. However, radiographs do not assess disease activity, and with improving treatment strategies structural damage has become less common.(1) Therefore, in recent years magnetic resonance imaging (MRI) is increasingly used in studies, as it detects damage with greater sensitivity than radiography, and in addition provides information about joint inflammation.

As part of The Outcomes in Rheumatology Clinical Trials (OMERACT), an RA MRI Working Group was set up that developed an RA MRI scoring system (RAMRIS) to standardise MRI-scoring for research-purposes.(2) This working group prioritised the wrist and metacarpophalangeal-(MCP)-joints due to their frequent involvement in RA and the large amount of MRI data on these joints.(2) However, studies in early RA have revealed MRI findings to be as prevalent in the metatarsophalangeal-(MTP)-joints as in the MCPs and wrists.(3-5) In addition, radiographic studies have shown that erosive change occurs more commonly in the feet than in the hands, and also earlier.(6-8) The RAMRIS has not been described for the MTPs by the working group. There seems to be a paradox between the notion that the feet are commonly affected in RA, and the priority given to MRI studies of hands over feet. The MRI in arthritis working group has recognized this, as their recently published updated recommendations call for validation of the existing RAMRIS in other joints than the hands, such as the MTPs.(9)

The OMERACT-group has developed a Filter that provides guidelines for the development and validation of outcome measures for use in clinical trials.(10-12) This systematic literature review set out to assess whether the existing RAMRIS, when applied to the MTP-joints in RA patients, meets the OMERACT Filter 2.1 of Truth, Discrimination and Feasibility. More specifically it was aimed to answer the question if there is currently enough evidence to conclude that applying the RAMRIS to MRI-scoring of the MTP-joints is a valid outcome measure in the assessment of joint inflammation and structural damage in RA, and subsequently to identify a research agenda for OMERACT criteria that still require studying for the MTP-joints.

Methods

Identification of studies

In cooperation with a medical librarian (JWS), a systematic literature search was performed to obtain all manuscripts reporting on studies that perform MRI of the MTP-joints in RA patients. Medical literature databases (PubMed, Embase, Web of Science, COCHRANE, Emcare, Academic Search Premier and ScienceDirect) were searched up to January 2018, using all variations of the following key words: 'foot', 'rheumatoid arthritis', and 'magnetic resonance imaging' (see Supplementary File for the exact search strings). Animal studies, reviews, abstracts and letters to the editor and in languages other than English were excluded from the search.

Inclusion criteria

All retrieved titles were screened, if deemed relevant abstracts were reviewed and finally full text articles were read by one reviewer (YJD). A random sample of 75 titles (10% of the titles identified by the literature search) was also reviewed by a second reviewer (AHM), resulting in a similar selection of titles. Therefore further extraction was done by a single reviewer. In case of uncertainties in the reviewing process by the single reviewer, these were discussed and solved by consensus with AHM. Retrieved studies that reported on diseases other than RA, that were not scored according to the RAMRIS applied to the foot, or that did not analyse data of the MTP-joints separately were excluded.

Studies reporting on the RAMRIS-measures in the MTP-joints in RA patients were evaluated and categorized according to the following OMERACT Filter items: Truth (subdivided into face, content and construct), Discrimination (subdivided into test-retest reliability, ability to discriminate in randomised controlled trials (RCTs)/ comparative studies, longitudinal construct validity and thresholds of meaning) and Feasibility, of which a detailed description is provided elsewhere.(10,12) Face and content validity of the Truth aspect were not part of the systematic literature search, as they are considered subjective measures and in the past have been assessed by consensus.(10) Hence the assumption was made that MRI captures the intended pathophysiologic feature for synovitis, bone marrow edema, erosions and joint space narrowing. For face and content validity of tenosynovitis on the other hand, anatomic atlases were explored to study whether the tendons have a sheath, and thus whether MRI is able to capture this intended pathophysiologic feature. Per OMERACT-item a PICO (participants, interventions, comparisons, outcomes) was made, this resulted in the following inclusion criteria per OMERACT-item:

- Construct validity was evaluated in studies comparing one or more RAMRIS-features to conventional radiography, ultrasound, computed tomography, histology, physical examination and symptoms. Both cross-sectional and longitudinal studies were included.
- Test-retest reliability was evaluated in studies comparing one or more RAMRIS-features in the same patients, either by the same performer over time or by different performers at the same time point. Both cross-sectional and longitudinal studies were included.
- Ability to discriminate in randomised controlled trials (RCT)/comparative studies (sensitivity to change) was evaluated in studies that measured change of one or more RAMRIS-features over time, either in randomised controlled trials (RCTs) if available, or from non-randomised studies or cohorts.
- Longitudinal construct validity (responsiveness) was evaluated in studies that measured change in one or more RAMRIS-features compared to change in other instruments like conventional radiography, ultrasound, computed tomography, histology, physical examination and symptoms. This differs from 'Construct validity' by the fact that it includes MRI at different time points rather than at one point in time.
- Thresholds of meaning was evaluated in studies that rate patients with a certain response to therapy (eg, minimum important difference or patient acceptable symptom state) as measured by a change in one or more RAMRIS-features.
- Feasibility was evaluated in studies describing the cost, patient and responder burden, equipment needs, sensitivity of content and overall ease of use of one or more RAMRIS-features. Both cross-sectional and longitudinal studies were included.

Studies that fulfilled the requirements for at least one of these items were included in this review.

After screening and including, next the articles were weighted by two reviewers (YJD and AHM) according to predefined criteria. First, to select MRI-data with high quality, the MRI had to be performed on ≥ 1.5 Tesla(T) MRI and to use gadolinium contrast-enhancement (CE) for synovitis and tenosynovitis. Second, the results were further weighted by the presence of replication studies. For the final conclusion, the validity of an OMERACT criterion was considered to be suggested if there were ≥ 2 studies with high-quality MRI-data of which $\geq 2/3^{\text{rd}}$ had a uniform

conclusion (meaning that the associations found in the studies point in the same direction of either a positive or a negative/absence of any association), this type of validity was categorized as '++' or '--' depending on the directionality of the effect. If only 1 article was available with regards to the type of validity, then according to the direction of the association it was categorized as '+' or '-', and the conclusion was drawn that limited data possibly suggested the validity to be present but more studies were needed for a more definite conclusion. If the high-quality MRI-articles were not uniform in their conclusion, or if articles were available but the MRI-data was not deemed to be of high quality, then it was categorized as '+/-', meaning data was available but insufficient for a conclusion. If there were no articles available at all then it was categorized as '?', meaning that there was no data available.

The MRI-features studied were synovitis, bone marrow edema (BME) and tenosynovitis as measures of inflammation, and erosions and joint space narrowing (JSN) as measures of structural damage. An updated RAMRIS has recently been published that now besides synovitis, BME and erosions also includes tenosynovitis and JSN.(9) Considering the short time interval between this systematic literature search and the publication of this updated RAMRIS definition, the systematic search included not only the updated RAMRIS, but also the old RAMRIS-definition for synovitis, BME and erosions, for tenosynovitis the score according to Haavardsholm et al, and for JSN the score that was proposed by Ostergaard.(2,13,14)

Statistical analyses

Due to the heterogeneity of the studies and the difference in outcome measures that were used it was not possible to perform a meta-analysis. Therefore, we chose to perform a descriptive review.

Results

Literature flow

After removing duplicate references, 749 unique references were identified (Figure 1). After reviewing 115 abstracts and 41 full-text articles, 13 articles were included in the review. Of the included studies, 9 fulfilled the inclusion criteria for evaluation of the construct aspect of Truth(15-23), 4 on Discrimination (of which 3 on test-retest reliability(5,24,25), 2 on longitudinal construct validity (5,25) and 1 on the ability to discriminate (26)), and none for Feasibility.

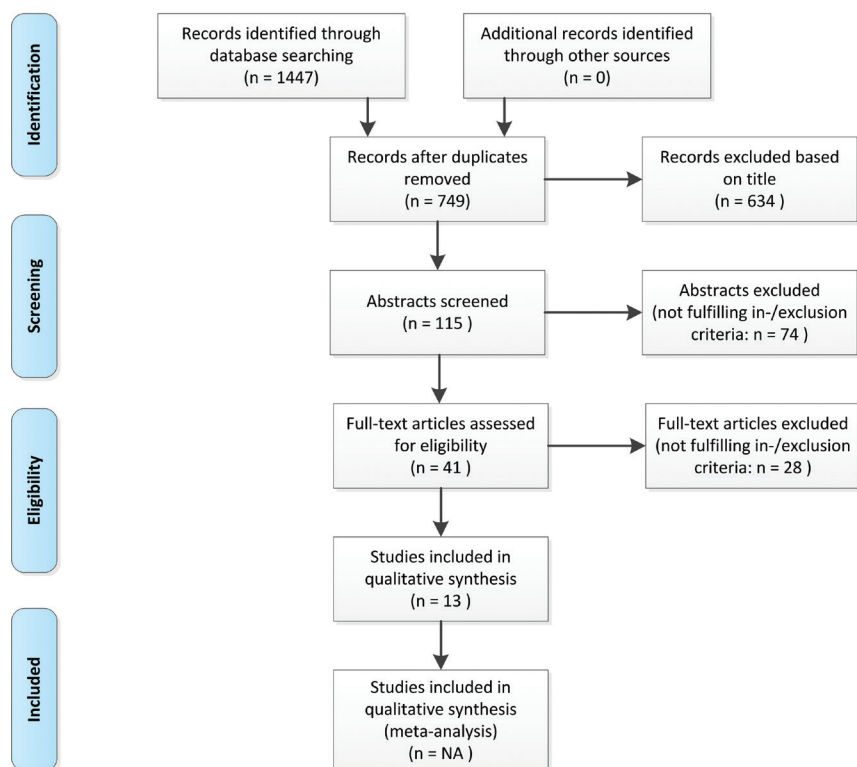


Figure 1. Overview of literature research. NA: not applicable.

Study characteristics

The 13 included studies are depicted in Tables 1–3, grouped according to the category of the OMERACT Filter that is addressed: Table 1 addresses articles on construct (aspect of Truth), Table 2 on test-retest reliability (aspect of Discrimination), and Table 3 on longitudinal construct validity and clinical trial discrimination (also aspects of Discrimination). These tables also depict the studies that fulfilled the inclusion criteria but were considered to have lower MRI-quality as described in the methods, and that thus were not part of the final conclusions drawn. Overall, the studies included a small number of patients, with a median number of 39. There were no randomised controlled trials, 9 studies were cross-sectional, and 4 longitudinal. MRI was most often performed on a 1.5T scanner (n=7).

The OMERACT Filter was applied to each MRI-measure separately. These results will be discussed per MRI-feature and are summarized in Table 4.

Synovitis

The RAMRIS defines MRI-detected synovitis as an area in the synovial compartment that shows above-normal post-gadolinium enhancement of a thickness greater than the width of the normal synovium.(2) As specified in the methods, face and content validity for MRI-detected synovitis were considered to be evident ('++' in Table 4).

Regarding construct validity, 3 studies were deemed to have MRI-data of high quality.(16,20,22) Synovitis was associated with plantar plate pathology, which represents a failure of the ligamentous system and displacement of the plantar plates of the forefoot leading to malformation.(22) When patients were followed for up to 24 months, MRI-detected synovitis was not associated with radiographic damage.(20) Correlations were found between MRI-detected synovitis in MTP-1 and a decrease in movement of the same joint.(16) Although this is a positive correlation, the outcome of decreased range of motion in MTP-1 is not typical for RA, but is affected in for instance osteoarthritis. Therefore this study was not considered in the final conclusion. Overall, 1 out of 2 studies found a positive association, therefore no uniform conclusion can be drawn on construct validity for MRI-detected synovitis ('+/-' in Table 4).

Test-retest reliability has been confirmed in one study that has shown excellent inter- and intrareader reliability for scoring synovitis ('+').(24) For longitudinal construct validity and the ability to discriminate in trials the two studies available did not meet the quality criteria for MRI ('+/-').(5,26) There were no data regarding thresholds of meaning or feasibility ('?').

Bone marrow edema

Also referred to as osteitis, BME is defined as a lesion within the trabecular bone, with ill-defined margins and signal characteristics consistent with increased water content.(2) Again, face and content validity were deemed present ('++').

Construct validity was examined in six studies that met the quality criteria for the MRI-protocol.(15,18-22) MRI-detected BME was associated with clinical swelling, with pain and CRP and with plantar plate pathology.(18,19,22) When MRI-detected BME in MTP-joints was assessed histologically, it was associated with the severity of osteitis.(19) One study found an association for BME with the development of MRI-detected erosions a year later, and reported that erosions were unlikely to develop in the absence of BME.(20) Two studies did not find an association

of BME with Disease Activity Score of 28 joints (DAS-28), Health Assessment Questionnaire (HAQ) or walking disability.(15,21) Overall, 4 out of 6 studies found a positive association, therefore the evidence suggested construct validity to be present ('++').

Test-retest reliability has been investigated in one study that proved good inter- and intrareader reliability ('+').(24) For the ability of MRI to discriminate in trials and for longitudinal construct validity only studies of lower quality were available ('+/-'). (5,26) There was no data on thresholds of meaning or feasibility ('?').

Tenosynovitis

Tenosynovitis is defined as tendon sheath fluid, sheath thickening and enhancement after intravenous contrast injection seen in two consecutive axial slices.(13) Thus for face and content validity it is essential for the imaged tendon to have a sheath. The anatomy books that were consulted, gave contradicting information. Regarding the extensor tendons some portrayed a sheath to be absent, but other anatomic atlases did not portray the extensor tendons at the MTP-region. At the flexor tendons of the MTP-joints some resources portrayed a sheath to be present, some did not or in some cases the region of interest was not depicted.(27-30) Thus it remains unclear whether a sheath is present around the tendons, and if so what its' exact localization is. This is relevant, as it questions the nature of the inflammation observed. Thus, face and content validity of tenosynovitis at the level of MTP-joints was absent ('?'). In addition, no studies concerning tenosynovitis at the MTP-joints have been performed to date ('?' for all OMERACT-elements).

Erosions

MRI-detected bone erosions are defined as a sharply marginated bone lesion, with correct juxta-articular localization and typical signal characteristics visible in two planes with a cortical break in at least one plane.(2) Face and content validity for erosions were assumed to be present ('++').

Five studies that met the criteria for the MRI-protocol were assessed for construct validity.(15,16,20-22) MRI-detected erosions were associated with plantar plate pathology and with decreased movement of MTP-1.(16,22).

Table 1. Summary of previous studies on 'Truth': Construct

Reference	N	Population	MRI-feature					MRI	CE	Method	Outcome
Clinical parameters											
			SYN	BME	TS	ERO	JSN				
Rondina, 2017 (21)	55	RA	+	+	-	+	-	15T	?	To evaluate the correlation between DAS28 and HAQ with MRI of the feet. MRI-protocol is not specified.	There is no correlation between synovitis, BME, erosions and DAS28 and HAQ. Patients in DAS28-remission still had inflammation on MRI.
Burgers, 2016 (15)	206	Early RA ^a	+	+	-	+	-	15T	-	To compare MRI-detected inflammation with functional disability.	There was no association with walking disability for synovitis (p=0.68), BME (0.83) or erosions (0.59).
Krabben, 2013 (18)	66	Early RA ^a	+	+	-	-	-	15T	-	To assess the concordance of inflammation on MRI with physical examination.	Synovitis and BME were associated with clinical swelling (OR2.0 and 1.4 respectively). Of all swollen MTP-joint 23% had MRI-detected synovitis and 21% BME.
Dubbeldam, 2013 (16)	25	RA	+	-	-	+	-	15T	+	To explore the relationship between clinical pathology and gait kinematics, in the forefoot MRI was performed of MTP-1.	An increase in erosion- and synovitis-score of MTP-1 correlated with less MTP-1 dorsiflexion at preswing (95%CI of -0.86 to -0.40 for erosions and -0.82 to -0.30 for synovitis)
Duer-Jensen, 2011 (11)	116	UA	-	+	-	+	-	0.6 and 1.0T	-	To determine the prognostic value of baseline MRI in UA patients that progress to RA.	BME is associated with future development of RA, as it is found in 14.8% of patients who develop RA, vs. 3.4% who did not. Erosions were present equally in both groups (18.5 vs 18.2%).

Histology											
McQueen, 2007 (19)	11	Longstanding RA	+	+	-	+	-	1.5T	+	To histologically examine resected bone samples from patients undergoing orthopaedic surgery. MRI was performed prior to resection.	MRI-detected BME was associated with histological presence and severity of osteitis, pain and CRP. Association of MRI-detected synovitis with histology was not examined.
Other imaging											
Siddle, 2012 (22)	24	RA	+	+	-	+	-	3T	+	To examine the relationship between plantar plate pathology on MRI and the RAMRIS of MTP 2-5.	Plantar plate pathology was associated with synovitis, BME and erosions, in MTP 4 and 5 in particular.
Mundwiler, 2009 (20)	50	Early RA	+	+	-	+	-	1.5T	+	To determine whether MRI BME progresses to MRI erosion, and whether MRI erosion progresses to erosions on radiographs, by MRI at baseline and after 6 months, and radiographs at baseline, and after 6, 12 and 24 months.	For BME PPV was 0.50 and NPV 0.99 to predict MRI-detected erosions after 1 year, for MRI-detected erosions PPV was 0.10 and NPV 0.995 to predict radiographic erosions after 1 year. Synovitis was not associated with radiographic damage.
Szkudlarek, 2004 (23)	40	RA	+	-	-	+	-	1.0T	+	To compare MRI radiography, US and physical examination.	MRI and US are more sensitive than radiography and clinical examination: Erosions were detected by MRI in 20 patients, US in 26 and radiographs in 11. Synovitis by MRI in 31 patients, US in 36, and clinical examination 20.

^a Study performed in a cohort of unselected early arthritis patients, sensitivity analyses were performed on patients with RA according to the 2010 criteria; results of the sensitivity analyses are shown. MRI: magnetic resonance imaging; SYN: synovitis; BME: bone marrow edema; TS: tenosynovitis; ERO: erosions; JSN, joint space narrowing; CE: gadolinium contrast-enhancement; T: Tesla; RA: rheumatoid arthritis; UA: undifferentiated arthritis; MTP: metatarsophalangeal joint; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; US: ultrasound; CRP: C-reactive protein; PPV: positive predictive value. NPV: negative predictive value.

Table 2. Summary of previous studies on ‘Discrimination’: test-retest reliability

Reference	N	Population	MRI	CE	Reading	Reliability per MRI-feature					Conclusion
						SYN	BME	TS	ERO	JSN	Foot
Baan, 2015 (24)	29	RA	1.5T	+	Inter Intra	0.94 0.85	0.77 0.70	-	0.95 0.89	-	-
Elbjerg, 2005 (25)	35	RA	0.2T	?	SDD	-	-	-	1.36	-	-
Sewerin, 2014 (5)	26	Early RA	0.2T	+	SDD	1.29	0.87	-	0.87	-	1.81

MRI: magnetic resonance imaging; CE: gadolinium contrast-enhancement; SYN, synovitis; BME, bone marrow edema; TS, tenosynovitis; ERO, erosions; JSN, joint space narrowing; RA: rheumatoid arthritis; T: Tesla; Inter: inter-reader reliability; intra: intra-reader reliability (assessed by quadratic-weighted κ scores); MTP: metatarsophalangeal joint; MCP: metacarpophalangeal joint; SDD: smallest detectable difference; RAMRIS; RA MRI score.

Table 3. Summary of previous studies on 'Discrimination': longitudinal construct validity and clinical trial discrimination

Reference	N	Population	MRI-feature				MRI	CE	Method	Outcome
			SYN	BME	TS	ERO	JSN			
Longitudinal construct validity										
Ejbjerg, 2005 (25)	35	RA	-	-	-	+	-	0.2T	?	To compare MRI-detected erosions to radiography with respect to sensitivity to change after one year.
										Progression of erosions was detected by MRI of MTPs in 14 patients, as opposed to 9 by radiography of hands and feet. However, when changes greater than SDD were considered this was 4 and 5 patients respectively.
Sewerin, 2014 (5)	26	Early RA	+	+	-	+	-	0.2T	+	To study MRI prior and after 6 months of methotrexate monotherapy.
										A decrease in synovitis and BME correlated to a change in DAS28, this correlation was not found for change in erosions.
Clinical trial discrimination										
Buchbender, 2013 (26)	39	RA and early RA	+	+	-	+	-	0.2-3T	+	To assess patterns of inflammation and changes under therapy by MRI at baseline and after 8 months follow-up.
										A change in BME was seen in 77% of MTP-joints, synovitis in 59%, erosions in 68%.

MRI: magnetic resonance imaging; CE: gadolinium contrast-enhancement; SYN, synovitis; BME, bone marrow edema; TS, tenosynovitis; ERO, erosions; JSN, joint space narrowing; RA, rheumatoid arthritis; T: Tesla; MTP: metatarsophalangeal joint; SDD: smallest detectable difference.

Table 4. Validity of MRI measures of the forefeet in their assessment of inflammation and structural damage in RA

A: Presence of type of validity given for every MRI-measure					
Type of validity	Inflammation			Structural damage	
	SYN	BME	TS	ERO	JSN
Truth					
Face	++	++	?	++	++
Content	++	++	?	++	++
Construct	+/-	++	?	++	?
Discrimination					
Test-retest reliability	+	+	?	+	?
Longitudinal construct validity	+/-	+/-	?	+/-	?
Clinical Trial Discrimination	+/-	+/-	?	+/-	?
Thresholds of meaning	?	?	?	?	?
Feasibility	?	?	?	?	?
B: Criteria handled for the interpretation of data					
Category	Definition		Criteria for conclusion		
++	Validity suggested for a positive association between MRI-measure and outcome		≥2 studies, ≥2/3rd have a uniform conclusion, and all of the following: MRI ≥1.5T CE for SYN and TS		
+	Validity possibly suggested for a positive association between MRI-measure and outcome		1 study with a positive association, and all of the following: MRI ≥1.5T CE for SYN and TS		
+/-	Insufficient data for a conclusion		Studies are available, but one of the following: No uniform conclusion MRI on <1.5T No CE for SYN and TS		

-	Validity possibly suggested for a negative association between MRI-measure and outcome	1 study with a negative association, and all of the following: MRI ≥1.5T CE for SYN and TS
- -	Validity suggested for a negative association between MRI-measure and outcome	≥2 studies, ≥2/3rd have a uniform conclusion, and all of the following: MRI ≥1.5T CE for SYN and TS
?	No data available	No studies available

*uniform conclusion: studies pointing in the same direction (either positive or negative) with regards to the association for the MRI-measurement with the outcome. SYN, synovitis; BME, bone marrow edema; TS, tenosynovitis; ERO, erosions; JSN, joint space narrowing; MRI: magnetic resonance imaging; T: Tesla; CE: gadolinium contrast-enhancement.

Also, MRI-detected erosions were associated with the development of radiographic erosions one year later, and in the absence of MRI-detected erosions radiographic erosions were unlikely to occur.(20) Two studies showed no correlation of MRI-detected erosions with DAS-28, HAQ or with walking disability.(15,21) Overall, 3 out of 5 studies found a positive association, therefore the evidence suggested construct validity to be present ('++').

With regards to Discrimination, reliability was excellent in one study showing high inter- and intrareader reliability ('+').(24) For longitudinal construct validity and ability to discriminate the found studies did not meet the criteria on the MRI-protocol ('+/-').(5,25,26) Thresholds of meaning and feasibility have not been studied ('?').

Joint space narrowing

JSN is defined as reduced joint space width compared to normal, as assessed in a slice perpendicular to the joint surface.(14) There is no reason to believe that face and content validity for JSN in the forefeet are not applicable ('++'). As of yet there are no studies on JSN in the forefeet in RA, therefore further validation is required ('?').

Discussion

This is the first SLR to assess the status of the development or application of the RAMRIS for the feet. From the limited evidence available, a foot RAMRIS-score would be useful to evaluate the impact of inflammation and damage in the feet on long term outcomes. Based on the results, as presented in table 4, construct validity is suggested for BME and erosions, but lacking for synovitis, tenosynovitis and JSN. Data for discrimination remain to be developed. A research agenda was formulated for the further evaluation of the validity of MRI of the forefoot, as presented in Table 5.

In contrast to previous OMERACT Filters, Filter 2.1 that was applied in this review does not distinguish between construct and criterion validity. Criterion validity assumes that the comparator instrument is a 'gold standard', for example histology for MRI-detected BME.(12) In addition, previous studies have subdivided criterion validity further into concurrent validity and predictive validity, where concurrent validity assumed that the comparator instrument is a gold standard, and predictive validity looked at a later status of for example a radiographic or functional outcome.(31) For the current study all these different types of measures were taken together as 'construct'. As a result, there were sufficient studies to conclude that construct validity was present BME and erosions. However, when one for example looks at only predictive validity, data is actually insufficient to draw conclusions on this aspect, as only 1 of the 9 studies included in construct looked at the predictive value.(20) This was taken into consideration when formulating the research agenda. Determining the possible added value of MRI of the MTP-joints to that of MRI of the wrist and MCPs, and assessing the value of MRI of MTP-1 are also subjects for future research.

When studying the predictive accuracy of forefoot MRI in future studies, it might be relevant to include data from healthy controls in the definition of disease-related MRI-features. Previous studies demonstrated that inclusion of information obtained from symptom-free persons from the general population increased the specificity and accuracy of MRI and that this finding also applies to the use of MRI of the MTP-joints.(32,33)

An updated version of the RAMRIS was recently published that now includes a definition of JSN and tenosynovitis to previous versions in addition to the previous version that only included BME, synovitis and erosions. For tenosynovitis the

updated RAMRIS shows subtle differences compared to the score developed by Haavardsholm et al that is generally used in MRI of wrist and MCPs.(9,13) No validity data on the updated RAMRIS are published to date. However, as the definition of synovitis, BME and erosions did not change, it is assumed that the observed results are also valid for the updated RAMRIS. No conclusions on the validity of tenosynovitis and JSN in the forefeet according to the older definitions or according to the updated RAMRIS could be drawn as there were no data available. Besides adding tenosynovitis and JSN, the updated RAMRIS also included novel recommendations on the scan-protocol, such as a slice thickness of $\leq 2\text{mm}$ in high quality MRI units. However it also states that the recommendations are not intended to be exclusive, but rather to provide common standards. In this review the quality of the MRI-protocol was only weighted regarding field strength and contrast-enhancement, more thorough details such as slice thickness and plane of scanning were not included in the evaluation.

The 13 included studies were heterogeneous in various aspects, such as the scan-protocols that were used and the type of RA-patients that were included (early versus established RA). Most studies mention the use of a coil, varying from dedicated extremity coils (19) to knee or wrist coils.(17) While most studies scanned all MTP-joints, some made a selection.(16,20,22) Not all studies used contrast-enhancement, potentially decreasing the reliability of synovitis scores. (34) Different field strengths were used, with a wide range of 0.2–3T, of which 1.5T was most common. Lower field MRI $< 1.5\text{T}$ generates lower imaging quality, which may influence the interpretability of the data. Therefore, for the final conclusions of this study, included studies were weighted depending on the use of contrast-enhancement for synovitis, an MRI field strength of $\geq 1.5\text{T}$ and the presence of replication studies. The importance of the presence of replication studies is underlined by the small number of patients included in the studies.

Although these weighing criteria (summarized in Table 4) are arbitrary, they served to give a more critical appraisal of the data and enhance the interpretability of the results. Future studies should focus on ACR core set measures for their outcomes to make comparison of studies more attainable. Finally, studies showing a negative correlation could potentially have remained unpublished leading to a reporting bias that may have affected the results of this review.

In conclusion, although for synovitis, tenosynovitis and JSN data was lacking, for MRI-detected BME and erosions, truth of the RAMRIS of the forefeet were

Table 5. Research agenda for the further validation of MRI of the forefeet

Evaluate whether MRI of the MTP-joints performs better than MRI of the MCPs and wrists in predicting radiographic and/or functional outcomes, and if it could be used solely
Study whether MRI of the MTP-joints has additional value to MRI of the MCPs and wrists in predicting radiographic and/or functional outcomes
Assessing the value of MRI of MTP-1
Determine the longitudinal construct validity, clinical trial discrimination and thresholds of meaning for all MRI measures
Evaluate the feasibility for all MRI measures
Assess the anatomy of sheaths of tendons adjacent to MTP-joints for face and content validity
Assess the association with clinical parameters for tenosynovitis and JSN for construct validity
Assess the predictive value of all MRI features with radiographic and/or functional outcomes
Assess the test-retest reliability of tenosynovitis and joint space narrowing and replicate this for synovitis, bone marrow edema and erosions
Assessment of validity in early RA versus established RA

MTP: metatarsophalangeal joint; JSN: joint space narrowing; MRI: magnetic resonance imaging; MCP: metacarpophalangeal joint.

suggested by the data. In contrast, studies on discrimination and on feasibility are needed or require validation. Thus, the validity of applying the RAMRIS to the forefeet still is insufficient on different aspects. Awareness of the gaps in the OMERACT Filter criteria prior to including MRI of the MTP-joints in the RAMRIS and its implementation in trials is essential for optimal interpretation of results obtained.

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Supplementary data

Supplementary methods are available at *RMD Open* online.

Chapter 3

*Reliability of Magnetic Resonance Imaging
(MRI)–scoring of the Metatarsophalangeal–joints
of the Foot According to the Rheumatoid
Arthritis–MRI Score (RAMRIS)*

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Abstract

Objective: The Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) is validated for hand-MRI. Its reliability applied to metatarsophalangeal (MTP-1-5)-joints is unknown and was studied in early arthritis and clinically suspect arthralgia.

Methods: Patients underwent 1.5T MRI of MTP-, metacarpophalangeal (MCP-2-5)- and wrist-joints. Two paired readers scored bone marrow edema (BME), synovitis, tenosynovitis and erosions. Interreader reliability was assessed of 441 consecutive early arthritis patients at baseline, 215 by two readers, the remaining 226 by two different readers. Two readers scored baseline MRIs of 82 consecutive patients with clinically suspect arthralgia, and 40 randomly selected patients by nine readers. Intrareader reliability was determined on a random set of 15 early arthritis patients, scored twice by two readers. For change-scores, 30 early arthritis patients with baseline and 1-year follow-up MRI were scored by two readers. Intraclass correlation coefficients (ICCs), Bland-Altman (BA)-plots and smallest detectable change (SDC) were determined. MRI-data of MTP-joints were compared to wrist- and MCP-joints.

Results: Interreader ICCs and mean scores in early arthritis were: BME ICC 0.91-0.92 (mean 1.5 (standard deviation (SD) 2.6)), synovitis 0.90-0.92 (1.3(1.7)), tenosynovitis 0.80-0.85 (1.1(1.8)) and erosions 0.88-0.89 (0.7(1.0)). In clinically suspect arthralgia-patients ICCs were comparable. Intrareader ICCs for inflammatory MRI-features were 0.84-0.98, for erosions 0.71 (reader 1) and 0.92 (reader 2). Change-score ICCs were ≥ 0.90 , except erosions (0.77). SDCs were ≤ 1.0 . BA-plots showed no systematic bias. Reliability-scores of MTP-joints were similar to MCP- and wrist-joints.

Conclusion: Status and change MRI-scores of BME, synovitis, tenosynovitis and erosions of MTP-joints can be assessed reliably by RAMRIS.

Introduction

Magnetic resonance imaging (MRI) is increasingly used in scientific research in patients with rheumatoid arthritis (RA), as it is a sensitive modality that can visualise inflammation and destruction.(1) As the complexity and large amount of information that is provided by MRI pose a challenge, the Outcomes in Rheumatology Clinical Trials (OMERACT) MRI in RA working group developed the RA MRI Score (RAMRIS) to standardise MRI-scoring for research purposes and clinical trials in particular.(2)

The RAMRIS has thus far been validated for use in the metacarpophalangeal(MCP)- and wrist-joints, but not for use in metatarsophalangeal(MTP)-joints.(3-5) This is unfortunate as joint inflammation in MTP-joints is just as prevalent as in the MCP-joints.(6,7) In addition, radiographic studies have shown that erosive change occurs more commonly in the feet than in the hands, and also in earlier phases of disease.(8,9) Thus there is a paradox between the notion that the feet are so commonly affected in early RA and their absence as an outcome measure in trials. Indeed, the RA MRI working group has recently called for validation of the RAMRIS in the MTP-joints.(10)

An important aspect of validation is the reliability of scoring.(11) Reliability studies have been performed for the hand, but cannot be directly extrapolated to the foot, as different joint areas in the past have been found to have different intraclass correlation coefficients (ICCs).(12) Previously, Baan et al. measured the reliability of the RAMRIS of the feet in a small subset of patients with longstanding RA (n=29).(13) However, tenosynovitis which is a common feature in early arthritis, was not included in this study. In addition, as no follow-up MRIs were included only the reliability of status scores was assessed. For change scores, one study has been performed by Ejbjerg et al. that assessed MRI-detected erosions only.(14) We therefore aimed to assess the inter- and intra-reliability of status scores and the reliability of change scores applied to the MTP-joints for the following MRI-outcomes: bone marrow edema (BME), synovitis, tenosynovitis and erosions. As the focus in rheumatology is shifting from established erosive RA to early arthritis and even to patients with arthralgia that are suspect to progress to arthritis(1), we performed our study in patients with early arthritis and also in patients with clinically suspect arthralgia without apparent arthritis upon physical examination. We added MRI-data of wrist and MCP-joints as comparison to data of MTP-joints.

Materials and methods

Patients

Early Arthritis Cohort

This longitudinal inception cohort included patients with clinically confirmed arthritis and symptom duration <2 years who were naïve to disease-modifying antirheumatic drugs (DMARDs). At baseline, questionnaires were completed, swollen joint counts were performed and serum samples were obtained. Unilateral 1.5 tesla(T) MRI of the MTP-, MCP- and wrist-joints of the most painful side, or the dominant side in the case of equally severe symptoms on both sides was made of patients who were consecutively included from June 2013 onwards.(15) Before contrast administration, T1-weighted fast spin-echo (FSE) sequences in the coronal plane were acquired for MCP- and wrist joints. After intravenous injection of gadolinium contrast, T1-weighted FSE sequences with frequency selective fat saturation (fatsat) were acquired in coronal and axial planes of the MCP-, wrist- and MTP-joints. Patients were asked to stop nonsteroidal anti-inflammatory drugs (NSAIDs) 24 hours before the scan, and the MRI was made before the start of DMARDs. Additional information on the scan-protocol is provided supplementary.

Consecutive patients included between June 2013 and April 2016 were studied for status scores. In the cohort, serial MRIs were made of patients included up until January 2015.

Clinically Suspect Arthralgia

This inception cohort included patients with clinically suspect arthralgia of the small joints with a symptom duration of <1 year that, according to the clinical expertise of the rheumatologist, was suspected to progress to RA over time. Per definition, clinically suspect arthralgia was not present if clinical arthritis was observed at physical examination or if another explanation for the arthralgia was more likely. (16) Patients consecutively included between July 2014 and February 2015 were studied, and underwent MRI according to the same MRI-protocol as patients with early arthritis.

Both cohorts were approved by the local Medical Ethical Committee (approval numbers Early Arthritis Cohort P10.108 and Clinically Suspect Arthralgia P11.210). All participants signed informed consent.

Readers

All readers were experienced with the OMERACT RAMRIS system and the method by Haavardsholm *et al.* for scoring tenosynovitis.(2,17) All readers have scored >400 MRIs according to these systems during a training period of several months prior to evaluating the MRIs that are part of this study.

MRI Scoring

All readers evaluated the images independently and in the following order: first the MTP-joints, next the MCP-joints and finally the wrist. The MRI-images were scored blinded to clinical data. BME, synovitis and erosions of MTP-, MCP- and wrist-joints were scored in line with the OMERACT RAMRIS, with the exception that BME was assessed on a contrast-enhanced T1-weighted fat-suppressed sequence,(18) as its use for depicting BME is recommended by the European Society of Musculoskeletal Radiology (ESSR) and previous studies have demonstrated that it has a strong correlation with the T2-weighted fat suppressed sequence that is advised by the RAMRIS.(19-22) In MTP- and MCP-joints erosions and BME were scored in the proximal and distal part of the joints. Tenosynovitis was scored as described by Haavardsholm *et al.* applied to the flexor and extensor tendons of MTP-1-5, MCP-2-5 and the wrist.(17) Additional information on the method of scoring is provided supplementary, in addition to an example of a score sheet with illustration of the scored tendons (Supplementary Figure 1).

A flowchart of scored patients and readers is presented in Figure 1. Intrareader reliability was assessed based on 441 consecutive early arthritis patients. The first 215 patients were scored by reader 1 and 2, the remaining 226 MRIs by reader 3 and 4. The MRIs of 82 arthralgia patients were scored by reader 5 and 6. Of these 82 MRIs, 40 were randomly selected and scored by seven additional readers, resulting in a total of 9 readers (readers 2-10). For intrareader reliability, the baseline MRIs of 15 early arthritis patients were randomly selected and rescored by reader 1 and 2 after an interval of respectively 6 and 4 months.

91 early arthritis patients underwent MRI at baseline and at 12-months, and were all scored by reader 9. The reliability of change scores was determined using MRIs of 30 patients, which were in addition also scored by reader 10. These 30 patients were selected as follows: 15 randomly, and 15 based on a high baseline MRI-score by reader 9. The 15 patients with a high baseline score were scored as part of a bigger set of patients that also included patients with lower scores; thus the images were scored by readers that were blinded for the MRI-score. We added

patients with high baseline scores as they were most prone to change over time. The MRIs were scored in chronological order by both readers.(23,24)

Statistical methods

For scores of MTP-, MCP- and wrist-joints separately, ICC-estimates and their 95%-confident intervals (95% CI) were calculated (2-way mixed-effects model, absolute-agreement).(25) For the intra-reader ICC the single measures were used, for interreader and change ICCs the average measures. ICC values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good and excellent reliability, respectively.(25) In addition to calculating ICC-values, Bland-Altman (BA) plots were drawn.(26)

For change scores, in addition to the ICC and Bland-Altman plots, the smallest detectable change (SDC) was calculated. SDC expresses the smallest change between two dependently obtained measures that can be interpreted as 'real', that is a change greater than the measurement error.(27) The SDC of each MRI-feature was calculated as follows:

$$\text{SDC} = (1.96 \times \text{SDdiff})/(\sqrt{k} \times \sqrt{2})$$

Here $k = 2$ as the SDC on the mean scores of both readers was used.(27)

The proportion of patients that showed change in the RAMRIS score was calculated in three ways: using a cut-off of >0 and of >0.5 (of the mean score of 2 readers), and by using the SDC as a cut-off.

Sub analyses for the interreader reliability were performed within the subgroup of patients with the following diagnoses: RA, unclassified arthritis (UA), psoriatic arthritis or spondyloarthritis (SpA) and inflammatory osteoarthritis (OA).

Data were analysed using SPSS version 23.

Results

Patient characteristics

Characteristics of patients with early arthritis and clinically suspect arthralgia are shown in Supplementary Table 1. In both cohorts, patients were predominantly female (61% and 84% respectively) and had a mean age of 55 and 46 years respectively. Characteristics of the 30 patients with follow-up MRIs are also presented in Supplementary Table 1, they had a higher swollen joint count than the overall early arthritis group (6 versus 3). Of these 30 patients, 29 were prescribed DMARDs after the baseline visit during the first year of follow-up, one received NSAIDs only.

Interreader reliability

The interreader ICCs and median and mean MRI-scores for patients with early arthritis and with arthralgia are presented in Table 1. The scores of the individual readers are depicted in Supplementary Table 2. For the MTP-joints in patients with early arthritis the mean scores varied from 0.6 (standard deviation (SD) 0.9) for erosions to 1.5 (SD 2.6) for BME. The corresponding ICCs for BME ranged from 0.91-0.92 (95%CI 0.90-0.93 and 0.90-0.94), for synovitis from 0.90-0.92 (95%CI 0.84-0.94 and 0.88-0.94), for tenosynovitis from 0.80-0.85 (95%CI 0.69-0.86 and 0.78-0.90) and for erosions from 0.88-0.89 (95%CI 0.84-0.91 and 0.86-0.92). In arthralgia patients, the mean and median scores of MRI-features were lower, but ICCs were similar and all >0.87 , except for BME that had an ICC of 0.77 (95%CI 0.64-0.85) when read by two readers, and an ICC of 0.95 (95%CI of 0.93-0.97) when there were 9 readers. The BA-plots indicated that systematic bias was low, as in Figure 2 the middle line, depicting the mean, was located around 0. Only for tenosynovitis there was a tendency towards more random variation with higher scores (heteroscedasticity).

The interreader reliability of the MRI-features for MCP- and wrists-joints were similar to the MTP-joints (Table 1).

As a sensitivity analyses we looked at the reliability in the separate diagnoses RA (n=157), UA (n=148), SpA (n=45) and inflammatory OA (n=23). The results of the sensitivity analyses of the separate diagnoses were similar to the results of the patients combined as presented above (Supplementary Table 4 and 5).

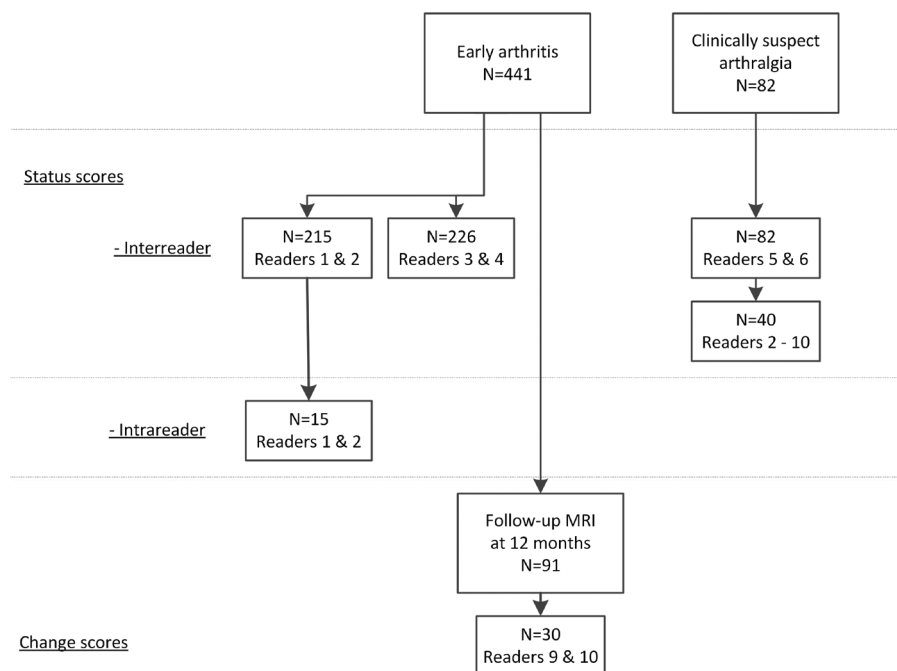


Figure 1. Flowchart of patient selection. The 441 early arthritis patients included the following diagnoses: RA according to the 2010 classification criteria (n=157), unclassified arthritis (n=148), psoriatic arthritis or spondyloarthritis (n=45), inflammatory osteoarthritis (n=23), crystal arthropathy (n=21), remitting seronegative symmetrical synovitis with pitting edema (n=12), reactive arthritis (n=7) and another diagnoses (n=28). The 30 early arthritis patients that were used to determine the reliability of change scores included the following diagnoses: RA according to the 2010 classification criteria (n=21), unclassified arthritis (n=6), inflammatory osteoarthritis (n=2), and remitting seronegative symmetrical synovitis with pitting edema (n=1). 29 out of the 30 patients received DMARDs, one received NSAIDs only

Intrareader reliability

The intrareader ICCs, mean and median scores are presented in Table 2. Mean scores of MRI-features in the MTP-joints varied from 0.4 (SD 0.6 SD) for erosions, to 1.7 (SD 2.9) for tenosynovitis. The ICC scores for BME ranged from 0.96-0.98 (95%CI 0.89-0.99 and 0.95-0.99), for synovitis from 0.90-0.98 (95%CI 0.74-0.97 and 0.94-0.99), for tenosynovitis from 0.84-0.97 (95%CI 0.58-0.94 and 0.91-0.99) and for erosions from 0.71-0.92 (95%CI 0.35-0.89 and 0.78-0.97). BA-plots indicated that systematic bias was low and are presented in Supplementary Figure 2.

The intrareader reliability of the MRI-features for MCP- and wrists-joints were similar to the MTP-joints (Table 2).

Reliability of change scores

The mean, median and ICCs of change scores after 1 year of follow-up of 30 early arthritis patients are presented in Table 3. The scores of the individual readers are depicted in Supplementary Table 3. The change in MRI-scores over time in the MTP-joints was small for erosions (mean 0.4 (0.6 SD)) and larger for the inflammatory MRI-features (≥ -1.3). The ICC for change scores were ≥ 0.90 for BME, synovitis and tenosynovitis, and 0.77 (95%CI 0.52–0.89) for erosions. The SDC was ≤ 1 for all MRI-features, suggesting a high potential to detect changes. The number of patients with true change by using the SDC as a cut-off was similar to the number of patients where change >0.5 was measured; then BME revealed change in 37% of patients, synovitis in 67%, tenosynovitis in 47% and erosions in 17% (Table 3). BA-plots indicated that systematic bias was low and are presented in Figure 3.

The same analyses were performed for the MCP- and wrist-joints, and are presented in Table 3, these results were similar to the MTP-joints.

Discussion

In RA-research, the scoring of MR-images is performed according to the RAMRIS, of which validation as an outcome measure for trials has thus far focussed on the hands.(2,3) In this study we investigated the reliability of the RAMRIS when applied to the MTP-joints. Overall, we observed good to excellent intra- and interreader reliability for status and change scores. In particular, ICCs for inflammatory features were generally >0.90 .

Previously, the reliability of status scores of BME, synovitis and erosions as well as change score of erosions in MTPs have been published and were found to be excellent.(13,14) Our study is the first to look at the reliability of scoring tenosynovitis at the MTP-joints and change scores of inflammatory MRI-features as measured by BME, synovitis and tenosynovitis in an early arthritis setting. To further support our findings, we also analysed data from the wrist- and MCP-joints to compare this to data of MTP-joints. The current data showed that scoring of MTP-joints was equally reliable. Finally, our findings obtained on hand joints are in concordance with previous MRI-studies of the hands which supports the validity of the present results.(28–30)

Table 1. Interreader intraclass correlation coefficients and average status scores according to the RAMRIS in early arthritis patients (n=441 in total) and patients with clinically suspect arthralgia (n=82)

Patient population	Early arthritis n=215, k=2	Early arthritis n=226, k=2	Clinically suspect arthralgia n=82, k=2	Clinically suspect arthralgia n=40, k=9
MTP-joints				
BME	ICC (95%CI)	0.91 (0.90-0.93)	0.92 (0.90-0.94)	0.95 (0.93-0.97)
	Median (IQR, max)	0.5 (0-1.5; 20)	0.5 (0-1.5; 18)	0.1 (0.0-0.4; 5.4)
	Mean (SD)	1.5 (2.6)	1.1 (2.0)	0.4 (0.9)
Synovitis	ICC (95%CI)	0.90 (0.84-0.94)	0.92 (0.88-0.94)	0.98 (0.97-0.99)
	Median (IQR, max)	1.0 (0-1.5; 8)	0.5 (0-1.5; 10)	0.2 (0.0-0.8; 6.2)
	Mean (SD)	1.3 (1.7)	1.2 (1.7)	0.5 (1.0)
Tenosynovitis	ICC (95%CI)	0.85 (0.78-0.90)	0.80 (0.69-0.86)	0.99 (0.98-0.99)
	Median (IQR, max)	0.0 (0-1.5; 9)	0.0 (0-1.5; 12)	0.0 (0-0.0; 7.5)
	Mean (SD)	1.1 (1.8)	1.1 (1.9)	0.3 (1.1) 0.0 (0.0-0.1; 6.8)
Erosions	ICC (95%CI)	0.88 (0.84-0.91)	0.89 (0.86-0.92)	0.96 (0.93-0.97)
	Median (IQR, max)	0.5 (0-1.0; 9)	0.0 (0-1.0; 7)	0.0 (0.0-0.7; 1.4)
	Mean (SD)	0.7 (1.0)	0.6 (0.9)	0.3 (0.5)
MCP-joints				
BME	ICC (95%CI)	0.60 (0.48-0.70)	0.90 (0.82-0.93)	0.93 (0.89-0.96)
	Median (IQR, max)	0 (0-0.5; 7.5)	0 (0-1; 14)	0 (0-0; 2)
	Mean (SD)	0.6 (1.3)	1.0 (1.4)	0.1 (0.4)
Synovitis	ICC (95%CI)	0.91 (0.88-0.94)	0.92 (0.89-0.94)	0.99 (0.98-0.99)
	Median (IQR, max)	0 (0-1; 6)	0 (0-1; 9)	0 (0-0; 4.9)
	Mean (SD)	0.9 (1.5)	0.8 (1.4)	0.2 (0.8)

Tenosynovitis	ICC (95%CI) Median (IQR, max) Mean (SD)	0.91 (0.88-0.93) 0 (0-2.5; 8.5) 1.5 (1.9)	0.91 (0.87-0.94) 1.5 (0-3; 13) 2.1 (2.4)	0.95 (0.92-0.97) 0 (0-1; 6) 0.8 (1.4)	0.98 (0.96-0.99) 0.1 (0-1; 5.0) 0.8 (1.3)
Erosions	ICC (95%CI) Median (IQR, max) Mean (SD)	0.93 (0.91-0.95) 0 (0-1; 5) 0.6 (1.0)	0.92 (0.90-0.94) 0 (0-5; 5) 0.7 (0.9)	0.93 (0.89-0.96) 0 (0-1; 4) 0.5 (0.9)	0.97 (0.95-0.98) 0 (0-0.9; 1.9) 0.4 (0.6)
Wrist					
BME	ICC (95%CI) Median (IQR, max) Mean (SD)	0.91 (0.88-0.93) 1 (0-2.5; 24) 2.2 (3.4)	0.93 (0.75-0.97) 2 (0.5-4; 27) 3.6 (4.8)	0.93 (0.90-0.96) 0.5 (0-1.5; 11) 1.1 (1.7)	0.96 (0.94-0.98) 0.3 (0.1-1.2; 3.4) 0.8 (1.0)
Synovitis	ICC (95%CI) Median (IQR, max) Mean (SD)	0.90 (0.87-0.92) 1 (0-3; 8) 1.8 (2.1)	0.93 (0.91-0.95) 2 (0.5-3.5; 8) 2.3 (2.1)	0.91 (0.87-0.94) 0.5 (0-1.5; 5.5) 0.9 (1.1)	0.96 (0.95-0.98) 0.4 (0-1.1; 3.4) 0.7 (0.9)
Tenosynovitis	ICC (95%CI) Median (IQR, max) Mean (SD)	0.93 (0.91-0.95) 1 (0-4; 11.5) 2.5 (3.0)	0.96 (0.95-0.97) 1.5 (0-5; 13) 2.8 (3.3)	0.97 (0.95-0.98) 0 (0-0; 10) 0.6 (1.7)	0.99 (0.98-0.99) 0.1 (0-0.4; 9.2) 0.8 (2.0)
Erosions	ICC (95%CI) Median (IQR, max) Mean (SD)	0.88 (0.84-0.91) 1.5 (0.5-3.5; 11) 2.2 (2.2)	0.94 (0.92-0.95) 1.8 (0.5-3; 14) 2.2 (2.2)	0.87 (0.79-0.92) 1 (0.5-2.5; 7.5) 1.5 (1.5)	0.96 (0.94-0.98) 0.6 (0.2-2.3; 4.2) 1.2 (1.2)

Results are based on a mean-rating, absolute agreement, two-way mixed effects model. RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Score; n: number of patients; k: number of readers; MTP: metatarsophalangeal; MCP: metacarpophalangeal; BME: bone marrow edema; ICC: intraclass correlation coefficients; CI: confidence interval; IQR: interquartile range; SD: standard deviation. Consecutive early arthritis patients were scored by four readers, the first 215 consecutive patients were scored by reader 1 and 2, the remaining 226 consecutive patients by reader 3 and 4. 82 consecutive patients with clinically suspect arthralgia were scored by reader 5 and 6. Of these 82 patients, 40 were randomly selected and in addition also scored by 7 other readers.

Table 2. Intrareader intraclass correlation coefficients and average status scores according to the RAMRIS in early arthritis patients (n=15) by two readers

Patient population		Early arthritis (n=15)	
		Reader 1	Reader 2
MTP-joints			
BME	ICC (95%CI)	0.96 (0.89–0.99)	0.98 (0.95–0.99)
	Median (IQR, max)	0.0 (0.0–2.5; 5)	0.0 (0.0–2.5; 8.5)
	Mean (SD)	1.1 (1.6)	1.4 (2.3)
Synovitis	ICC (95%CI)	0.90 (0.74–0.97)	0.98 (0.94–0.99)
	Median (IQR, max)	0.5 (0.0–1.0; 3.5)	1.0 (0.0–2.0; 5.5)
	Mean (SD)	0.8 (1.2)	1.3 (1.8)
Tenosynovitis	ICC (95%CI)	0.97 (0.91–0.99)	0.84 (0.58–0.94)
	Median (IQR, max)	0.0 (0.0–3.5; 8)	0.0 (0.0; 4.5)
	Mean (SD)	1.7 (2.9)	0.6 (1.4)
Erosions	ICC (95%CI)	0.71 (0.35–0.89)	0.92 (0.78–0.97)
	Median (IQR, max)	0.0 (0.0–1.0; 2)	0.0 (0.0–1.0; 4.5)
	Mean (SD)	0.4 (0.6)	0.7 (1.2)
MCP-joints			
BME	ICC (95%CI)	0.86 (0.61–0.95)	0.80 (0.51–0.93)
	Median (IQR, max)	0 (0–0.5; 2.5)	0 (0–0.5; 2.5)
	Mean (SD)	0.4 (0.8)	0.3 (0.7)
Synovitis	ICC (95%CI)	0.88 (0.68–0.96)	0.96 (0.89–0.99)
	Median (IQR, max)	0 (0–1; 2)	0 (0–1; 4)
	Mean (SD)	0.5 (0.7)	0.9 (1.3)
Tenosynovitis	ICC (95%CI)	0.97 (0.91–0.99)	0.94 (0.83–0.98)
	Median (IQR, max)	1 (0–3.5; 4.5)	0 (0–2; 3.5)
	Mean (SD)	1.4 (1.8)	1.0 (1.3)
Erosions	ICC (95%CI)	0.94 (0.82–0.98)	0.99 (0.96–1.00)
	Median (IQR, max)	0 (0–1. 4.5)	0 (0–1; 5.5)
	Mean (SD)	0.7 (1.3)	0.8 (1.6)

Wrist			
BME	ICC (95%CI)	0.77 (0.45-0.92)	0.90 (0.72-0.96)
	Median (IQR, max)	0.5 (0-1.5; 3.5)	0 (0-2; 5)
	Mean (SD)	0.8 (1.0)	1.2 (1.6)
Synovitis	ICC (95%CI)	0.92 (0.71-0.98)	0.95 (0.81-0.98)
	Median (IQR, max)	0 (0-1.5; 3.5)	0.5 (0-1; 5)
	Mean (SD)	0.8 (1.4)	1.1 (1.5)
Tenosynovitis	ICC (95%CI)	0.99 (0.97-1.00)	0.99 (0.98-1.00)
	Median (IQR, max)	0 (0-1; 6)	0.5 (0-2; 6)
	Mean (SD)	1.1 (1.9)	1.4 (2.0)
Erosions	ICC (95%CI)	0.95 (0.86-0.98)	0.97 (0.90-0.99)
	Median (IQR, max)	1 (0-3.5; 6.5)	1 (0-3; 5)
	Mean (SD)	1.9 (2.1)	1.4 (1.7)

Results are based on a single-measure, absolute agreement, two-way mixed effects model. Based on the repeated scoring of randomly selected patients (patients are scored twice by each reader).n: number of patients; MTP: metatarsophalangeal; MCP: metacarpophalangeal; BME: bone marrow edema; ICC: interclass correlation coefficient; CI: confidence interval; IQR: interquartile range; SD: standard deviation

A pitfall of ICCs is that they are sensitive to a lack of variability among sampled subjects.(25) We found the intrareader reliability of erosions to be moderate for reader 1 (0.71, 95%CI 0.35-0.89), but excellent for reader 2 (0.92, 95% CI 0.78-0.97). The mean score of erosions was low (0.4 (SD 0.6)), which corresponds to a lack of variability among these subjects that could have resulted in a moderate ICC. In addition, for change scores the reliability of erosions was lower than the inflammatory MRI-features (0.77, 95% CI 0.52-0.89), but still good.(25) Also here the mean change in the score of MRI-features was lowest for erosions (0.4 (SD 0.6)) compared to ≥ -1.3 for the other features, see Table 3). Besides ICCs, BA-plots, and for change scores SDCs, are important to take into consideration as measures of reliability. BA-plots visualise the data and illustrate that levels of agreement were acceptable in both cases (Figure 2 and 3), and for change scores the low SDC suggests a good reliability.(31)

For change scores we selected early arthritis patients that had high baseline scores and were thus most prone to change over time, specifically a decrease in inflammation and possibly an increase in erosions. The mean change scores were low for all MRI-features, and for erosions in particular (at the MTPs the mean change score was 0.4 (SD 0.6)). This is expected, as 29 of the 30 patients received

DMARDs, inhibiting the occurrence or progression of erosions.

The focus in rheumatology is shifting from established erosive RA to early arthritis and even to patients with clinically suspect arthralgia. Therefore, we included patients with clinically suspect arthralgia and found the scoring of status scores to be reliable. In different stages of disease, MRI-detected lesions may be more or less frequent, which may influence the reliability of scoring. (32)

MRI-detected inflammation was subclinical by definition, as there was no apparent arthritis upon physical examination. As expected, absolute MRI scores for arthralgia patients were lower than those with early arthritis, but the reliability overall was good. This is encouraging for MRI-studies in the pre-arthritis phase.

Radiographic studies have shown that erosive lesions occur more commonly in the feet than in the hands, and also in earlier phases of disease.(8,9) In our results, the scores of the MRI-features were higher in the hands than in the MTPs, especially in the wrist. This is in concordance with a recent study performed in patients with undifferentiated arthritis on the development of RA, where adding MRI of the foot did not improve predictive accuracy compared to MRI of the hand alone.(33) This was explained by the finding that inflammation in the foot was indeed an early phenomenon, but it almost never occurred without inflammation in the hands.

A strength of this study is that it included a large number of patients from two different cohorts, and scoring was performed by numerous readers with considerable experience with the RAMRIS. We studied an unselected group of patients with early arthritis, rather than a specific group of patients that met stringent inclusion criteria of trials. Reliability studies in this patient population are infrequent, the present data are important for future studies in early arthritis. As a sensitivity analyses we looked at the reliability of scoring in the following diagnoses separately: RA, Ua, SpA and inflammatory OA. This was done for reader 1/2 and reader 3/4 separately, and thus resulted in small numbers of patients, especially in the SpA and inflammatory OA groups (SpA n=15 and 30, and OA n=12 and 11). For the RA and UA groups the reliability of scoring was overall good, for the latter two diagnoses caution should be given when interpreting the results.

The aspect discrimination of the OMERACT Filter was not addressed in our study, and should be subject for further research.(11) In addition, whether the measured change is clinically relevant needs to be determined in studies evaluating the

minimal clinical important difference (MCID). The scorings were not timed and thus unfortunately it was not possible to make a statement concerning feasibility.

We applied the RAMRIS that is developed for the wrist and MCP-joints to the MTP-joints, and for tenosynovitis the commonly used score developed by Haavardsholm et al.(2,17) The RAMRIS was recently updated, and now includes joint space narrowing and a slightly modified tenosynovitis-score published by Glinatsi et al.(10,34) The RAMRIS was not yet updated at the start of this study and was therefore not used here. We applied the tenosynovitis score of Haavardsholm et al. to the flexor and extensor tendons of the MCP- and MTP-joints. Although the extensor tendons at the MTP- and MCP-joints seem to lack a synovial sheath, inflammation around the extensor tendons at the MCP-joints have been described in RA.(35) And thus, even though the nature of this inflammation is unclear, we believe it is important to further study and validate the scoring of the inflammation observed around the extensor tendons, which includes assessing its' reliability.

According to the RAMRIS-method, T2-weighted fat suppressed or short tau inversion recovery (STIR) sequences should be used to assess bone marrow edema (BME). Previous studies have demonstrated that a contrast enhanced T1-weighted fat suppressed sequence has a strong correlation with T2-weighted fat suppressed sequences.(19-21) In addition, the European Society of Musculoskeletal Radiology (ESSR) Arthritis Subcommittee also recommends the use of contrast enhanced T1-weighted fat suppressed sequences for depiction of BME.(22) We therefore used the contrast enhanced T1-weighted fat suppressed sequence as it allowed a shorter scan time and has a higher signal to noise ratio. We thus believe that this did not influence the reliability of scoring BME, although we did not strictly follow the RAMRIS-protocol for depicting BME.

The MTP-images were acquired after gadolinium contrast was given for the acquisition of hand images. The time window between contrast administration and imaging of the foot was approximately 12 minutes. Previously it was shown that small time variations are not of major importance to measured synovial membrane volumes, as during a one-hour post-contrast follow up period the measured volumes remained almost unchanged.(36) We therefore believe this has not influenced our results.

In conclusion, scoring of status and change scores of BME, synovitis, tenosynovitis and erosions of the MTP-joints according to the RAMRIS was reliable. This is

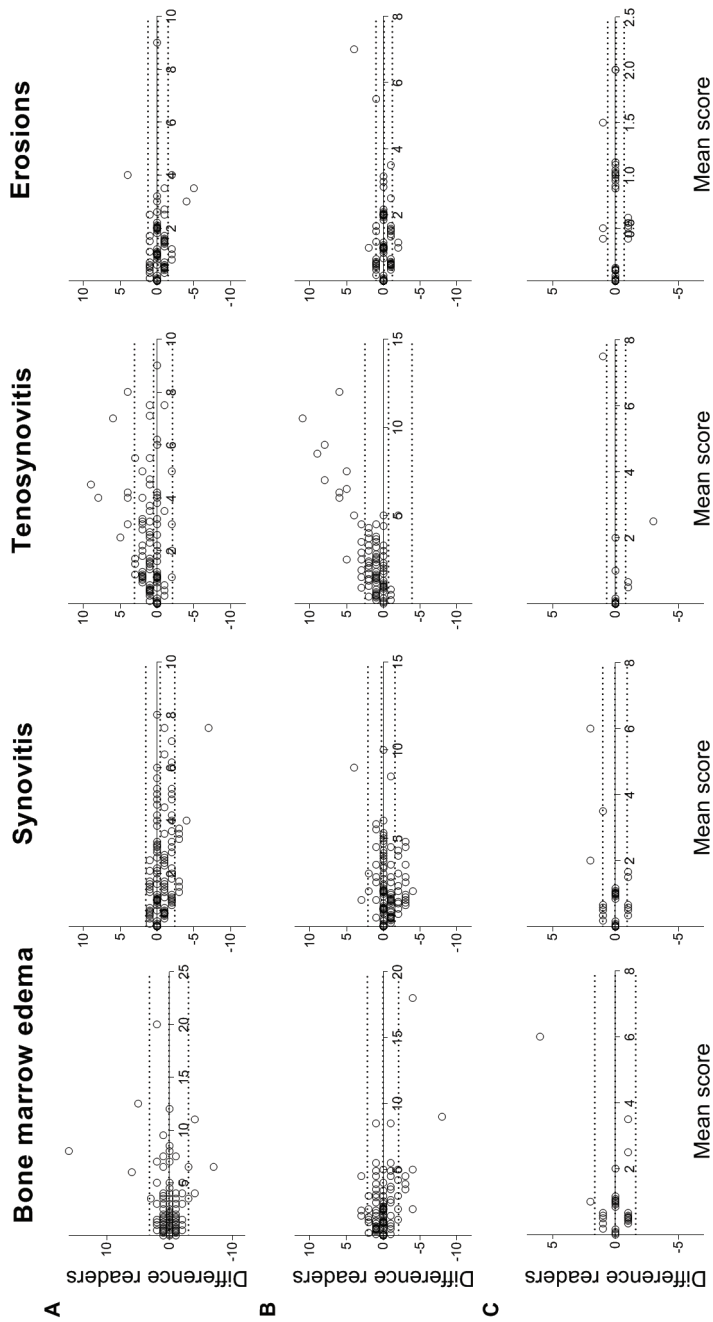


Figure 2: Bland-Altman plot depicting interreader agreement of status scores of the metatarsophalangeal-joints for the two groups of early arthritis patients and for patients with clinically suspect arthralgia. Bland-Altman plots of assessment of agreement of scores of the two readers. The Y-axes demonstrates the absolute difference between reader 1 minus reader 2. The X-axes denotes the average value between the two readers (reader 1-reader 2)/2. The middle dotted line depicts the mean difference, the upper and lower dotted lines depict the $\pm 95\%$ limits of agreement. Different cohorts of patients are depicted; A) 215 early arthritis patients scored by reader 1 and 2, B) 226 early arthritis patients scored by reader 3 and 4, C) 82 patients with clinically suspect arthralgia scored by reader 5 and 6. From left to right the following MRI-lesions are depicted: bone marrow edema (BME), synovitis, tenosynovitis and erosions

encouraging for the use of the scoring system also for MTP-joints in trials in early phases of RA.

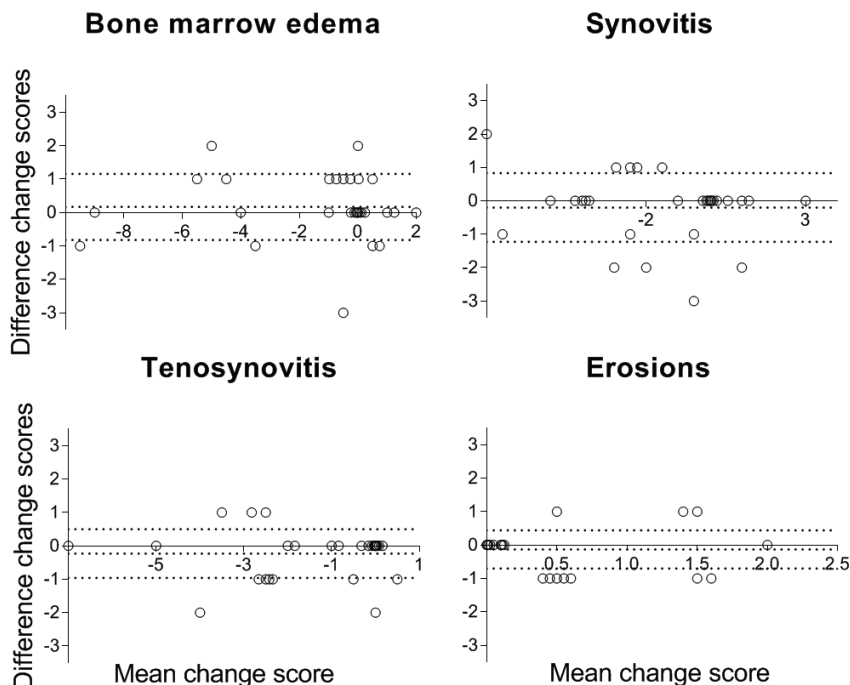


Figure 3. Bland-Altman plot depicting interreader agreement of change scores of the metatarsophalangeal-joints in early arthritis patients (n=30) from baseline until 12 months of follow-up. Bland-Altman plots of assessment of agreement of change scores of the two readers. The Y-axes demonstrates the difference in the change scores (12 months minus baseline score) for reader 1 minus reader 2. The X-axes denotes the average change score between the two readers ((change score reader 1 - change score reader 2)/2). The middle dotted line depicts the mean difference, the upper and lower dotted lines depict the $\pm 95\%$ limits of agreement. From left to right and top to bottom the following MRI-lesions are depicted: bone marrow edema (BME), synovitis, tenosynovitis and erosions

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Table 3. Change scores intraclass correlation coefficients and average scores according to the RAMRIS in early arthritis patients (n=30) from baseline until 12 months of follow-up by two readers

	Median change (IQR)	Mean change (SD)	Median change (IQR)	Mean change (SD)	Median change (IQR; max)	Mean change (SD)	ICC change (95% CI)	SDC	Change >0, n (%)	Change >0.5, n (%)	Change >SDC, n (%)
	Reader 1	Reader 1	Reader 2	Reader 2	Average both readers	Average both readers					
MTP											
BME	0 (-2-0)	-1.2 (2.9)	0 (-1-0)	-1.4 (2.9)	0 (-1-0,-9.5)	-1.3 (2.9)	0.97 (0.94-0.99)	1.0	20 (67)	11 (37)	11 (37)
Synovitis	-1 (-4-0)	-1.6 (2.3)	-1 (-3-0)	-1.4 (2.5)	-0.75 (-3-0,-7)	-1.5 (2.4)	0.90 (0.90-0.98)	1.0	22 (73)	20 (67)	20 (67)
Tenosynovitis	-1 (-3-0)	-1.5 (1.9)	0 (-2-0)	-1.2 (1.9)	-0.25 (-2.5-0,-7)	-1.4 (1.8)	0.96 (0.91-0.98)	0.7	16 (53)	14 (47)	14 (47)
Erosions	0 (0-0)	0.3 (0.7)	0 (0-1)	0.4 (0.7)	0 (0-0.52)	0.4 (0.6)	0.77 (0.52-0.89)	0.6	11 (37)	5 (17)	5 (17)
MCP											
BME	0 (-2-0)	-0.9 (1.9)	0 (-2-0)	-0.8 (1.9)	0 (-1.5-0,-6.5)	-0.9 (1.8)	0.94 (0.88-0.97)	0.9	16 (53)	13 (43)	13 (43)
Synovitis	-2 (-3-0)	-1.3 (2.8)	-2 (-3-0)	-1.4 (2.7)	-1.5 (-3-0.5,-6.5)	-1.4 (2.7)	0.97 (0.93-0.98)	1.0	26 (87)	25 (83)	25 (83)
Tenosynovitis	0 (-3-0)	-1.4 (2.7)	0 (-2-0)	-1.3 (2.6)	0 (-2.5-0,-10)	-1.3 (2.6)	0.97 (0.94-0.99)	0.9	15 (50)	14 (47)	14 (47)
Erosions	0 (0-1)	0.4 (0.7)	0 (0-1)	0.4 (0.6)	0 (0-1.2)	0.4 (0.6)	0.94 (0.87-0.97)	0.3	11 (37)	9 (30)	11 (37)

	Median change (IQR)	Mean change (SD)	Median change (IQR)	Mean change (SD)	Median change (IQR; max)	Mean change (SD)	ICC change (95% CI)	SDC	Change >0, n(%)	Change >0.5, n(%)	Change >SDC, n(%)
	Reader 1	Reader 1	Reader 2	Reader 2	Average both readers	Average both readers					
Wrist											
BME	-1 (-3-0)	-2.8 (5.4)	-1 (-5-0)	-2.9 (4.8)	-1 (-4-0; -19)	-2.8 (5.0)	0.98 (0.96-0.99)	1.5	25 (83)	20 (67)	14 (47)
Synovitis	-1 (-4-0)	-1.6 (2.8)	-2 (-4-0)	-2.3 (2.8)	-1.5 (-4-0; -7.5)	-2.8 (5.0)	0.96 (0.81-0.98)	0.9	24 (80)	20 (67)	20 (67)
Tenosynovitis	-2 (-4-0)	-2.6 (3.3)	-2 (-5-0)	-2.6 (3.1)	-1.5 (-4.5-0; -10.5)	-2.6 (3.2)	0.98 (0.96-0.99)	0.9	23 (77)	19 (63)	19 (63)
Erosions	0 (0-1)	1.0 (2.3)	0 (0-1)	0.7 (1.6)	0 (0-1.8)	0.9 (1.9)	0.91 (0.81-0.96)	1.1	18 (60)	9 (30)	5 (17)

IQR: interquartile range; SD: standard deviation; ICC: intraclass correlation coefficient; CI: confidence interval; SDC: smallest detectable change; n: number; MTP: metatarsophalangeal; MCP: metacarpophalangeal; BME: bone marrow edema. The change scores of individual readers (reader 1 and reader 2) are depicted, in addition to the average change over time of both readers ('median change' and 'mean change'). Change ICCs are based on a mean-rating, absolute agreement, two-way mixed effects model. 'Change, n' is defined as the numbers of patients with change of more than an average of both readers of >0 or >0.5. 'Change >SDC, n' represents the number of patients with change after using the SDC as a cut-off.

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Supplementary data

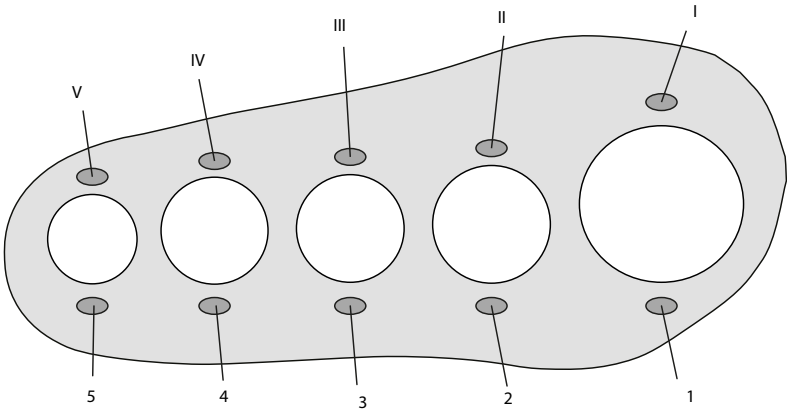
Supplementary methods are available at Journal of Rheumatology online.

Supplementary Table 1. Baseline characteristics of all early arthritis patients and patients with clinically suspect arthralgia assessed for status scores and early arthritis patients assessed for change scores.

	Patients for status scores		Patients for change scores
	Early arthritis N=441	Arthralgia N=82	Early arthritis N=30
Age, mean (SD)	55 (16)	46 (13)	57 (17)
Female, n(%)	267 (61)	69 (84)	21 (70)
Symptom duration, in weeks, median (IQR)	9 (4-27)	17 (9-34)	15 (7-44)
Swollen joint count, median (IQR)	3 (1-7)	0	6 (4-8)
HAQ, median (IQR)	0.8 (0.4-1.3)	0 (0-1)	0.9 (0.5-1.4)
CRP, mg/L, (IQR)	7 (3-20)	3 (3-4)	9 (3-30) median
ACPA positive, n (%)	156 (37)	8 (10)	13 (43)
RF positive, n (%)	157 (36)	14 (19)	15 (50)

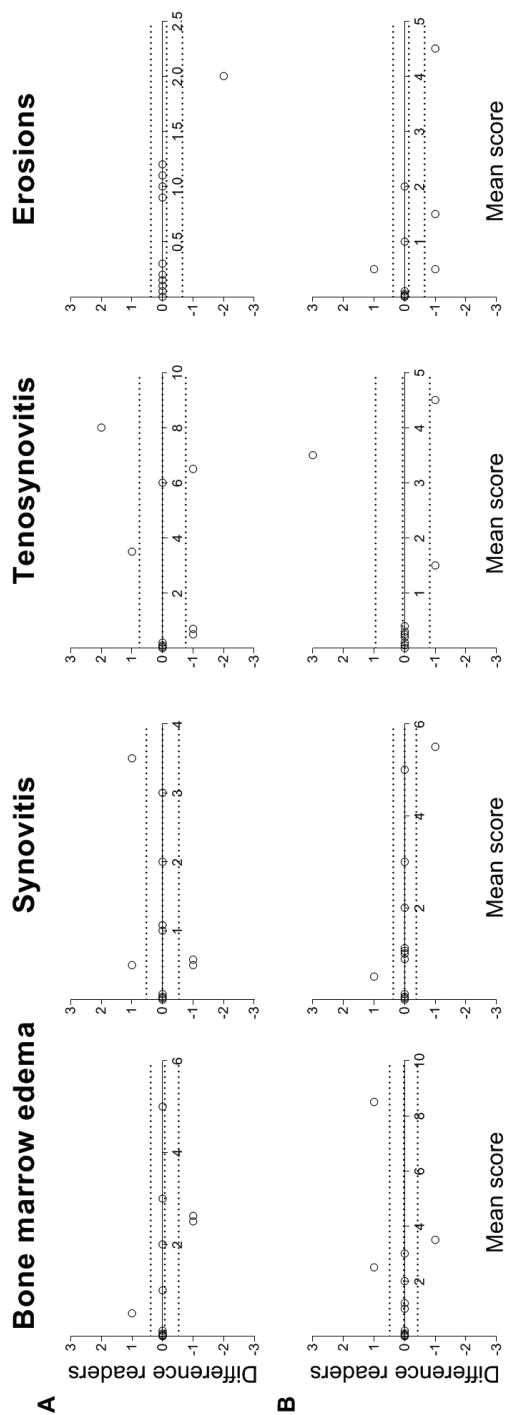
N: number; SD: standard deviation; IQR: interquartile range; HAQ: Health Assessment Questionnaire; CRP: C-reactive protein; ACPA: Anti-citrullinated protein antibody; RF: rheumatoid factor.

MTP JOINTS		5. finger	4. finger	3. finger	2. finger	1. finger
Bone erosions (score 0-10)	Distal					
	Proximal					
Bone marrow edema (score 0-3)	Distal					
	Proximal					
Synovitis (score 0-3)						
Teno-synovitis (score 0-3)	Flexor					
	Extensor					



Abbreviations: MTP: metatarsophalangeal; 1: flexor hallucis longus; 2-5: second to fifth common flexor digitorum longus and flexor digitorum brevis; I: extensor hallucis longus; II-V: extensor digitorum longus.

Supplementary Figure 1. Score sheet for the metatarsophalangeal joints



Supplementary Figure 2. Bland-Altman plot depicting intrareader agreement of status scores of the metatarsophalangeal-joints for the two different readers. Bland-Altman plots of assessment of agreement of scores between the two readings. The Y-axes demonstrates the absolute difference between the first time reading minus the second time. The X-axes denotes the average value between the two readings ((time 1+time 2)/2). The middle dotted line depicts the mean, the upper and lower dotted lines depict the $\pm 95\%$ limits of agreement. A: reader 1, B: reader 2, N=15 patients. From left to right the following MRI-lesions are depicted: bone marrow edema (BME), synovitis, tenosynovitis and erosions.

Supplementary Table 2. Status scores of individual readers according to the RAMRIS

Patient population	Early arthritis (n=215)			Early arthritis (n=226)			Arthralgia (n=82)		
	Reader 1	Reader 2	Reader 3	Reader 4	Reader 5	Reader 6			
MTP-joints									
BME	Median (IQR; max)	1 (0-2; 21)	1 (0-2; 19)	0 (0-1; 20)	1 (0-2; 16)	0 (0-0; 9)	0 (0-1; 4)		
	Mean (SD)	1.6 (2.8)	1.5 (2.6)	1.1 (2.2)	1.2 (1.8)	0.4 (1.1)	0.4 (0.8)		
Synovitis	Median (IQR; max)	1 (0-2; 8)	1 (0-2; 11)	0 (0-1; 11)	1 (0-2; 10)	0 (0-1; 7)	0 (0-0; 5)		
	Mean (SD)	1.1 (1.6)	1.5 (2.0)	1.0 (1.7)	1.3 (1.8)	0.4 (1.0)	0.3 (0.8)		
Tenosynovitis	Median (IQR; max)	0 (0-2; 10)	0 (0-1; 9)	0 (0-2; 16)	0 (0-1; 9)	0 (0-0; 8)	0 (0-0; 7)		
	Mean (SD)	1.4 (2.2)	0.9 (1.7)	1.4 (2.6)	0.7 (1.4)	0.2 (0.9)	0.2 (0.9)		
Erosions	Median (IQR; max)	0 (0-1; 9)	0 (0-1; 9)	0 (0-1; 5)	0 (0-1; 9)	0 (0-0; 2)	0 (0-0; 2)		
	Mean (SD)	0.6 (1.0)	0.8 (1.2)	0.6 (0.9)	0.5 (1.0)	0.2 (0.5)	0.3 (0.5)		
MCP-joints									
BME	Median (IQR; max)	0 (0-1; 12)	0 (0-0.5; 7)	0 (0-1; 16)	0 (0-2; 12)	0 (0-0; 3)	0 (0-0; 2)		
	Mean (SD)	0.7 (1.8)	0.5 (1.1)	0.8 (1.9)	1.3 (2.1)	0.2 (0.5)	0.1 (0.4)		
Synovitis	Median (IQR; max)	0 (0-1; 6)	0 (0-2; 8)	0 (0-1; 11)	0 (0-1; 8)	0 (0-0; 6)	0 (0-0; 4)		
	Mean (SD)	0.8 (1.3)	1.0 (1.7)	0.7 (1.5)	0.9 (1.5)	0.2 (0.7)	0.1 (0.6)		
Tenosynovitis	Median (IQR; max)	1 (0-3; 9)	1 (0-2; 8)	1 (0-4; 16)	1 (0-3; 10)	0 (0-1; 7)	0 (0-1; 4)		
	Mean (SD)	1.7 (2.0)	1.4 (1.9)	2.3 (2.9)	1.8 (2.1)	0.8 (1.6)	0.5 (0.9)		
Erosions	Median (IQR; max)	0 (0-1; 5)	0 (0-1; 6)	0 (0-1; 6)	0 (0-1; 4)	0 (0-1; 4)	0 (0-1; 4)		
	Mean (SD)	0.7 (1.0)	0.6 (1.0)	0.7 (0.9)	0.6 (0.9)	0.5 (0.9)	0.5 (0.9)		

Patient population	Early arthritis (n=215)			Early arthritis (n=226)			Arthralgia (n=82)		
	Reader 1	Reader 2	Reader 3	Reader 4	Reader 5	Reader 6	Reader 5	Reader 6	Reader 6
Wrist									
BME	Median (IQR; max)	1 (0-2; 23)	1 (0-3; 25)	1 (0-3; 28)	3 (1-6; 28)	0 (0-1; 11)	0 (0-1; 11)	0 (0-2; 11)	0.5 (0-2; 11)
	Mean (SD)	2.1 (3.6)	2.3 (3.5)	2.8 (4.6)	4.4 (5.2)	1.0 (1.9)	1.0 (1.9)	1.1 (1.8)	1.1 (1.8)
Synovitis	Median (IQR; max)	1 (0-3; 8)	1 (0-3; 8)	2 (0-4; 9)	2 (0-3; 7)	0 (0-2; 6)	0 (0-2; 6)	0.5 (0-1; 5)	0.5 (0-1; 5)
	Mean (SD)	1.8 (2.2)	1.8 (2.1)	2.3 (2.4)	2.2 (1.9)	0.9 (1.2)	0.9 (1.2)	0.8 (1.1)	0.8 (1.1)
Tenosynovitis	Median (IQR; max)	1 (0-4; 12)	1 (0-4; 11)	1 (0-5; 15)	2 (0-5; 12)	0 (0-0; 11)	0 (0-0; 11)	0 (0-0; 9)	0 (0-0; 9)
	Mean (SD)	2.3 (3.1)	2.6 (3.2)	2.8 (3.6)	2.9 (3.2)	0.6 (1.8)	0.6 (1.8)	0.6 (1.5)	0.6 (1.5)
Erosions	Median (IQR; max)	1 (1-3; 10)	2 (0-3; 12)	2 (1-3; 13)	2 (1-3; 15)	1 (0-2; 6)	1 (0-2; 6)	1 (0-3; 9)	1 (0-3; 9)
	Mean (SD)	2.2 (2.2)	2.3 (2.4)	2.2 (2.3)	2.3 (2.2)	1.5 (1.6)	1.5 (1.6)	1.6 (1.6)	1.6 (1.6)

Reader 1				Reader 2				
	Baseline		Change		1 year		Change	
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)
MTP								
BME	1 (0-4)	2.4 (3.7)	0 (0-2)	1.2 (1.6)	-1.2 (2.9)	2.4 (3.8)	0 (0-2)	1.1 (1.7)
Synovitis	3 (0-4)	2.9 (2.6)	1 (0-2)	1.3 (1.4)	-1.6 (2.3)	3.0 (2.8)	1 (0-2)	1.5 (1.6)
Tenosynovitis	1 (0-3)	1.6 (1.9)	0 (0-0)	0.1 (0.4)	-1 (-3-0)	1.4 (1.9)	0 (0-0)	0.2 (0.6)
Erosions	1 (0-2)	1.2 (1.8)	1 (0-2)	1.5 (2.1)	0 (0-0)	1.1 (1.7)	1 (0-2)	1.5 (2.0)
MCP								
BME	0 (0-2)	1.4 (2.3)	0 (0-0)	0.5 (1.1)	-0.9 (1.9)	1.4 (2.3)	0 (0-0)	0.6 (1.4)
Synovitis	3 (0-6)	3.3 (3.1)	2 (0-3)	1.9 (2.1)	-1.3 (2.8)	3.3 (2.9)	1 (0-3)	1.9 (1.9)
Tenosynovitis	1 (0-4)	2.2 (2.9)	0 (0-1)	0.8 (1.8)	-1.4 (2.7)	2.1 (2.7)	0 (0-1)	0.8 (1.7)
Erosions	0 (0-1)	0.6 (1.1)	1 (0-1)	1.0 (1.5)	0.4 (0.7)	0.7 (1.2)	1 (0-1)	1.1 (1.5)
Wrist								
BME	5 (0-1)	6.2 (7.3)	2 (1-5)	3.4 (6.9)	-1 (-3-0)	6.3 (7.0)	2 (1-3)	3.4 (6.3)
Synovitis	3 (2-7)	4.1 (3.0)	2 (1-3)	2.5 (2.5)	-1 (-4-0)	4.6 (3.1)	2 (0-3)	2.3 (2.5)
Tenosynovitis	3 (0-6)	3.4 (3.6)	0 (0-1)	0.8 (2.1)	-2 (-4-0)	3.5 (3.4)	0 (0-1)	0.8 (1.9)
Erosions	2 (1-4)	3.1 (3.0)	4 (1-6)	4.1 (4.0)	0 (0-1)	3.1 (4-4)	3 (2-6)	4.1 (3.6)
				</				

Supplementary Table 4. Interreader intraclass correlation coefficients and average status scores according to the RAMRIS in patients with rheumatoid arthritis (RA; n=157 total) and undifferentiated arthritis patients (UA; n=148 total)

Patient population		RA n=91, k=2	RA n=66, k=2	UA n=66, k=2	UA n=82, k=2
MTP-joints					
BME	ICC (95%CI)	0.94 (0.91-0.96)	0.92 (0.86-0.95)	0.65 (0.44-0.79)	0.93 (0.88-0.96)
	Median (IQR, max)	1 (0-3.5; 20)	0.75 (0-2.5; 8.5)	0.5 (0-1; 8)	0 (0-1; 8.5)
	Mean (SD)	2.2 (3.3)	1.5 (1.8)	1.0 (1.8)	0.7 (1.4)
Synovitis	ICC (95%CI)	0.89 (0.77-0.93)	0.95 (0.92-0.97)	0.90 (0.82-0.94)	0.85 (0.73-0.91)
	Median (IQR, max)	10 (0-30; 8)	1 (0-3; 10)	0.5 (0-1; 5)	0 (0-1; 4.5)
	Mean (SD)	1.9 (2.0)	2.0 (2.4)	0.9 (1.2)	0.7 (1.1)
Tenosynovitis	ICC (95%CI)	0.79 (0.62-0.87)	0.76 (0.49-0.87)	0.95 (0.91-0.97)	0.92 (0.87-0.95)
	Median (IQR, max)	10 (0-3; 8)	0.5 (0-3; 12)	0 (0-0.5; 7.5)	0 (0-1; 5)
	Mean (SD)	1.8 (2.2)	2.1 (2.9)	0.6 (1.4)	0.6 (1.1)
Erosions	ICC (95%CI)	0.86 (0.79-0.91)	0.92 (0.87-0.95)	0.95 (0.91-0.97)	0.92 (0.83-0.95)
	Median (IQR, max)	0.5 (0-1.0; 9)	0.5 (0-1.0; 5.5)	0 (0-1; 3.5)	0 (0-1; 3)
	Mean (SD)	0.9 (1.3)	0.6 (0.9)	0.5 (0.8)	0.5 (0.7)
MCP-joints					
BME	ICC (95%CI)	0.57 (0.35-0.72)	0.91 (0.80-0.95)	0.83 (0.73-0.90)	0.88 (0.79-0.93)
	Median (IQR, max)	0 (0-2.5; 6)	0.5 (0-1.5; 14)	0 (0-0.5; 6.5)	0 (0-1; 8.5)
	Mean (SD)	0.7 (1.5)	1.4 (2.5)	0.4 (1.0)	0.7 (1.6)
Synovitis	ICC (95%CI)	0.87 (0.77-0.93)	0.95 (0.91-0.97)	0.92 (0.87-0.95)	0.86 (0.78-0.91)
	Median (IQR, max)	0.5 (0-2.5; 6)	0.75 (0-2.5; 9)	0 (0-0.5; 4)	0 (0-0.5; 4)
	Mean (SD)	1.4 (1.7)	1.5 (2.0)	0.5 (1.0)	0.4 (0.9)

Tenosynovitis	ICC (95%CI) Median (IQR, max) Mean (SD)	0.91 (0.86-0.94) 2 (0.5-3; 8.5) 2.2 (2.0)	0.92 (0.83-0.96) 2.5 (0.5-4; 13) 3.0 (2.8)	0.94 (0.90-0.97) 0.25 (0-2; 5) 1.2 (1.6)	0.89 (0.82-0.93) 1 (0-1.5; 10.5) 1.4 (2.0)
Erosions	ICC (95%CI) Median (IQR, max) Mean (SD)	0.93 (0.90-0.96) 0 (0-1; 5) 0.7 (1.0)	0.94 (0.90-0.96) 0.5 (0-1.5; 5) 0.9 (1.1)	0.88 (0.81-0.93) 0 (0-1; 4) 0.5 (0.8)	0.92 (0.88-0.95) 0 (0-1; 3.5) 0.5 (0.7)
Wrist					
BME	ICC (95%CI) Median (IQR, max) Mean (SD)	0.89 (0.84-0.93) 1.5 (0-3.5; 17) 2.7 (3.6)	0.90 (0.72-0.95) 2.25 (1-5.5; 23) 3.9 (4.1)	0.82 (0.70-0.89) 0.5 (0-1.5; 9.5) 1.4 (2.2)	0.95 (0.83-0.98) 2 (0-4; 27) 3.9 (6.2)
Synovitis	ICC (95%CI) Median (IQR, max) Mean (SD)	0.91 (0.86-0.94) 2 (0-4.5; 8) 2.4 (2.2)	0.93 (0.89-0.96) 2.5 (1.5-4; 8) 2.8 (2.1)	0.83 (0.72-0.90) 0.5 (0-3; 7) 1.5 (1.8)	0.93 (0.90-0.96) 1.5 (0-3.5; 7.5) 2.1 (2.2)
Tenosynovitis	ICC (95%CI) Median (IQR, max) Mean (SD)	0.93 (0.88-0.95) 2.5 (1-5.5; 11.5) 3.4 (3.1)	0.96 (0.93-0.98) 2.25 (0.5-6; 13) 3.6 (3.7)	0.94 (0.90-0.96) 0 (0-3.5; 11) 1.9 (2.8)	0.95 (0.93-0.97) 1 (0-4.5; 12) 2.5 (3.1)
Erosions	ICC (95%CI) Median (IQR, max) Mean (SD)	0.80 (0.69-0.87) 1.5 (1-3.5; 7.5) 2.2 (1.9)	0.92 (0.88-0.95) 2 (1-3; 14) 2.4 (2.3)	0.91 (0.85-0.94) 1 (0.5-3.5; 9.5) 2 (2.1)	0.95 (0.92-0.97) 1.5 (0.5-3.5; 10) 2.2 (2.2)

Supplementary Table 5. Interreader intraclass correlation coefficients and average status scores according to the RAMRIS in patients with spondyarthropathy (SpA; n=45 total) and inflammatory osteoarthritis (OA; n=23 total)

Patient population		SpA n=15, k=2	SpA n=30, k=2	Inflam. OA n=12	Inflam. OA n=11
MTP-joints					
BME	ICC (95%CI)	0.98 (0.94-0.993)	0.93 (0.85-0.97)	0.85 (0.40-0.96)	0.72 (0.1-0.92)
	Median (IQR, max)	0.5 (0-1; 9.5)	1 (0-2.5; 18)	1 (0.25-1; 2.5)	1 (0-1; 2.5)
	Mean (SD)	1.2 (2.4)	2.1 (3.7)	0.8 (0.7)	0.9 (0.8)
Synovitis	ICC (95%CI)	0.94 (0.84-0.98)	0.75 (0.49-0.88)	0.86 (0.53-0.96)	0.80 (0.30-0.94)
	Median (IQR, max)	0.5 (0-1; 6)	1 (0-2; 3.5)	1 (0-1; 1.5)	1 (0-2; 5)
	Mean (SD)	0.9 (1.6)	1.1 (1.1)	0.7 (0.5)	1.4 (1.6)
Tenosynovitis	ICC (95%CI)	0.99 (0.98-0.99)	0.82 (0.46-0.93)	0.92 (0.72-0.98)	0.76 (0.04-0.94)
	Median (IQR, max)	0 (0-0.5; 6)	0.75 (0-2; 4.5)	0 (0-0; 1.5)	0.5 (0-1.5; 4)
	Mean (SD)	1 (2.0)	4.5 (1.1-1.4)	0.2 (0.5)	1.1 (1.5)
Erosions	ICC (95%CI)	1.0 (NA)	0.44 (-0.21-0.73)	0.55 (-0.7-0.87)	0.81 (0.28-0.95)
	Median (IQR, max)	0 (0-1; 1)	0 (0-0.5; 1)	0.75 (0.5-1; 2)	0.5 (0-1; 2.5)
	Mean (SD)	0.3 (0.5)	0.3 (0.4)	0.8 (0.5)	0.7 (0.8)
MCP-joints					
BME	ICC (95%CI)	0.84 (0.52-0.95)	0.97 (0.94-0.99)	0.62 (-0.14-0.9)	0.63 (-0.24-0.90)
	Median (IQR, max)	0 (0-1; 3)	0 (0-1.5; 7)	0 (0-1; 1.5)	0.5 (0.5-1.5; 4)
	Mean (SD)	0.6 (0.9)	1.3 (2.2)	0.4 (0.6)	1.3 (1.4)
Synovitis	ICC (95%CI)	0.98 (0.94-0.99)	0.79 (0.57-0.9)	0.83 (0.39-0.95)	0.74 (0.14-0.93)
	Median (IQR, max)	0 (0-0.5; 6)	0 (0-1.5; 3.5)	0 (0-0.25; 1.5)	0.5 (0-2; 4)
	Mean (SD)	0.6 (1.6)	0.8 (1.1)	0.3 (0.5)	1 (1.2)

Tenosynovitis	ICC (95%CI) Median (IQR, max) Mean (SD)	0.79 (0.39-0.93) 0 (0-0; 2) 0.2 (0.6)	0.92 (0.78-0.97) 0.25 (0-1.5; 5) 1 (1.4)	0.89 (0.62-0.97) 0 (0-0.5; 3.5) 0.5 (1.0)	0.93 (0.76-0.98) 3 (1.5-5.5; 10) 3.3 (2.9)
Erosions	ICC (95%CI) Median (IQR, max) Mean (SD)	0.93 (0.78-0.98) 0 (0-1; 2) 0.5 (0.7)	0.93 (0.84-0.96) 0 (0-1; 2) 0.45 (0.6)	0.96 (0.87-0.99) 0 (0-1.5; 3) 0.7 (1.1)	0.90 (0.61-0.97) 1 (0.5-2; 2.5) 1.1 (0.8)
Wrist					
BME	ICC (95%CI) Median (IQR, max) Mean (SD)	0.99 (0.98-0.99) 0.5 (0-1; 14.5) 1.4 (3.7)	0.90 (0.49-0.97) 1.25 (0-4; 12.5) 2.5 (3.1)	0.98 (0.93-0.99) 1.25 (0.3-4.3; 24) 4.1 (7.0)	0.94 (0.10-0.99) 3.5 (2.5-7; 19.5) 6.2 (6.2)
Synovitis	ICC (95%CI) Median (IQR, max) Mean (SD)	0.93 (0.81-0.98) 0 (0-1; 4.5) 1.4 (3.7)	0.91 (0.81-0.96) 0.75 (0-1.5; 5) 1.1 (1.3)	0.97 (0.88-0.99) 0.5 (0.54-5; 6.5) 2.0 (2.3)	0.94 (0.78-0.98) 2.5 (1.5-5; 7.5) 3.1 (2.2)
Tenosynovitis	ICC (95%CI) Median (IQR, max) Mean (SD)	0.94 (0.83-0.98) 0 (0-1; 3.5) 0.5 (0.9)	0.95 (0.89-0.98) 0 (0-1.5; 8) 1.1 (2.1)	0.83 (0.36-0.96) 0 (0-3; 8) 1.4 (2.5)	0.97 (0.88-0.99) 1.5 (0.5-8; 13) 3.5 (4.3)
Erosions	ICC (95%CI) Median (IQR, max) Mean (SD)	0.97 (0.90-0.99) 1 (0-2; 9) 1.8 (2.3)	0.81 (0.60-0.91) 1.5 (0-2.5; 6.5) 1.5 (1.5)	0.73 (0.04-0.92) 3.25 (2.3-5; 8) 3.6 (1.9)	0.98 (0.92-0.99) 3 (2-4.5; 12) 4.1 (3.2)

Caution should be given when interpreting the results due to low number of patients.

4

Chapter 4

4

*Rheumatoid arthritis and tenosynovitis
at the metatarsophalangeal joints:
An anatomical and MRI study of the
forefoot tendon sheaths*

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Abstract

Background: While tenosynovitis in the hands is associated with rheumatoid arthritis (RA) it is unknown whether tenosynovitis of the forefoot is associated with RA.

Purpose: To determine the anatomy of tendon sheaths of the forefoot and the relationship between MRI-detected tenosynovitis at metatarsophalangeal(MTP) joints and rheumatoid arthritis.

Materials and Methods: 14 forefeet of donated bodies were examined at flexor-tendons and extensor-tendons for the presence and course of tendon sheaths. In the prospective study between June 2013 and March 2016, newly presenting patients with RA, patients with other early arthritides, and healthy controls all underwent MRI of unilateral MTP (1-5)-joints. MRI studies were scored by two independent readers for tenosynovitis, synovitis and bone marrow edema. The association of the presence of these features with RA were examined using logistic regression.

Results: Macroscopically, all extensor and flexor tendons crossing MTP joints demonstrated sheaths surrounding tendons. Microscopically a synovial sheath was present. 634 participants were evaluated by MRI: 157 newly presenting patients with RA (109 women; mean age 59 years $\pm$ 11 SD), 284 patients with other early arthritides (158 women; 56 years $\pm$ 17 SD), and 193 healthy controls (136 women; 50 years $\pm$ 16 SD). MRI-detected tenosynovitis was associated with RA, both when compared to patients with other arthritides (odds ratio (OR) 2.5 (95%CI 1.7-3.9, P <0.001) and healthy controls (OR 46, 95%CI 14-151, P <0.001). The association was OR 2.4, (95%CI 1.5-3.8, P <0.001) for flexor and OR 3.1, (95%CI 1.9-5.2, P <0.001) for extensor tendons. The sensitivity of tenosynovitis in RA was 65/157 (12%, 95%CI 35-50). The specificity was 63/284 (78%, 95%CI 72-82) compared to other arthritides, and 3/193 (98%, 95%CI 96-99) compared to healthy controls.

Conclusion: Tendons at metatarsophalangeal-joints are surrounded by tenosynovium. MRI-detected tenosynovitis at metatarsophalangeal-joints was specific for rheumatoid arthritis when compared to patients with other arthritides and healthy controls.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by inflammation of the synovial joints.(1) MRI is recommended for the early detection of inflammation in RA-research, as it is sensitive in measuring synovitis, bone marrow edema (BME) and tenosynovitis.(2) Tenosynovitis is defined as inflammation of the synovial lining of the tendon sheaths. MRI-studies have showed that tenosynovitis at the level of metacarpophalangeal(MCP) and wrist joints is an early phenomenon in patients at risk for RA that is predictive for RA-development,(3-5) and when compared to patients with arthritis with another diagnosis, is highly specific for RA.(6) In addition, tenosynovitis is associated with functional impairment in daily life.(7,8)

Tendon sheaths help prevent tendon injury and help with load bearing.(9) Not all tendons possess a sheath; for example at the MCP-joints, a sheath is present around the flexor tendons but believed to be absent around the extensor tendons.(6) Regarding the metatarsophalangeal(MTP) joints, there is no consensus in the anatomic literature on the presence or absence of a tendon sheath. On the extensor side of the MTP joints, some sources portrayed extensor tendons without sheaths,(10-12) while other sources neglect to provide information about this region.(13) Regarding the flexor side of MTP joints there is controversy between sources: in one example a fibrous and synovial sheath was portrayed around the distal flexor tendons,(10) in another case it was described as solely fibrous,(14) and others did not provide any information on this matter.(11,12)

In addition to the lack of consistent information on the normal human anatomy, the prevalence of inflammation at the level of the tendons of MTP joints and its association with RA are unknown. A few MRI studies reported on the presence of tenosynovitis, but these studies were small (≤ 30 patients with RA), did not include information at joint level, and/or did not compare findings of patients with RA with reference populations (15-18). The sensitivity and specificity of MRI-detected inflammation of the tendon sheath at the MTP level for RA thus remain unknown.

This study aimed to 1) elucidate the anatomical presence of a tendon sheath at the flexor- and extensor-side of the MTP joints in an anatomical study to clarify if contrast-enhancement around the tendons at MTP level can be interpreted as tenosynovitis, and 2) unravel whether MRI-detected tenosynovitis at MTP joints is associated with RA, in a large cross-sectional MRI study comparing patients

newly presenting with early RA with patients diagnosed with other arthritides and healthy controls.

Materials and methods

Anatomical dissection

Macroscopy

This section of the study was conducted on 11 formalin-phenol embalmed and 3 fresh-frozen human feet at the Anatomy & Embryology lab of the Leiden University Medical Center in Leiden, The Netherlands. All specimens were obtained from bodies that were donated according to the Dutch Burial and Cremation Act to the department of Anatomy and Embryology at the Leiden University Medical Center for use in scientific research and medical education.

The cutis and subcutis at the flexor side of 11 embalmed feet (8 man, 1 woman, 2 unknown sex; age range 70-95yrs) and at the extensor side of three fresh-frozen feet (sex and age unknown) were removed. Tissue surrounding the tendons of interests were injected with epoxy resin at the flexor side and with silicone rubber at the extensor side. Gentle massage was used to promote dissemination of the fluids. Photographs were taken of all specimens. For a more detailed description, see the Supplementary Methods and Figures.

Microscopy

After dissection of the plantar cutis and subcutis of a non-injected foot, a block containing the flexor hallucis longus tendon and the surrounding connective tissue was removed 1-2 cm proximal to the MTP joint. In a separate non-injected foot, a block containing the extensor hallucis longus tendon and surrounding connective tissue was removed. Harvested tissues were embedded in paraffin. The paraffin blocks were transversely sliced in sections of 10 μm . The morphology of all tissues was examined by a hematoxylin and eosin (HE) staining and interpreted by an anatomist (FJ, 5 years experience) and pathologist (AC, 11 years experience) blinded to clinical data.

Imaging studies

Study Participants

In this prospective study, between June 2013 and March 2016, 447 consecutive patients newly presenting with clinically confirmed arthritis and symptom

duration <2 years who were naïve to disease-modifying antirheumatic drugs were included in the Leiden Early Arthritic Clinic (EAC).(19) This is an inception cohort where at baseline, swollen joint counts were performed, serum samples were taken and patients underwent MRI. MRIs of 6 patients were excluded because of inhomogeneous fat suppression. RA was defined as a clinical diagnosis plus fulfillment of the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria during the first year of follow-up.(1)

Healthy controls were recruited by advertisements in local newspapers and websites, as previously reported.(20) They had no history of inflammatory rheumatic disease, no joint symptoms during the last month and no arthritis at physical examination.

Studies using data from the EAC and from the healthy controls have been published in the past,(20,21) however MRI-data of tenosynovitis at the MTP joints has thus far not been evaluated.

The early arthritis and the healthy control studies were both approved by the local medical ethics committee (approval numbers P10.108 and P11.210, respectively). Written informed consent was obtained from all participants.

MRI protocol

Patients underwent unilateral MRI of MTP 1-5 joints of the most painful side or the dominant side in the case of equally severe symptoms on both sides ≤2 weeks after the first presentation and before starting disease-modifying antirheumatic drugs. In healthy controls, the dominant side was scanned. A musculoskeletal-extremity 1.5T-MRI scanner (Oni, General Electric, Wisconsin, Madison) was used using a 145mm coil for the foot. After intravenous injection of gadolinium contrast the following sequences were obtained: T1-weighted fast spin-echo (FSE) with fat suppression in the axial plane (TR/TE 700/9.5ms; acquisition matrix 364x224, ETL 2) and: T1-weighted FSE with fat suppression in the coronal plane (perpendicular to the axis of the MTPs) (TR/TE 540/7.5ms; acquisition matrix 320x192, ETL 2). Field-of-view was 140mm. Coronal sequences had 20 slices with a slice thickness of 3mm and a slice gap of 0.3mm. Axial sequences had a slice thickness of 3mm and a slice gap of 0.3mm with 14 slices.

MRI evaluation

Tenosynovitis of the MTP joints was scored according to the method by

Haavardsholm et al.(22) This method is developed and validated for scoring tenosynovitis in the wrist. BME and synovitis were scored according to The Outcome Measures in Rheumatology Clinical Trials Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (OMERACT-RAMRIS),(23) with the exception that BME was assessed on a contrast enhanced T1-weighted fat-suppressed sequence, as it allows a shorter scan time and has a higher signal to noise ratio.(24-26) The method by Haavardsholm and the OMERACT-RAMRIS have been designed for scoring inflammation in the hands, and were found reliable when applied to the-MTP joints.(27,28) All tendons, joints and bones were scored on a scale of 0-3. For tenosynovitis the score is based on the thickness of peritendinous effusion or synovial proliferation with enhancement (normal, <2, 2-5, >5mm), for synovitis on the presumed volume of enhancing tissue in the synovial compartment (none, mild, moderate, severe) and for BME based on the affected volume of the bone (no BME, <33%, 33-66%, >66%). Tenosynovitis was scored at the flexor and extensor tendons at the MTP joints, and BME was scored in the proximal and distal part of the MTP joint. Proximal and distal BME-scores were summed per joint.

Each MRI was scored independently by two trained readers, blinded to clinical data. A total of 6 readers scored the images: The first 215 EAC-patients were scored by WN and EN, the remaining 226 EAC-patients by DB and AB and 193 healthy controls by HS and LM. All 6 readers were medical doctors and PhD candidates in the field of Rheumatology and Radiology that had scored >400 MRIs according to the scoring systems during a training period of several months prior to evaluating the MRIs that are part of this study, with 1-2 years of experience with the scoring systems. Intraclass correlation coefficients (ICCs) were calculated. Interreader ICC was ≥ 0.93 , intrareader ICCs ≥ 0.88 for arthritis patients (Supplementary Table 1). The inter- and intrareader ICCs of the two readers of the healthy controls were ≥ 0.96 .(20)

Statistical Analysis

Non-normally distributed MRI-scores were analyzed using Kruskal-Wallis tests followed by a Bonferroni correction for all pairwise comparisons. Next, data of MRI scores were dichotomized per MTP joint; tenosynovitis, synovitis and BME were considered present if scored ≥ 1 by both readers. Logistic regression analysis was used to compare MRI-detected tenosynovitis in patients with RA to other arthritides and to healthy controls. Multivariable logistic regression analyses comparing RA to other arthritides corrected for MRI-detected synovitis and BME in the same joint and subsequent analyses additionally corrected for age, swollen joint count, C-reactive protein and anti-citrullinated peptide antibodies. Test

characteristics were calculated for MRI-detected tenosynovitis.

SPSS 23.0 was used (IBM, Chicago, Ill). P-values <0.05 were considered significant.

Results

Anatomical studies

Macroscopy

Hardened resin (flexor side) and silicone rubber (extensor side) were found to be confined to a sharply demarcated 'sheath-like' structure surrounding the flexor and extensor tendons of all five digits in the foot, as is presented in Figure 1 (additional examples are presented in Supplementary Figure 1). This resembled the expected image of tendon sheaths surrounding their tendons. On both the flexor and the extensor side the distal extensions of all tendon sheaths crossed the MTP joints. There was no exception in this pattern, but variation existed in the distal termination, which reached as far as the distal phalanx. For a more detailed description, see Supplementary Results.

Microscopy

Surrounding the flexor hallucis longus tendon a completely delimited space was noticed (Figure 2A,B). Deep to the tendon, two cul-de-sacs connecting the parietal and visceral part of the sheath were visible and a vinculum between these cul-de-sacs was also visible, allowing vasculature to reach the tendon. 40x magnification showed the delimiting cells as squamous epithelial cells representing synoviocytes (Figure 2C). At the extensor hallucis longus tendon, similar results were observed (Figure 2D,E,F).

As a tendon sheath was present at both the flexor and extensor side, we assumed that MRI-detected contrast enhancement around the tendons at both sides of the MTP joints represents tenosynovitis.

Imaging studies

Patient characteristics

Of the 441 included EAC-patients, 157 were classified as RA (109 women; mean age 59 ± 11 years standard deviation (SD)), the remaining 284 received alternative diagnoses and were grouped together as 'other arthritides' (158 women; mean age 56 ± 17 SD) (Figure 3). 193 healthy controls were recruited (136 women; mean

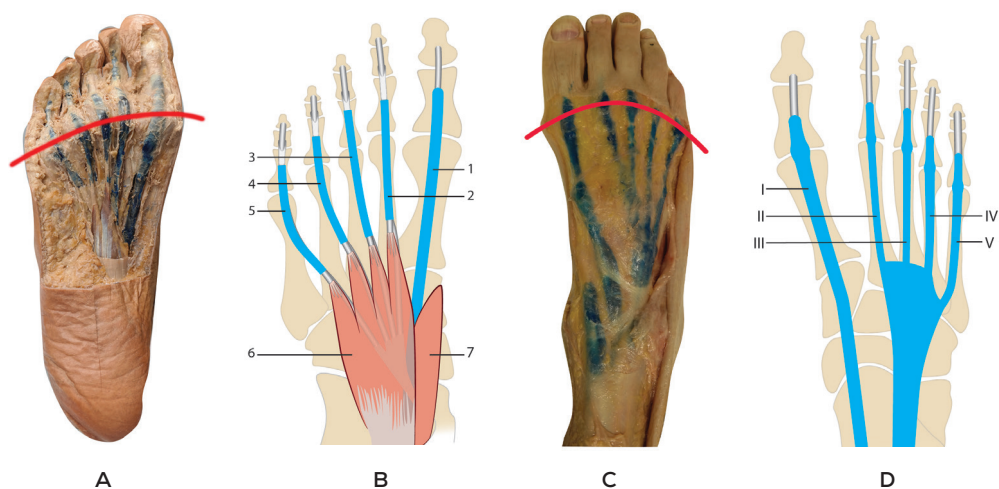


Figure 1. Macroscopic images and schematic drawings of tendon sheaths in the forefeet. Red lines represent level of the metatarsophalangeal (MTP) joints. Sheaths are in blue. A: Plantar view of a foot with resin in the flexor tendon sheaths, extending proximal and distal from the MTP joints; B: Schematic plantar view shows tendon sheaths of the musculus flexor hallucis longus tendon (FHL) (1) and the common musculus flexor digitorum longus (FDL) and common flexor digitorum brevis (FDB) tendons (2-5). Proximally the four tendons of the FDL run deep of the FDB muscle (6) and extend distally with a common tendon sheath for the FDL and FDB tendons. The tendons of the FDB split to course in a more dorsal position before inserting into the middle phalanx; the tendon of the FDL continue in a straight course and attach to the base of the distal phalanx. The tendon of the FHL (1) proximally runs deep from the musculus abductor hallucis (7) and FDB and inserts at the base of the distal phalanx. C: Dorsal view of foot with silicone in extensor tendon sheaths, extending from the anterior ankle to distal aspect of MTP joints; D: Schematic dorsal view shows tendon sheaths of the extensor hallucis longus (EHL) (I) and extensor digitorum longus tendons (EDL) (II-V), forming a common sheath from proximal of the metatarsals to the anterior ankle. The EHL and EDL insert at the dorsal aspect of the distal phalanges. The extensor digitorum brevis (EDB) tendons insert into the EDL II-IV tendons at the MTP-joints and are not portrayed

age 50 ± 16 SD). The baseline characteristics are presented in Table 1. Patients with RA had a median symptom duration of 10 weeks (interquartile range (IQR) 5-28) and 59% were anti-citrullinated peptide antibody-positive. The semiquantitative MRI-tenosynovitis scores were higher in patients with RA than in patients with other arthritides (1.9 and 0.7, respectively, $P < 0.001$, Table 1). Next, the presence of tenosynovitis was dichotomized as described in the methods.

Association of MTP tenosynovitis at patient-level with RA compared to other arthritides

Tenosynovitis was present at ≥ 1 MTP-location in 65 out of 157 (41%) patients with early RA and 63 out of 284 (22%) of patients with other early arthritides (odds ratio (OR) 2.54 (95% confidence interval (CI) 1.65-3.87), $P < 0.001$) (Table 2).

Tenosynovitis regularly co-occurred with synovitis and BME. Therefore, a multivariable analysis including the three types of MRI-detected inflammation was performed that showed tenosynovitis was independently associated with RA (OR 2.25 (95% CI 1.4-3.5), $P < 0.001$) after controlling for the presence of synovitis (OR 1.6, 95% CI 1.0-2.5, $P = 0.06$) and BME (OR 0.9, 95% CI 0.6-1.5, $P = 0.68$) (Table 2 and Supplementary Table 2). In a subsequent multivariable analysis that also adjusted for age, swollen joint count, C-reactive protein, and anti-citrullinated peptide antibodies, tenosynovitis remained associated with RA (OR 1.68, 95% CI 1.0-2.9, $P = 0.048$) (Table 2).

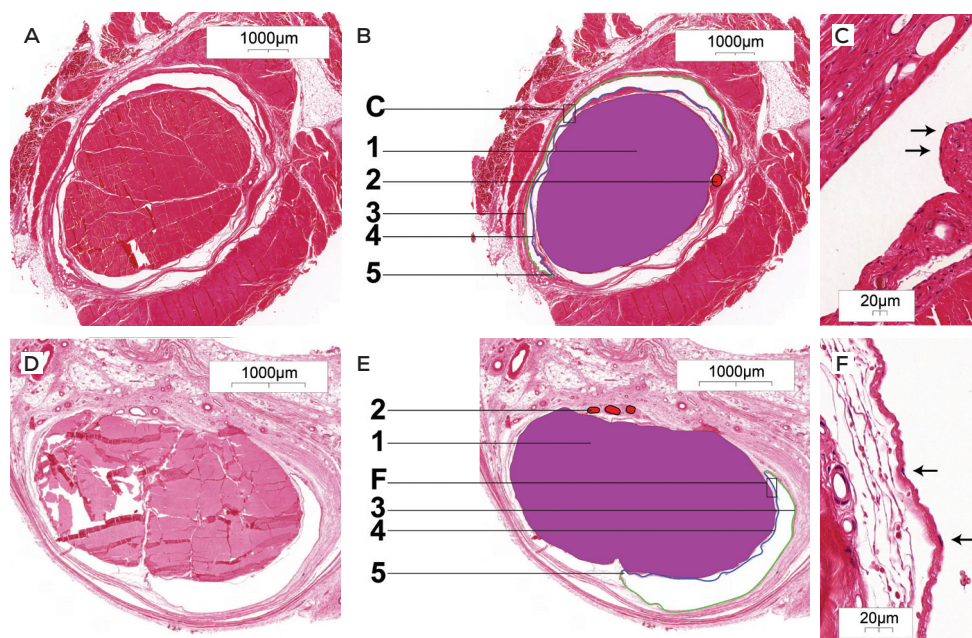


Figure 2. Histology of HE-stained, transversely sectioned tendon sheath of the flexor hallucis longus tendon (A, B and C) and of the extensor hallucis longus tendon (D, E and F). A. Overview of tendon sheath surrounding flexor hallucis longus tendon. B. Overlay with 1. tendon; 2. artery in vinculum; 3. parietal layer of tendon sheath; 4. visceral layer of tendon sheath; 5. cul-de-sac of tendon sheath. C. detail of fig. B. with visible synoviocytes (arrows). D. Overview of tendon sheath surrounding extensor hallucis longus tendon. E. Overlay with 1. tendon; 2. vessels in vinculum; 3. parietal layer of tendon sheath; 4. visceral layer of tendon sheath; 5. cul-de-sac of tendon sheath. F. detail of fig. E. with visible synoviocytes (arrows)

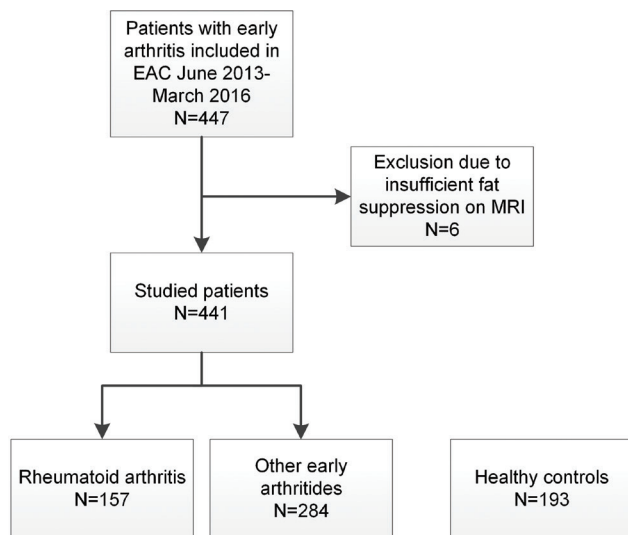


Figure 3. Flowchart of participant selection. EAC: early arthritis cohort; MRI: magnetic resonance imaging. RA was defined according to clinical diagnosis plus fulfilment of the 2010 classification criteria. The ‘other early arthritides’ included the following diagnoses: unclassified arthritis (n=148), psoriatic arthritis or spondyloarthritis (n=45), inflammatory osteoarthritis (n=23), reactive arthritis (n=7), crystal arthropathy (n=21), remitting seronegative symmetrical synovitis with pitting edema (n=12) and other diagnoses (n=28)

Next, presence of any tenosynovitis at the flexor and extensor side were studied separately. When compared to other arthritides, both presence of tenosynovitis at the flexor and the extensor side was associated with RA (OR 2.4, 95% CI 1.5–3.8, $P<0.001$ and OR 3.1, 95% CI 1.9–5.2, $P<0.001$, respectively). Tenosynovitis at flexor and extensor tendons remained statistically associated with RA after controlling for local synovitis and BME and after additional correction for clinical characteristics (Table 2).

Association of MTP tenosynovitis at joint level with RA compared to other arthritides

Then, tenosynovitis was studied at the level of individual joints. Frequencies per joint are provided in Figure 4. In univariable analyses, the following features were associated with RA: flexor tenosynovitis at all MTP joints, extensor tenosynovitis at MTP-1 and MTP-5 (Table 2). After correction for BME and synovitis, flexor and extensor tenosynovitis at MTP-1 were associated with RA (OR 2.2, 95% CI 1.0–4.9, $P=0.049$ and OR 3.9, 95% CI 2.0–7.5, $P<0.001$, respectively) and flexor tenosynovitis at MTP-5 (OR 5.3, 95% CI 1.1–26, $P=0.04$). After correction for clinical characteristics similar results were obtained (Table 2). Examples of MRI-detected tenosynovitis are presented in Figure 5.

Association of MTP tenosynovitis with RA compared to healthy controls To further characterize MRI-detected tenosynovitis, the occurrence of tenosynovitis in patients with RA was compared to healthy controls. In the latter group tenosynovitis at the MTP joints was rare, as it occurred in 3 out of 193 persons (1.6%, compared to 42% of patients with RA). Consequently, a strong association for RA compared to healthy controls was observed for the presence of any tenosynovitis at ≥ 1 location (OR 46, 95% CI 14–151, $P < 0.001$) (Supplementary Table 3). Also, flexor tenosynovitis and extensor tenosynovitis were both separately highly associated with RA when compared to healthy controls (OR 45, 95% CI 11–187, $P < 0.001$ and OR 78, 95% CI 11–570, $P < 0.001$, respectively).

Test characteristics of MRI-detected tenosynovitis

Finally, the test characteristics for the presence of tenosynovitis were determined. The sensitivity of MRI-detected tenosynovitis at any MTP joint was 42%. The specificity of tenosynovitis at the level of MTPs was 78% compared to other arthritides and 98% with healthy controls as reference (Supplementary Table 4). Analyses for flexor and extensor tenosynovitis separately showed that tenosynovitis at the flexor side had a sensitivity of 32%, and a specificity of 84% when compared to other arthritides, and 99% when compared to healthy controls. For tenosynovitis at the extensor side, these numbers were 29%, 89%, and 99%, respectively.

Discussion

The forefoot is a preferential location for inflammation in rheumatoid arthritis (RA).^(29,30) Nonetheless, the feet are less often evaluated than the small joints of the hands. For instance, the Disease Activity Score 28 does not include the feet. Also, the majority of MRI-studies performed thus far did not scan the feet.⁽³¹⁾ This prompted us to study tenosynovitis at the level of the forefeet in a large MRI-study of patients with early arthritis. Moreover, since anatomical literature did not provide consistent information of the presence of a tendon sheath at the flexor- and extensor-side of the MTP joints we also performed an anatomical study to determine if tenosynovial sheaths are indeed present at the MTP joints. The aim of this post-mortem and MRI study was to increase the comprehension of the involvement of inflammation surrounding the tendons in RA. In all feet that were examined anatomically, we found a sheath to be present surrounding all extensor and flexor tendons at MTP joints. Histology showed an image fitting a synovial

Table 1. Baseline characteristics of patients with rheumatoid arthritis, patients with other arthritides, and healthy control participants

Parameter	RA	Other arthritides*	P-value RA vs other arthritides	Healthy controls	P-value RA vs healthy controls
	n=157	n=284		n=193	
Clinical parameters					
Age, mean (SD)	59 (14)	56(17)	0.07	50 (16)	<0.001
Woman, n(%)	109 (69)	158 (56)	0.005	136 (70)	0.83
BMI, mean (SD)	26 (5)	27 (4)	0.52	25 (4)	0.003
Current smoker, n (%)	31 (21)	44 (18)	0.44	17 (9)	0.001
Symptom duration in weeks, median (IQR)	10 (5-28)	8 (4-26)	0.13	-	-
Swollen joint count, median (IQR)	7 (2-11)	2 (1-4)	<0.001	-	-
CRP, mg/L, median (IQR)	9 (4-26)	6 (3-16)	<0.001	-	-
RF positive, n (%)	106 (68)	51 (18)	<0.001	-	-
ACPA positive, n (%)	87 (59)	69 (25)	<0.001	-	-
MRI features					
Tenosynovitis, mean (SD)	1.9 (2.5)	0.7 (1.3)	<0.001	0.1 (0.3)	<0.001
Synovitis, mean (SD)	1.9 (2.2)	0.9 (1.2)	<0.001	0.2 (0.4)	<0.001
BME, mean (SD)	1.9 (2.8)	1.0 (1.9)	<0.001	0.3 (0.8)	<0.001

RA: rheumatoid arthritis; SD: standard deviation; BMI: body mass index; IQR: interquartile range; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; BME: bone marrow edema; the 66 swollen joint count was assessed. *This included the following diagnoses: unclassified arthritis (n=148), psoriatic arthritis or spondyloarthritis (n=45), inflammatory osteoarthritis (n=23), reactive arthritis (n=7), crystalarthropathy (n=21), remitting seronegative symmetrical synovitis with pitting edema (n=12) and other diagnoses (n=28).

Table 2. Results of logistic regression analyses for the association of metatarsophalangeal joint tenosynovitis with early rheumatoid arthritis vs. other early arthritides

	Patients with MRI-features, n (%)		Univariable analyses		Multivariable analyses: adjusted for local synovitis and BME		Multivariable analyses: adjusted for local synovitis and BME and age, SJC, CRP and ACPA	
	Rheumatoid arthritis	Other arthritides	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Presence of								
Any tenosynovitis	65 (41)	63 (22)	2.5 (1.7-3.9)	<0.001	2.3 (1.4-3.5)	<0.001	1.7 (1.0-2.9)	0.048
Any flexor tenosynovitis*	49 (31)	46 (16)	2.4 (1.5-3.8)	<0.001	2.1 (1.3-3.4)	0.002	1.9 (1.0-3.4)	0.040
Any extensor tenosynovitis*	44 (28)	32 (11)	3.1 (1.9-5.2)	<0.001	2.7 (1.6-4.6)	<0.001	2.1 (1.1-3.9)	0.017
Flexor tenosynovitis								
MTP 1	18 (12)	13 (5)	2.7 (1.3-5.7)	0.009	2.2 (1.0-4.9)	0.049	2.7 (1.0-6.9)	0.04
MTP 2	26 (17)	27 (10)	1.9 (1.1-3.5)	0.03	1.3 (0.7-2.6)	0.41	1.4 (0.6-3.3)	0.44
MTP 3	27 (17)	20 (7)	2.8 (1.5-5.2)	0.001	1.9 (0.9-3.8)	0.81	1.8 (0.7-4.3)	0.22
MTP 4	26 (17)	19 (7)	2.8 (1.5-5.3)	0.001	1.8 (0.8-3.7)	0.14	1.6 (0.7-3.8)	0.31
MTP 5	14 (9)	2 (1)	14.0 (3.1-62.5)	0.001	5.3 (1.1-25.7)	0.04	9.3 (1.5-57.0)	0.015
Extensor tenosynovitis								
MTP 1	31 (20)	15 (5)	4.5 (2.3-8.6)	<0.001	3.9 (2.0-7.5)	<0.001	3.1 (1.4-6.9)	0.005
MTP 2	4 (3)	4 (1)	1.8 (0.5-7.4)	0.40	1.0 (0.2-4.4)	0.98	0.5 (0.1-2.9)	0.46
MTP 3	10 (6)	14 (5)	1.3 (0.6-3.0)	0.53	0.7 (0.3-1.9)	0.51	0.9 (0.3-2.5)	0.89
MTP 4	4 (3)	8 (3)	0.9 (0.3-3.1)	0.90	0.6 (0.2-2.0)	0.37	0.3 (0.1-1.6)	0.32
MTP 5	14 (9)	4 (1)	7.0 (2.3-21.6)	0.001	2.9 (0.8-9.8)	0.09	3.5 (0.9-13.1)	0.07

Tenosynovitis was considered present if scored ≥1 by both readers. BME: bone marrow edema; SJC66: swollen joint count; CRP: C-reactive protein; ACPA: anti-citrullinated peptide antibodies; OR: odds ratio; CI: confidence interval; MTP: metatarsophalangeal joint. Other arthritides: patients with early arthritis pre-senting with arthritis with a diagnosis other than RA. *In some patients, flexor tenosynovitis and extensor tenosynovitis occurred simultaneously, therefore the percentages of patients with any flexor tenosynovitis and any extensor tenosynovitis do not add up to the percentage of patients with any tenosynovitis.

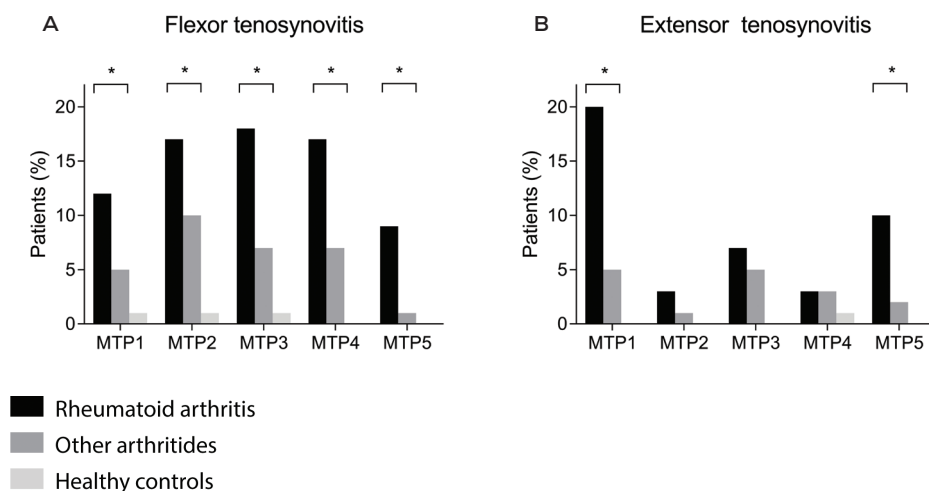


Figure 4. Frequencies of the presence of (A) flexor and (B) extensor tenosynovitis per MTP-joint of patients newly presenting with rheumatoid arthritis, patients presenting with other early arthritides and of healthy controls. MTP: metatarsophalangeal joints. *P<0.05 in univariable logistic regression analyses when comparing RA-patients with other arthritides

tendon sheath. Because of these anatomical findings, we assumed that MRI-detected contrast-enhancement around the tendons at both sides represented tenosynovitis. This MRI-detected tenosynovitis was associated with RA ($P<0.001$) and had a high specificity for RA, both when compared to patients with other arthritides (78%) and to healthy controls (98%). Together these data showed that tenosynovitis at MTP level is a characteristic of RA.

Our results are in line with previous studies of the hands that found MRI-detected tenosynovitis to be specific for RA.(6) MRI-detected inflammation is increasingly used as an outcome measure in clinical trials in RA.(2) Our data imply that tenosynovitis at MTP level can be included in this outcome; this would require further validation according to the OMETACT-Filter.(31,32)

In our study imaging was performed with MRI. Ultrasound is an alternate imaging modality that is used, and both methods are recommended in the clinical management of RA.(2) Both modalities have advantages and disadvantages. While ultrasound is easily available, it is operator dependent. MRI is more expensive but is generally considered to yield more reproducible results and also depicts BME that is not depicted by ultrasound. A recent study found ultrasound to be less

sensitive than MRI in detecting tenosynovitis.(33) This supports the choice of using MRI in our current study.

The function of a tendon sheath is to provide a smooth gliding surface and thus prevent tendon injury.(9) Although the presence of a tenosynovium at a high-friction location like the MTP joints seems logical, it is surprising that anatomical literature thus far left it undetermined if tendons at these joints possess a synovial sheath, and some even portrayed this sheath to be absent. In this anatomic literature, no source studies were mentioned.(10-14) For the dissection, we started with embalmed bodies for the flexor side and when fresh-frozen bodies became available, they were used for the extensor side. The injection of tendon sheaths was performed in a similar fashion on both sides, therefore, we believe that the different methods of preserving the bodies have not negatively affected our results.

Microscopy indicated an image that was typical for a tendon sheath, with a visceral synovial layer covering the tendon surface, a parietal synovium attached to the

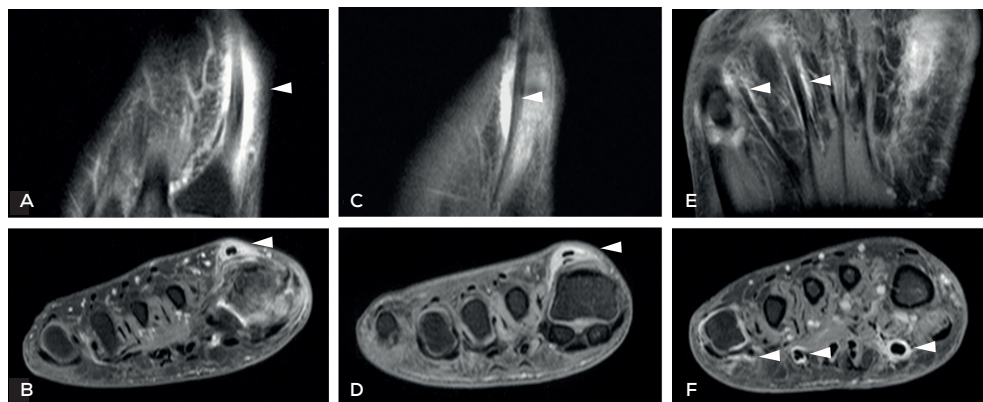


Figure 5. Contrast-enhanced 1.5T MRI of the forefoot in three different patients in corresponding axial (A, C and E) and coronal (B, D and F) planes showing extensor tenosynovitis at MTP 1 (A, B, C, D) and flexor tenosynovitis at MTP 1, 3, 4, 5 (E, F). All images are T1-weighted fast spin-echo (FSE) with fat suppression after intravenous contrast administration. In A and B circular enhancement is seen of the extensor hallucis longus tendon, shown from the level of MTP 1 to the base of MT1, consistent with tenosynovitis (arrowheads). Synovitis of MTP 1 is visualized and edema of the skin and subcutis medially (arrow). The axial sequences (A) illustrate that the tenosynovitis is 'sheath-like' and continues distally to the MTP-joints (arrowheads). In C and D circular enhancement is present at the extensor hallucis longus tendon without concomitant synovitis of MTP 1 (arrowhead). In E and F circular enhancement is present at the tendons of the flexor hallucis and common flexor digitorum of MTP 1, 4 and 5 (arrowheads). There is coexisting synovitis at MTP 5 (arrow)

surrounding tissues, and a vinculum for the intrinsic blood supply of the tendon.(9).

Our study has several limitations. Microscopically studying these lesions in patients with RA would be the optimal proof that MRI-detected contrast enhancement around the tendons at MTP level is tenosynovitis. This, however, was unfeasible as it would either require biopsies from tenosynovial sheaths at the MTPs from living patients with RA, or the use of donated bodies of patients with RA that had MRI-detected tenosynovitis at the end of their life. In addition, the MRI-scoring systems used are validated for the hand but not for the foot. However, our intra- and inter-reader ICCs were high, indicating a high reliability of scoring. The RAMRIS was recently updated, and now includes tenosynovitis.(34) For tenosynovitis we used the method described by Haavardsholm, as the updated RAMRIS was not yet published at the start of our study.(22) The included patients had an established diagnosis of RA. MRI-studies in other early arthritis populations are relevant to validate the diagnostic value of tenosynovitis at the MTP joints. For the predictive value, we recently observed in a longitudinal study that MTP-tenosynovitis in undifferentiated arthritis is associated with the development of RA,(35) which underlines the possible diagnostic value of tenosynovitis at MTP joints. It is important to note that while tenosynovitis at the MTP joints is specific for RA, the sensitivity of 42% is low. On the other hand, RA is known to be a disease where the hands and feet are involved. A recent study in the hands has revealed a sensitivity 75% for tenosynovitis at the hands.(6) Combining hands and feet will presumably yield a higher sensitivity for tenosynovitis in RA.

In conclusion, this anatomical and imaging study shows that tendons at the MTP joints possess a synovial sheath (both macro- and microscopically, and at flexor and extensor sides), and that MRI-detected tenosynovitis at the MTP joints is associated with, and highly specific for, RA. This study has increased the comprehension of tissues that can be involved in the feet of patients with RA by showing that MRI-detected tenosynovitis at the MTP joints is a feature of RA.

Acknowledgements

The authors thank pathologist A.H.G. Cleven for interpreting the microscopy images, and G. Kracht for the schematic drawings of the tendons at the MTP joints.

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Supplementary data

Supplementary methods are available at Radiology online.

Supplementary Table 2. Results of logistic regression analyses for the association of tenosynovitis, synovitis and bone marrow edema with RA

	Univariable analyses		Multivariable analyses: adjusted for local synovitis and BME	
	OR (95% CI)	P value	OR (95% CI)	P value
Presence of				
Any tenosynovitis	2.5 (1.7–3.9)	<0.001	2.3 (1.4–3.5)	<0.001
Any synovitis	2.0 (1.3–2.9)	0.001	1.3 (0.8–2.1)	0.28
Any bone marrow edema	1.9 (1.3–2.8)	0.002	1.4 (0.9–2.1)	0.20

Supplementary Table 3. Results of logistic regression analyses for the association of tenosynovitis with RA when compared with healthy controls

	P value	OR (95% CI)
Any tenosynovitis	<0.001	46.3 (14.2–151.2)
Any flexor tenosynovitis	<0.001	44.6 (10.6–186.9)
Any extensor tenosynovitis	<0.001	77.5 (10.5–570.4)

Due to the low frequency of tenosynovitis in healthy controls only univariable analyses were performed.

Supplementary Table 4. Test characteristics of tenosynovitis for RA compared with other arthritides and to symptom-free controls at the flexor and extensor side of MTP-joints

	Specificity, vs other arthritides (%)	Specificity, vs healthy arthritides (%)	Sensitivity (%)
Any tenosynovitis	78 (72–82)	98 (96–99)	42 (35–50)
Flexor side	84 (79–87)	99 (97–100)	32 (25–40)
Extensor side	89 (84–92)	99 (96–100)	29 (22–36)

MTP = metatarsophalangeal joint.

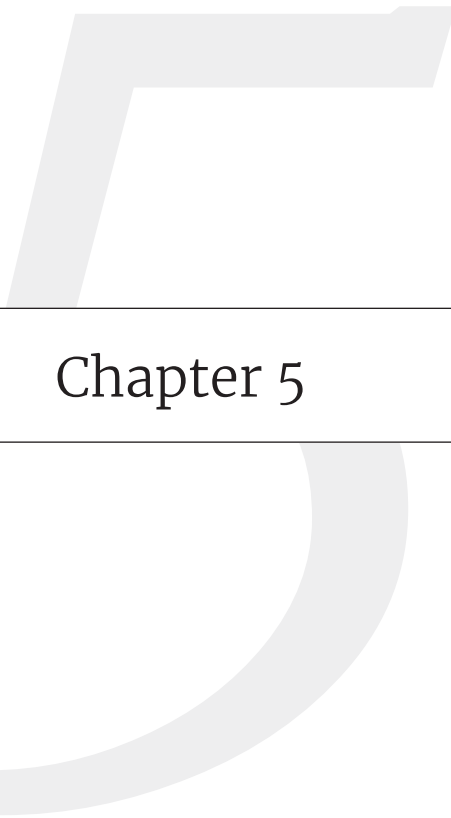
A. Plantar



B. Dorsal



Supplementary Figure 1. Additional examples of macroscopic images of tendon sheaths in the forefeet.



Chapter 5

*Increased frequency of intermetatarsal and
submetatarsal bursitis in early rheumatoid arthritis:
A large case–controlled MRI study*

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Submitted

Abstract

Background: The forefoot is a preferential location for joint and tendon-sheath inflammation in rheumatoid arthritis (RA). It also contains bursae, of which the intermetatarsal bursae have a synovial lining. Some small imaging studies suggested that intermetatarsal bursitis (IMB) and submetatarsal bursitis (SMB) are involved in RA, but their association has not been thoroughly explored. Healthy control studies suggested that lesion-size might be relevant. We studied the relation between IMB and SMB in early RA, compared to other arthritides and healthy controls, and the relevance of lesion-sizes.

Methods: 634 participants were studied: 157 consecutive patients presenting with early RA, 284 other arthritides and 193 healthy controls. All underwent unilateral contrast-enhanced MRI of the forefoot at presentation. Two readers independently scored IMB and SMB, and measured transverse and dorsoplantar diameters, blinded to clinical data. Subsequently consensus was reached. Intra-reader ICC was 0.89. Logistic regression models were used, test characteristics were calculated.

Results: IMB and SMB associated with RA independent of each other ($P < 0.001$) and independent of age, gender, BMI, RA-MRI-inflammation and anti-CCP-antibodies ($P = 0.041$). Sensitivity for RA of IMB was 69%, for SMB 25%. Specificity for IMB was 70% compared to other arthritides, 84% compared to healthy controls. For SMB this was 94% and 97% respectively. Regarding lesion-size, the groups had considerable overlap: no cut-off size for RA could be distinguished with high sensitivity and specificity.

Conclusion: Intermetatarsal and submetatarsal bursitis associated with early rheumatoid arthritis, contributing to the emerging evidence that inflammation of juxta-articular soft tissues are an early feature of RA.

Background

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic, persistent inflammation of the synovium-lined joints and tendon-sheaths. (1, 2) Preferential locations are the small joints of hands and feet. It has become apparent that early treatment with disease modifying anti-rheumatic drugs (DMARDs) improves disease outcome of RA-patients.(3) Since prompt treatment has limited radiographic detectable damage, the European League against Rheumatism (EULAR) recommends MRI for the early detection and follow-up of RA as it sensitively measures inflammation. According to the RA-MRI-score (RAMRIS) inflammation is defined as synovitis, tenosynovitis and bone marrow edema/osteitis.(4, 5) In the forefoot, however, imaging also reveals the presence and/or inflammation of bursae. So far bursitis in the forefeet has gained little attention in RA-literature.

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Interestingly, naturally present bursae possess a synovial lining similar to synovial joints and tendon-sheaths.(6) In the forefoot intermetatarsal bursae are present, anatomically without a connection to the metatarsophalangeal(MTP)-joints.(7) Two ultrasound studies have reported intermetatarsal bursitis (IMB) in patients with established RA.(8, 9) Additionally, one MRI-study in 70 asymptomatic volunteers reported on fluid in the intermetatarsal spaces as a sign of IMB.(10) Gadolinium contrast-enhancement was not used as a measure of inflammation. The authors suggested that a transverse diameter of $\leq 3\text{mm}$ could be considered physiologic, however these results have not been validated.(10) Thus, while data suggest that IMB may be associated with RA, its involvement in early disease has not been studied systematically.

In the subcutaneous fat, submetatarsal bursae that lack a synovial lining may develop due to high pressure and friction, leading to collagen degradation and localized fluid-collection that is visible on imaging as a sharply demarcated area in the submetatarsal space.(11) An ultrasound study reported submetatarsal bursitis (SMB) in patients with established RA.(12) However, this has also been observed in healthy controls. To the best of our knowledge, regarding IMB and SMB, no direct comparison has been made between RA and other arthritides, which is a comparison that is clinically relevant.(13) Also no comparison has been made between RA and healthy controls, to analyze whether these findings could be normal.

Additionally, in the forefoot, Morton's neuroma (MN) and diffuse submetatarsal alterations (DSMA) in the subcutis have been described. MN may emerge due to mechanical irritation, or secondary to IMB, and has been described in RA as well as asymptomatic volunteers.(14-16) DSMA consist of fibrosis or inflammatory tissue that may be induced by mechanical stress and may represent early stages in the development of SMB, particularly under the first and fifth metatarsal heads.(17)

Overall, the current available literature does not give a fulfilling and thorough picture of the prevalence of IMB and SMB in RA-patients. Therefore, this large cross-sectional MRI-study was set up to study: 1) the association of these lesions in RA, compared to other arthritides and to healthy controls, and 2) whether the size of these lesions can differentiate between diseases and healthy controls. Although not the main focus of this study, MN and DSMA were studied in subanalyses.

Materials and methods

Participants

Between June 2013 and March 2016, 447 consecutive patients newly presenting with clinical arthritis of a symptom duration <2 years who were naïve to DMARDs were included in the Leiden Early Arthritis Cohort (EAC).(18) The Leiden University Medical Center is the only rheumatology referral center within the Leiden area. Inclusion in the EAC of consecutive early arthritis patients has been part of regular care since 1993.(19) Contrast-enhanced MRI of the forefoot was added to the protocol in June 2013. At baseline, swollen joint counts were performed, serum samples were obtained and patients underwent MRI. Six MRI-examinations were excluded because of inhomogeneous fat suppression, 441 examinations remained (flowchart in Supplementary Figure S1). RA was defined as a clinical diagnosis of RA plus fulfilment of the 2010 RA-criteria during the first year of follow-up.(1) The remaining patients received alternative diagnoses and were grouped together as 'other arthritides' (Table 1).

Healthy controls were recruited by advertisements in local newspapers and websites, as reported previously.(20) Participants had no history of inflammatory rheumatic disease, no joint symptoms during the last month and no arthritis at physical examination.

The EAC and healthy control study were approved by the local medical ethics

committee (approval numbers P10.108 and P17.261). Informed consent was obtained.

MRI scanning

Patients and symptom-free persons were scanned according to our routine MRI-protocol as described in Supplementary Data S1. They underwent unilateral MRI of the hand and forefoot of the more painful side, or the dominant side in case of symmetrical symptoms, ≤ 2 weeks after the first presentation and before start of DMARDs. In symptom-free persons the dominant side was scanned. A musculoskeletal extremity 1.5-T MRI unit (Oni; GE Healthcare, Madison, Wis) was used with a 145-mm coil. Acquired sequences for the forefoot after intravenous injection of gadolinium contrast included: axial T1-weighted fast spin-echo with fatsuppression (repetition time msec/echo time msec 700/9.5; acquisition matrix 364x224, echo train length 2) and coronal T1-weighted fast spin-echo with fatsuppression (540/7.5; acquisition matrix 320x192, echo train length 2). Field-of-view was 140mm, slice thickness 3mm and slice gap 0.3mm for both planes. Axial sequences had 14 slices, coronal sequences 20 slices.

MRI evaluation

Anatomy and scoring system

The forefoot was divided into four intermetatarsal and five submetatarsal spaces (Figure 1).(21) The intermetatarsal space is dorsally bound by the deep dorsal aponeurosis and plantar by the superficial transverse metatarsal ligament.(6, 7) It is divided into a superior and inferior level by the deep transverse metatarsal ligament. The intermetatarsal bursae lie in the superior intermetatarsal spaces,(6) the neurovascular bundle, from which MN originates, lies in the inferior intermetatarsal space and has a close cohesion with the synovial lining of the intermetatarsal bursae.(6, 7) The submetatarsal spaces lie in the subcutis, plantar to the superficial transverse metatarsal ligament, and extend until the epidermis. We used the following definitions:

- Intermetatarsal bursitis (IMB): contrast-enhancement in the superior intermetatarsal space with or without rim-enhancement.
- Submetatarsal bursitis (SMB): a sharply demarcated area with contrast-enhancement in the submetatarsal space with or without rim-enhancement.
- Morton's neuroma (MN): an isolated spindle-shaped lesion in the inferior intermetatarsal space with or without contrast-enhancement, without

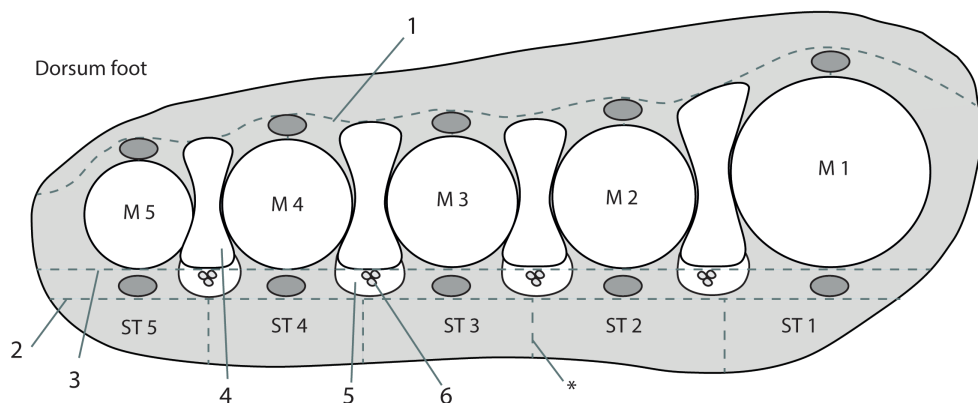


Figure 1. Schematic illustration of the forefoot at the metatarsal heads with intermetatarsal and submetatarsal spaces. Legend: The intermetatarsal space is demarcated at the dorsal side by the deep dorsal aponeurosis (1) and at the plantar side by the superficial transverse metatarsal ligament (2). The deep transverse metatarsal ligament (3) divides the intermetatarsal space into a superior (4) and inferior part (5), respectively, containing the bursa and neurovascular bundle (6). The submetatarsal spaces (ST) are located in the subcutis and are artificially bordered by the midline of the intermetatarsal space (*). M: metatarsal heads. Grey ovals represent extensor and flexor tendons of the forefoot.

Scoring

Two raters (a musculoskeletal radiologist with 23 years of experience, and a trained MD with 2 years of experience in RAMRIS-scoring and has scored >400 MRIs according to this system during a training period of several months prior to evaluating the MRIs that are part of this study),(22, 23) who were blinded to all clinical data, independently scored the MRIs. The two raters determined the final scores by consensus: a lesion was only regarded to be present if both readers agreed on this. First, all early arthritis patients were scored, followed by healthy controls. To exclude observer bias introduced by knowing that images belonged to healthy controls, MRIs of healthy controls were randomly mixed with 20 MRIs from EAC-patients. Based upon these 20 patients that were scored twice an intra-reader intraclass correlation coefficients (ICC) was determined that was 0.89.

In addition, to explore whether intermetatarsal and submetatarsal lesions were associated with RA independent of RAMRIS-inflammation, the MRIs were also scored for synovitis, tenosynovitis and osteitis at MTP-joints in line with the RAMRIS by two independent readers, also blinded to clinical data, as is described in Supplementary Data S1.(22-25) RAMRIS-inflammation was considered present when synovitis, tenosynovitis and/or osteitis were scored as ≥ 1 by both readers.

Analyses

IMB and SMB were studied in RA-patients, other arthritides and healthy controls. First, as patients could have more than one lesion, e.g. one patient could have IMB at more than one location, the mean number of lesions in RA-patients was compared to patients with other arthritides and to healthy controls using Mann-Whitney U tests.

Next, the data was dichotomized for presence per lesion: e.g. whether a patient had IMB at any location. Logistic regression analysis was used to compare RA to other arthritides and to healthy controls. Multivariable models corrected for the simultaneous occurrence of the different lesions and for age, gender, BMI, presence of RAMRIS-inflammation and anti-citrullinated peptide antibodies (anti-CCP), as these may be important in the relation between these lesions and RA.(26, 27) Test characteristics for RA were determined. Heatmaps were plotted with the percentage of participants with a lesion per location. Finally, measured transverse and dorsoplantar diameters were plotted to assess whether a cut-off for disease could be observed.

As subanalyses the analyses were repeated for MN and DSMA.

Calculations were performed with SPSS Statistics, version 23.0; IBM, Armonk, NY. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Of the 441 consecutively included EAC patients, 157 were classified as early RA, 284 patients had other arthritides (Table 1). 193 healthy controls were recruited. RA-patients were predominantly female (69%) and had a median symptom duration of 10 weeks (interquartile range: 5–28).

RA-patients had a higher number of IMB and SMB lesions per patient compared to other arthritides and to healthy controls (all $P < 0.001$)(Table 1). Next, the presence of a lesion was dichotomized as described in the Methods.

Table 1. Baseline characteristics of all participants

	RA	Other arthritides ¹	P-value RA vs other arthritides	Healthy controls	P-value, RA vs healthy controls
	n=157	n=284		n=193	
Clinical features					
Age, mean (SD)	59 (14)	56 (17)	0.07	50 (16)	<0.001
Female, n (%)	109 (69)	158 (56)	0.005	136 (71)	0.83
BMI, mean (SD)	26 (5)	27 (4)	0.52	25 (4)	0.003
Symptom duration, in weeks, median (IQR)	10 (5–28)	8 (4–26)	0.13	NA	NA
Swollen joint count, median (IQR)	7 (2–11)	2 (1–4)	<0.001	NA	NA
CRP, mg/L, median (IQR)	9 (4–26)	6 (3–16)	<0.001	NA	NA
RF positive, n (%)	106 (68)	51 (18)	<0.001	NA	NA
ACPA positive, n (%)	87 (59)	69 (25)	<0.001	NA	NA
MRI features					
Mean number of lesions per patient; n (SD)					
- Intermetatarsal bursitis	1.6 (1.4)	0.6 (1.0)	<0.001	0.2 (0.7)	<0.001
- Morton's neuroma	0.6	0.06 (0.3)	<0.001	0.03 (0.2)	<0.001
- Submetatarsal bursitis	0.4 (0.8)	0.07 (0.3)	<0.001	0.04 (0.2)	<0.001
- Diffuse submetatarsal alterations	0.5 (1.1)	0.3 (0.9)	0.068	0.3 (0.9)	0.092

RA: rheumatoid arthritis; SD: standard deviation; BMI: body mass index; IQR: interquartile range; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antigen; MRI: magnetic resonance imaging; NA: not applicable. This group included the following diagnoses: unclassified arthritis (n=148), psoriatic arthritis or spondyloarthritis (n=45), inflammatory osteoarthritis (n=23), reactive arthritis (n=7), crystal arthropathy (n=21), remitting seronegative symmetrical synovitis with pitting oedema (n=12) and other diagnoses (n=28).

Association of inter- and submetatarsal lesions with RA

The number of participants with lesions are given in Table 2. RA-patients more often had IMB and SMB than other arthritides (all $P<0.001$).

Since IMB and SMB were both associated with RA, and in addition age, gender, BMI, RAMRIS inflammation and anti-CCP-antibodies may be important in the relation between the lesions and RA, a multivariable model was performed that included both lesions and these clinical parameters.(26, 27) IMB and SMB remained associated with RA independent of these factors (Table 2); the effect size was largest for IMB (OR 4.5, 95%CI 2.7-7.8).

The analyses were repeated comparing RA-patients to healthy controls, revealing similar results (Supplementary Table S1).

Table 2. The association of intermetatarsal and submetatarsal lesions with early RA compared to other early arthritides

	Participants with MRI-features, n (%)		Univariable analyses	
	RA	Other arthritides	OR (95% CI)	P-value
Intermetatarsal bursitis	109 (69)	84 (30)	5.4 (3.5-8.3)	<0.001
Submetatarsal bursitis	39 (25)	17 (6)	5.2 (2.8-9.5)	<0.001
Morton's neuroma	30 (19)	10 (4)	6.7 (3.2-14.2)	<0.001
Diffuse submetatarsal alterations	36 (23)	45 (16)	1.6 (0.9-2.6)	0.067
	Multivariable analysis ¹		Multivariable analysis ²	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Intermetatarsal bursitis	4.5 (2.7-7.8)	<0.001	3.7 (2.1-6.6)	<0.001
Submetatarsal bursitis	2.2 (1.03-4.5)	0.041	2.3 (1.1-4.8)	0.031
Morton's neuroma	-	-	3.1 (1.3-7.7)	0.012
Diffuse submetatarsal alterations	-	-	0.9 (0.5-1.8)	0.86

The results of logistic regression analyses are presented. RA: rheumatoid arthritis; OR: odds ratio; CI: confidence interval. ¹Multivariable model including intermetatarsal bursitis, submetatarsal bursitis, age, gender, anti-CCP and RAMRIS-inflammation (defined as the presence of synovitis, tenosynovitis and/or osteitis). ²Multivariable model including intermetatarsal bursitis, submetatarsal bursitis, Morton's neuroma, diffuse submetatarsal alterations, age, gender, BMI, anti-CCP antibodies and RAMRIS-inflammation

Test characteristics of inter- and submetatarsal lesions for RA

Next, test characteristics were determined for IMB and SMB (Supplementary Table S2). Sensitivity for IMB was 69%, for SMB 25%. Specificity of IMB compared to other arthritides was 70%, and compared to healthy controls 84%. For SMB this was 94% and 97% respectively.

Heatmap of lesions for RA, other arthritides and healthy controls

The distribution of the lesions was plotted in heatmaps (Figure 2, Supplementary Table S3). In RA, IMB affected the 3rd intermetatarsal space most (57% of patients). Regarding SMB, the first and fifth submetatarsal space were most affected: in 13% and 12% of patients respectively.

Similarly, in other arthritides and healthy participants the 3rd intermetatarsal space was affected by IMB most often, but with lower frequency (20% and 11% respectively). For SMB at the first and fifth submetatarsal space this was 2% and 4% respectively in other arthritides and 1% and 2% in healthy controls. MRI-examples are given in Figure 3.

Transverse and dorsoplantar diameter of lesions for patients with rheumatoid arthritis, other arthritides and healthy controls

Next, the transverse and dorsoplantar diameters of IMB and SMB were measured (in mm) and plotted in histograms (Figure 4). We evaluated cut-offs based upon the histograms (Supplementary Table S4).

First the transverse diameter of IMB was studied. From the histograms it was apparent that lesions ≥ 4 mm were infrequent in other arthritides (3% of patients) and healthy controls (2%). We studied whether this could be used as a cut-off for RA: however lesions ≥ 4 mm were also less frequent in RA (13%). In all groups the majority of lesions were ≤ 3 mm: 68% of RA-patients had a lesion ≤ 3 mm, compared to 29% other arthritides and 15% of healthy controls. Hence, a cut-off of 3mm increased specificity to 97% compared to other arthritides and 98% to healthy controls, at the cost of a decrease in sensitivity to 13%.

Theoretically, IMB may be limited by the metatarsal heads in its ability to distend transversely and may, therefore, upon inflammation, distend dorsoplantar. A dorsoplantar diameter of IMB ≥ 15 mm was infrequent in the control groups (Figure 4). Taking ≥ 15 mm as a cut-off increased specificity for RA compared to other arthritides (95%) and healthy controls (100%). Sensitivity, however, decreased to 16%.

Similarly, regarding SMB no cut-off could be determined that did not lead to a substantial decrease in sensitivity for RA (Supplementary Table S4).

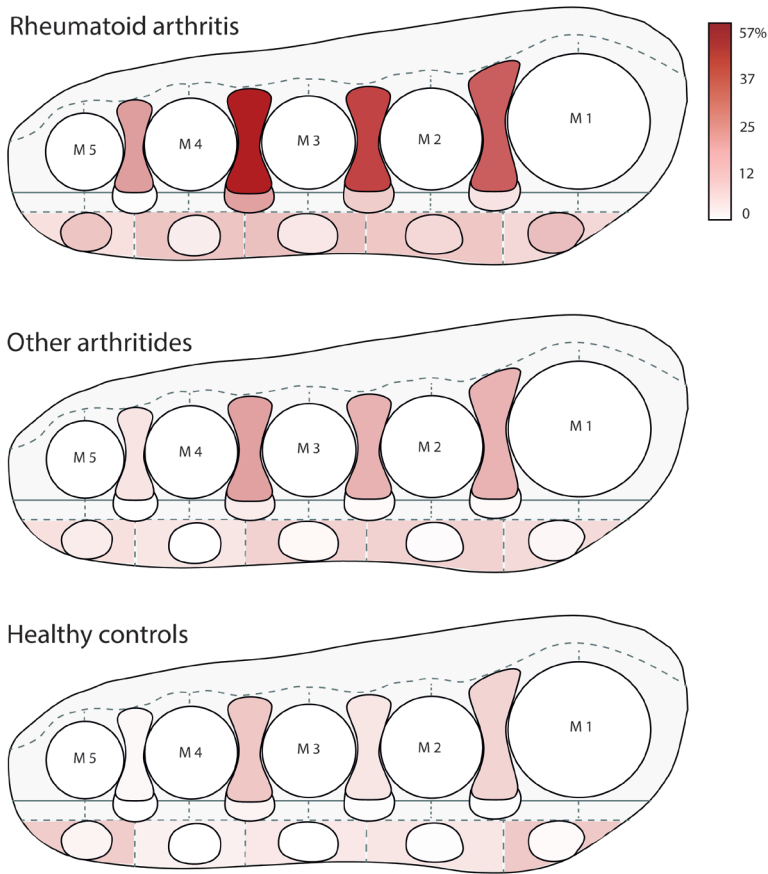


Figure 2. Heatmap of intermetatarsal bursitis, submetatarsal bursitis, Morton's neuroma and diffuse submetatarsal alterations for every population. Legend: Schematic illustration in coronal view of the frequency of lesions in each compartment of the forefoot at the level of the metatarsal heads (See also supplementary Table S3). The frequency of the lesions (% of participants in the respective group) is represented by an increase in color intensity. The compartments are defined in Figure 1. Morton's neuroma (MN) is demarcated plantar to intermetatarsal bursitis (IMB). In the subcutis, submetatarsal bursitis (SMB) is illustrated as a demarcated oval. The remainder of the subcutis represents diffuse submetatarsal alterations (DSMA). IMB, SMB and MN are most frequently seen in RA. The second and third IMB are preferred locations whereas the fourth is the least involved. In the subcutis of RA-patients DSMA is seen under MTP 2,3 and 4, whereas in healthy controls this is seen under MTP 1 and 5. SMB dominates under MTP 1 and 5 in RA-patients. M: metatarsal heads.

Subanalyses for MN and DSMA

MN was associated with RA compared to other arthritides in univariable and multivariable analyses that included IMB, SMB, MN, DSMA and clinical parameters ($P<0.001$ and $P=0.012$ respectively). DSMA was not associated ($P=0.069$ and $P=0.86$ respectively) (Table 2). Similar results were obtained when compared to healthy controls (Supplementary Table S1).

The test characteristics for MN were determined and were as follows: sensitivity 19%, specificity 96% compared to other arthritides and 98% compared to healthy controls. For DSMA this was not determined as it was not associated with RA.

MN and DSMA were incorporated in the heatmaps in figure 4 (Supplementary Table S3 presents the exact frequency per location). MN occurred most frequently in the third intermetatarsal space (20% of RA-patients). DSMA in the first and fifth submetatarsal space were relatively more common in healthy controls (both locations 10%).

Regarding Lesion-size for MN, a transverse diameter of $\geq 7\text{mm}$ was infrequent in control groups (Figure 4): using this cut-off increased specificity for RA, however sensitivity decreased to 12%. Additionally, literature suggests a cut-off of $\geq 5\text{mm}$, this decreased sensitivity to 16%. (10, 28) Similarly, for the dorsoplantar diameter, using a $\geq 4\text{mm}$ cut-off based on Figure 4 decreased sensitivity to 13% (Supplementary Table S4). DSMA was not measured as, per definition, it has no sharply demarcated borders.

Discussion

This cross-sectional study aimed to explore MRI-detected IMB and SMB in consecutive patients presenting with early RA, compared to other arthritides and healthy controls. We observed that both IMB and SMB were associated with and specific for RA (specificity ranging from 70–97%). In addition, we studied whether lesion-size might be relevant and found considerable overlap in size between the groups; therefore no cut-off for RA could be distinguished with high sensitivity and specificity. To our knowledge, our study is the largest to date to systematically study involvement of bursae in the forefoot in RA.

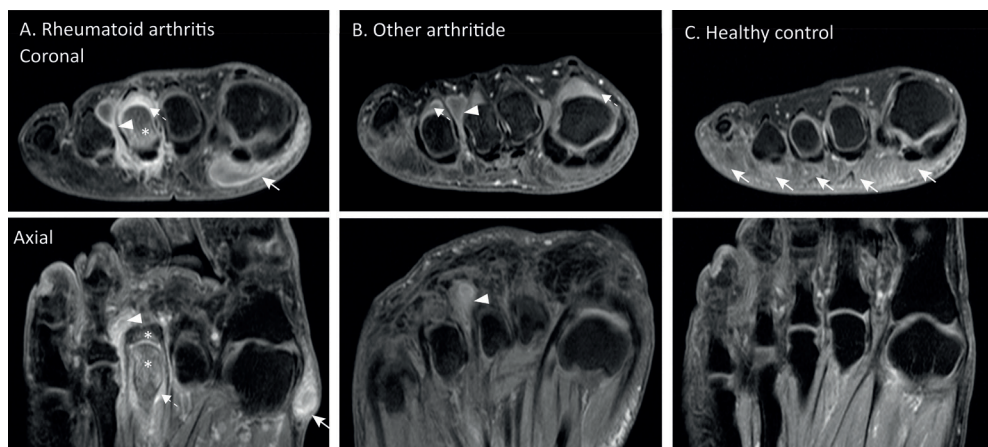


Figure 3. MR examples of intermetatarsal and submetatarsal bursae. Legend: Coronal and axial fat suppressed T1-weighted FSE gadolinium enhanced images of the forefoot at the level of the metatarsal heads. (A) female participant with RA (age 61 years) with intermetatarsal (IMB) and submetatarsal bursitis (SMB). IMB in the 3rd intermetatarsal space (arrowhead) with peripheral enhancement protruding dorsal (dumbbell-shape) and plantar (teardrop-shape) of the metatarsal heads. Peripheral enhancement of a mass in the first submetatarsal space, consistent with SMB (white arrow). Synovitis of MTP 3 (dotted arrow), as well as osteitis in the head of the third metacarpal bone and proximal phalanx (*). (B) female participant with another arthritide (diagnosis of viral reactive arthritis, age 34 years) and IMB at the 3rd intermetatarsal space (arrowhead) with dorsal protrusion. Additional synovitis of MTP 1 and 4 (dotted arrows). (C) female healthy control (age 50 years) with diffuse submetatarsal alterations (DSMA) in all submetatarsal spaces, predominantly visible at the 1st, 2nd and 4th submetatarsal spaces (arrows). Intense linear contrast-enhancement at the 2nd intermetatarsal space is consistent with a small vessel on the consecutive slices (not shown), there is no IMB visible on the axial images.

IMB results from inflammation of a naturally present, synovium-lined, structure. (6) Since RA is a disease of the synovium, the bursae might be a primary focus of disease, previously unnoticed. It can be hypothesized that IMB occurs secondary to concomitant arthritis, however there is no anatomical connection between intermetatarsal bursae and MTP-joints and in our study IMB associated with RA independent of the presence of RAMRIS-inflammation, defined as synovitis, tenosynovitis and osteitis.(7)

In the plantar subcutaneous fat of the forefoot SMB was scored as sharply demarcated submetatarsal areas of contrast-enhancement with or without rim-enhancement that may develop secondary to mechanical loading.(17) These non-native (adventitious) bursae form at sites of friction, but have imaging features similar to native bursae.(29)

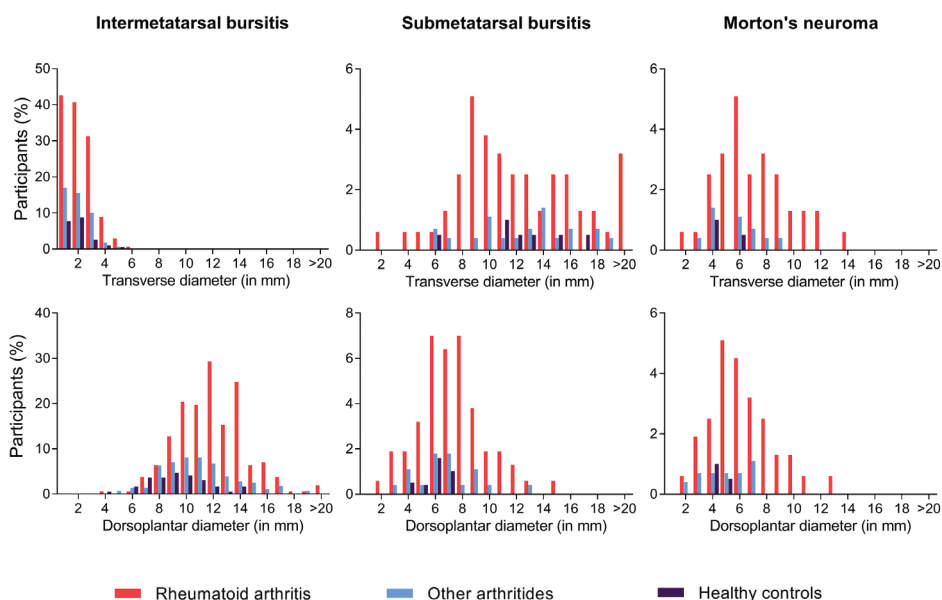


Figure 4. Distribution of transverse and dorsoplantar diameters (mm) of intermetatarsal bursitis, submetatarsal bursitis and Morton's neuroma. Legend: The x-axis displays the diameter (in mm), the Y-axis the percentage of participants with the corresponding diameter. Participants could have more than one lesion, therefore the percentage of participants with a lesion does not add up to the total amount of participants. The metatarsal bones limit the IMB in the transverse plane, squeezing the bursa outwards in the dorsoplantar plane. The SMB expands more in the transverse than dorsoplantar plane in the subcutis. The detected MN are predominantly round and larger than 5 mm.

In addition MN and DSMA were scored, of which MN was also associated with RA. This association remained present after correcting for age, gender and BMI; features that may relate to other pathologies predisposing to MN. Thus MN seems to be increased in RA. Within RA, IMB has previously been suggested as a cause of MN.(14, 30) Inflamed bursae may irritate the common plantar digital nerve,(6, 30) with secondary MN formation.(7, 30) This may explain why MN mostly occurred at locations where IMB was most frequent (second and third intermetatarsal spaces). For the definition of MN, besides the shape and location, it was important in our study that the lesion did not have any rim-enhancement that was continuous with the IMB. This might be especially challenging at the second and third intermetatarsal spaces, where enlarged intermetatarsal bursae can extend below the deep transverse metatarsal ligament towards the neurovascular bundle.(10). In the literature the prevalence for MN varies between studies, from 15% in symptomatic volunteers, to 54% in asymptomatic volunteers.(10, 16, 31) An explanation for the

low frequency of 20% in our study could be the challenging differentiation between MN and IMB and potential co-existence of the two, especially for smaller MN. The limited MRI-protocol, without T1 and fluid sensitive sequences, may underscore fibrous MN.(32) Therefore no definitive conclusion regarding the frequency of MN can be drawn from our study. We do not believe this undermines the association that was found of MN with RA, as the protocol restriction applies for all study groups.

DSMA, interestingly, occurred in healthy controls specifically under the first and fifth metatarsal heads. These locations are consistent with a previous study and are considered a normal finding based on mechanical loading.(17) In RA DSMA occurred predominantly under MTP 2, 3 and 4, whereas under MTP 1 and 5 SMB were seen (Figure 2).

It is difficult to compare our findings to previous studies in RA, as they utilized ultrasound and included patients with established RA receiving treatment rather than early disease.(8, 33)

The intermetatarsal space is limited in the transverse plane by the metatarsal bones. Thus, bursitis is squeezed either dorsal and or plantar, especially at the second and third intermetatarsal spaces, respectively called a dumbbell or a teardrop phenomenon (Figure 1), explaining the larger dorsoplantar diameter that is found (Figure 4).(7, 21)

Our study has some limitations. First, the scoring method is not validated, therefore reading was done by consensus rather than by independent readers, as this may be necessary in the setting of preliminary findings.(34) However for determining the validity of an outcome-measure it is crucial to demonstrate the reliability of scoring between independent readers.(34, 35) The Intrareader-ICC, however, was determined and was reassuring. Second, our MRI-protocol contained no fluid-sensitive sequences, as the protocol was originally intended to score RAMRIS-inflammation. Therefore small amounts of fluid in the bursae may have remained undetected, leading to an underestimation of observed lesions. Nevertheless, the use of contrast-enhancement might be a strength, which previous studies in early arthritis found essential for optimal assessment of MRI-detected synovitis and tenosynovitis.(25, 36) Because intermetatarsal bursae have a synovial lining we assumed that contrast-enhancement would increase sensitivity of synovial hypertrophy in (active) bursitis. Thus, although theoretically small amounts of fluid

in a bursa may be missed without a fluid sensitive sequence, this could be normal in a bursa and rarely occurs at this location without enhancing synovial hypertrophy. (10, 37) The greater prevalence of contrast-enhancing (teno-)synovitis might be expected to occur in RA. To account for this we included RAMRIS-inflammation in our multivariable model. Third, although the lesions were associated with RA independent of the factors that were adjusted for, additional factors might be of influence to the occurrence of these lesions, such as physical activity and type of shoes that were unaccounted for and may potentially be a source of bias. Also, we did not include a comparison with weightbearing radiographs.(38, 39) Finally, our study was cross-sectional in nature. Thus although our study suggests that these lesions may aid the clinician as a (differential) diagnostic tool, prospective studies are warranted to further establish the diagnostic relevance of these lesions.

Conclusion

IMB and SMB are both associated with RA. As IMB has a synovial lining, these results contribute to the emerging evidence that in early RA, besides intra-articular synovitis, juxta-articular synovial inflammation is common. Previously tenosynovitis was reported,[18,36] and now IMB as well. The current findings pose questions on whether the bursitis correlated to symptoms, responds to therapy, or has diagnostic value, e.g. in predicting RA-development in the early phases of disease.

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Supplementary data

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

Supplementary Table S1. Results of logistic regression analyses for the association of intermetatarsal and submetatarsal lesions with early RA compared to healthy controls

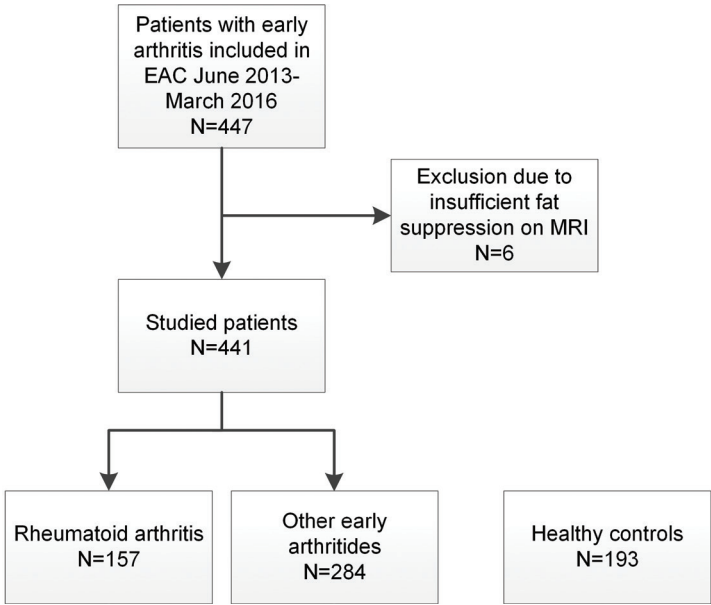
	Participants with MRI-features, n (%)		Univariable analyses	
	RA	Other arthritides	OR (95% CI)	P-value
Intermetatarsal bursitis	109 (69)	31 (16)	11.9 (7.1-19.8)	<0.001
Submetatarsal bursitis	39 (25)	3 (2)	15.6 (4.7-52)	<0.001
Morton's neuroma	30 (19)	6 (3)	10.3 (4.2-25.1)	<0.001
Diffuse submetatarsal alterations	36 (23)	31 (16)	1.6 (0.9-2.7)	0.11
	Multivariable analysis ¹		Multivariable analysis ²	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Intermetatarsal bursitis	6.9 (3.9-12.5)	<0.001	5.5 (3.0-10.2)	<0.001
Submetatarsal bursitis	3.7 (1.2-11.3)	0.023	3.7 (1.2-11.7)	0.023
Morton's neuroma	-	-	4.0 (1.0-15.5)	0.047
Diffuse submetatarsal alterations	-	-	1.0 (0.5-2.3)	0.93

RA: rheumatoid arthritis; OR: odds ratio; CI: confidence interval. ¹Multivariable model including intermetatarsal bursitis, submetatarsal bursitis, age, gender, anti-CCP and RAMRIS-inflammation (defined as the presence of synovitis, tenosynovitis and/or bone marrow edema). ²Multivariable model including intermetatarsal bursitis, submetatarsal bursitis, Morton's neuroma, diffuse submetatarsal alterations, age, gender, BMI, anti-CCP antibodies and RAMRIS-inflammation

Supplementary Table S2. Test characteristics for intermetatarsal and submetatarsal lesions for RA

	RA	RA vs. other arthritides	RA vs. healthy controls
	Sensitivity	Specificity	Specificity
Intermetatarsal bursitis	69 (62-72)	70 (65-75)	84 (78-88)
Submetatarsal bursitis	25 (19-32)	94 (91-96)	97 (93-99)
Morton's neuroma	20 (14-26)	96 (94-98)	98 (96-100)

RA: rheumatoid arthritis; Values are depicted in % with their corresponding 95% confidence intervals between brackets



Supplementary Figure S1. Flow chart of participants. RA was defined according to clinical diagnosis of RA plus fulfilment of the 2010 classification criteria. The 'other early arthritides' included the following diagnoses: unclassified arthritis (n=148), psoriatic arthritis or spondyloarthritis (n=45), inflammatory osteoarthritis (n=23), reactive arthritis (n=7), crystal arthropathy (n=21), remitting seronegative symmetrical synovitis with pitting oedema (n=12) and other diagnoses (n=28). This flowchart is similar as described in Dakkak, et al 2020.

Supplementary Table S3. Frequency of intermetatarsal bursitis, submetatarsal bursitis, Morton’s neuroma and submetatarsal diffuse alterations per location in patients with rheumatoid arthritis (RA), other arthritides and healthy controls.

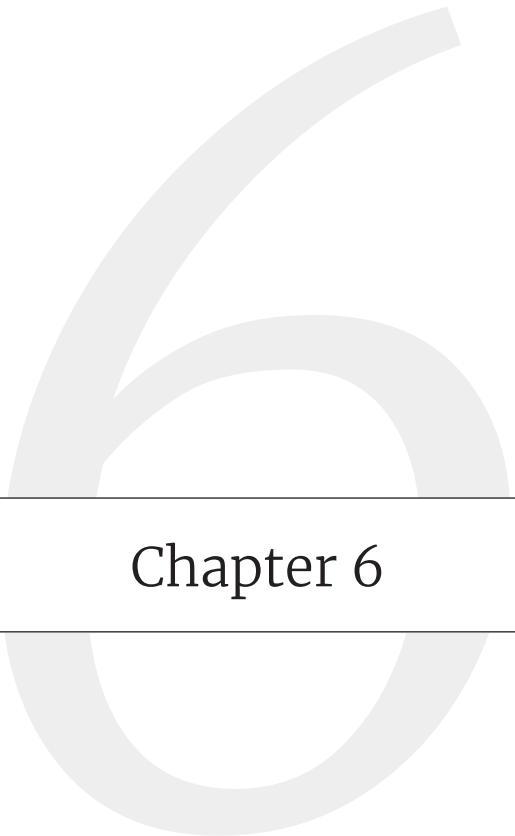
	RA	Other arthritides	Healthy controls
	n (%)	n (%)	n (%)
Intermetatarsal bursitis			
- IT 1	59 (38)	43 (18)	15 (8)
- IT 2	70 (45)	44 (16)	9 (5)
- IT 3	90 (57)	56 (20)	21 (11)
- IT 4	32 (20)	14 (5)	3 (2)
Submetatarsal bursitis			
- ST 1	20 (13)	5 (2)	2 (1)
- ST 2	11 (7)	2 (1)	1 (1)
- ST 3	7 (5)	2 (1)	0 (0)
- ST 4	5 (3)	0 (0)	0 (0)
- ST 5	18 (12)	10 (4)	4 (2)
Morton’s neuroma			
- IT 1	8 (5)	3 (1)	1 (1)
- IT 2	15 (10)	3 (1)	1 (1)
- IT 3	31 (20)	10 (4)	4 (2)
- IT 4	1 (1)	1 (0)	0 (0)
Submetatarsal diffuse alterations			
- ST 1	11 (7)	19 (7)	20 (10)
- ST 2	17 (11)	23 (8)	9 (5)
- ST 3	19 (12)	24 (9)	8 (4)
- ST 4	18 (12)	13 (5)	5 (3)
- ST 5	9 (6)	16 (6)	19 (10)

RA: rheumatoid arthritis; IT: intermetatarsal space; ST: submetatarsal space.

Supplementary Table S4. Test characteristics for rheumatoid arthritis (RA) determined by using cut-off points for transverse and dorsoplantar diameters for intermetatarsal bursitis, submetatarsal bursitis and Morton's neuroma.

	RA	RA vs. other arthritides	RA vs. healthy controls
	Sensitivity, %	Specificity, %	Specificity, %
Intermetatarsal bursitis			
- Transverse diameter $\geq 4\text{mm}$	13 (20/157)	97 (9/284)	98 (4/193)
- Dorsoplantar diameter $\geq 15\text{mm}$	16 (25/157)	95 (14/284)	100 (0/193)
Submetatarsal bursitis			
- Transverse diameter ^a	NA	NA	NA
- Dorsoplantar diameter $\geq 8\text{mm}$	13 (20/157)	98 (5/284)	100 (0/193)
Morton's neuroma			
- Transverse diameter $\geq 7\text{mm}$	12 (19/157)	99 (3/284)	100 (0/193)
- Transverse diameter $\geq 5\text{mm}$	16 (25/157)	99 (4/284)	97 (6/193)
- Dorsoplantar diameter $\geq 4\text{mm}$	13 (20/157)	98 (6/284)	100 (0/193)

Cut-offs are based upon histograms: when a diameter was infrequent in the control groups it was used as a cut-off point. a: No cut-off could be determined for the transverse diameter as there was overlap regarding all sizes, as is visualized in the histograms in Figure 4. NA: not applicable.



Chapter 6

*The relation between physical joint
examination and MRI-depicted inflammation of
metatarsophalangeal-joints in early arthritis*

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Abstract

Background: The relationship between physical joint examination (PE) and MRI-detected inflammation in early inflammatory arthritis has mostly been studied in the hands. Physical examination of MTP-joints is considered difficult and for these joints this relationship is unknown. Therefore we studied the concordance of PE with MRI-inflammation in MTP-joints. Metacarpophalangeal(MCP)-joints were included for comparison.

Methods: 1759 MTP(2-5)- and 1750 MCP(2-5)-joints of 441 consecutive patients with early arthritis underwent PE (for joint-swelling) and MRI, all evaluated by two assessors. MRI was scored for synovitis, tenosynovitis and osteitis (summed MRI-inflammation). Synovial intermetatarsal bursae may enlarge upon inflammation and become palpable and were therefore also assessed. Analyses (frequencies, GEE) were performed on joint-level.

Results: PE and MRI were concordant in 79% of MTP-joints. Of 1606 non-swollen MTP-joints, 83% showed no MRI-inflammation, 17% showed subclinical MRI-inflammation. Of 153 swollen MTP-joints, 48% had MRI-inflammation, 52% (79 MTP-joints) did not. Of these 79 swollen MTP-joints without MRI-inflammation, 31 showed intermetatarsal bursitis, 48 joints had none of these MRI-abnormalities (this concerned 31% of swollen MTP-joints). MTP-swelling was statistically independently associated with tenosynovitis (OR2.21, 95%CI 1.1-4.3) and intermetatarsal bursitis (OR2.91, 95%CI 1.8-4.8).

MTP-joints showed subclinical inflammation less often than MCP-joints (17% vs. 34%, $P<0.001$). Swollen MTP-joints showed MRI-inflammation less often than swollen MCP-joints (48% vs. 88%, $P<0.001$).

Conclusions: Absence of swelling of MTP-joints in early arthritis is mostly accompanied by absence of MRI-detected inflammation. Swollen MTP-joints are, in addition to synovitis, also explained by tenosynovitis and intermetatarsal bursitis, and partly unexplained by MRI. Their clinical relevance must be determined in longitudinal studies.

Introduction

Rheumatoid arthritis (RA) is characterized by chronic joint inflammation, especially of the small joints.(1,2) In recent-onset RA, the metatarsophalangeal (MTP)-joints are often involved, which can generate walking disabilities.(3-5) Physical joint examination (PE) for joint swelling upon palpation is a crucial element in the assessment of the clinical status of RA-patients. It is however known that PE of the MTP-joints can be difficult.(6)

Magnetic resonance imaging (MRI) of the hands is more sensitive than PE in detecting inflammation, and its use has been recommended in the management of RA.(7) However, the relation between inflammation detected at PE and with MRI at the MTP-joints is unclear. Studies on this relationship focussed on the wrist- and metacarpophalangeal (MCP)-joints.(8-10) Only two studies investigated the feet; the first study was relatively small (n=40) and was performed in patients receiving disease modifying anti-rheumatic drugs (DMARDs) and not in untreated patients.(11) The second study did not use contrast-enhancement,(10) limiting the conclusions that could be drawn as contrast-enhancement is required to sensitively depict synovitis.(12) Also, neither evaluated tenosynovitis at the MTP-joints.

In addition to the classic inflammatory features (synovitis, tenosynovitis and osteitis), intermetatarsal bursitis (IMB) is also prevalent in inflammatory arthritis.(13,14) Interestingly intermetatarsal bursae in the forefoot have a synovial lining and are located between the metatarsal heads immediately above the deep transverse metatarsal ligament; a schematic illustration of the forefoot with the anatomic position of these bursae is given in Figure S1 [Additional File 1].(15) Inflammation may lead to enlargement and dorsal protrusion of the bursae, above the metatarsal heads.(16,17) Theoretically, IMB can therefore be palpable. IMB have not previously been studied in respect to swelling upon PE and were therefore also included in this study.

The currently available literature does not give a fulfilling and thorough representation of the relationship between PE and MRI of the MTP-joints. To increase the understanding of this relationship, we performed a large cross-sectional study in early arthritis patients, and assessed the concordance of arthritis upon PE and MRI-detected inflammation at the MTP-joints. MCP-joints were included for comparison.

Table 1. Baseline characteristics of patients that presented with early arthritis

	Patients (n=441)
Age, mean (SD)	57 (16)
Female, n(%)	267 (61)
Symptom duration, in weeks, median (IQR)	9 (4-27)
66-Swollen joint count, median (IQR)	3 (1-7)
CRP (mg/L), median (IQR)	7 (3-20)
ACPA positive, n (%)	156 (37)
Diagnosis, n(%)	
Rheumatoid arthritis (RA)	157 (36)
Unclassified arthritis	148 (33)
Psoriatic arthritis or spondyloarthritis	45 (10)
Inflammatory osteoarthritis	23 (5)
Reactive arthritis	7 (2)
RS3PE	12 (3)
SLE and MCTD	5 (1)
Other diagnoses	44 (10)

SD: standard deviation; IQR; interquartile range; CRP: C-reactive protein; ACPA: anti-citrullinated peptide antigen; RA: rheumatoid arthritis according to clinical diagnosis and 2010 criteria during the first year of follow-up; RS3PE: remitting seronegative symmetrical synovitis with pitting edema; SLE: systemic lupus erythematosus; MCTD: mixed connective tissue disease. The 66 swollen joint count was assessed.

Methods

Participants

447 consecutive patients newly presenting with clinically confirmed arthritis were included in the Leiden Early Arthritis Cohort between June 2013 and March 2016. Included patients had a symptom duration <2 years and were naïve to DMARDs. (18) At baseline, PE of joints was performed, serum samples were taken and an MRI was performed before DMARD-initiation. The median time between PE and MRI was 7 days (95% confidence interval (CI) 3-14 days).

MRIs of 6 patients were excluded because of inhomogeneous fat suppression. Of the remaining 441 patients, 157 were classified as RA, defined as a clinical diagnosis plus fulfilment of the 2010 RA-criteria during the first year of follow-up.

[1] The remaining 284 patients received alternative diagnoses and are presented in Table 1.

Physical joint examination

The presence of joint swelling upon PE was evaluated by two independent assessors, a rheumatologist and a trained research nurse, with the patient in supine position on the exam table. Research nurses held regular consensus exercises for swollen joint assessment led by a rheumatologist to maintain high interobserver agreement. In this study, PE was considered positive for joint swelling if both assessors independently scored its presence in the same joint.

MRI scanning and scoring

Unilateral scans were acquired of the MTP- and MCP-joints of the most painful side, or the dominant side in case of equally severe symptoms, on a 1.5T extremity MRI (General Electric, WI, USA). Gadolinium contrast was administered intravenously. Sequences acquired were pre-contrast coronal T1-weighted fast spin echo (T1), and post-contrast coronal and axial T1-weighted fast spin echo with frequency-selective fat saturation (T1Gd) of MCP-joints, and post-contrast coronal and axial T1 of the MTP-joints. For a more detailed description of the MRI-protocol, see the Supplementary Methods 1 [Additional file 1].

Synovitis and osteitis of MTP(2-5)- and MCP(2-5)-joints were scored in line with the RAMRIS.(19) with the exception that osteitis was assessed on a contrast-enhanced T1-weighted fat-suppressed sequence, as its use for depicting osteitis is recommended by the European Society of Musculoskeletal Radiology (ESSR) and previous studies have demonstrated that it has a strong correlation with the T2-weighted fat suppressed sequence that is advised by the RAMRIS.(20-23) For tenosynovitis, the score as described by Havaardsholm et al was applied to the extensor and flexor tendons of the MTP- and MCP-joints.(24) Additional information on the method of scoring is provided in the Supplementary Methods 2 [Additional File 1]. Each MRI was scored by two independent readers, blinded to clinical data. Interreader and intrareader intraclass correlation coefficients (ICCs) were generally ≥ 0.90 and were published previously.(25) MRI-detected inflammation was positive per joint if synovitis, tenosynovitis and/or osteitis were scored as ≥ 1 by both readers independently.

Scoring of IMB was done at intermetatarsal spaces by two readers blinded to clinical data adjusted from Cherry et al, as is described below.(26) The first reader

(MR) was a trained musculoskeletal radiologist with 23 years of experience, the second reader (YD) was an MD who had scored >400 MRIs according to the RAMRIS method during a training period of 12 months prior to evaluating the MRIs that are part of this study. IMB was defined as a contrast-enhanced lesion with or without rim-enhancement that was located between the metatarsal heads above the deep transverse metatarsal ligament, that could protrude at the dorsal side of the metatarsal heads, as is illustrated in Figure S1 [Additional File 1]. IMB was scored as present when visible on two consecutive slices in both axial and coronal planes. As this is not a validated scoring-method, scoring was done in consensus: IMB at MTP-joints was considered positive if found present by both readers in consensus.

As mentioned, MCP-joints were included as comparison. Synovitis, tenosynovitis and osteitis were scored as in the MTP-joints. Bursae between MCP-joints are unknown in the literature, and were not scored routinely. However, literature can be incomplete, and therefore, in the subgroup of joints that were swollen but MRI-negative, one reader explored whether there could be intermetacarpal bursitis. This revealed no signs of local bursitis, therefore further efforts to search for bursitis at the MCP-joints were deemed unnecessary.

Analyses

Analyses were performed separately for MTP- and for MCP-joints: the main analysis was of MTP-joints, MCP-joints were included for comparison. Frequency of concordance/discordance of PE and MRI were evaluated on joint-level. The MRI values of 19 out of 3528 joints (5 MTP-joints and 14 MCP-joints) were missing, as these joints could not be scored due to movement artefacts or inhomogeneous fat suppression. None of these 5 MTP-joints were swollen upon PE, 5 out of the 14 MCP-joints were swollen. Joint-level analyses were performed, therefore these values were not imputed.

For the joint level analyses of PE and IMB the nearby location was considered; e.g. when studying PE of MTP3, IMB in the second and third intermetatarsal spaces were considered. Generalized estimating equations (GEE) were done to assess the association of MRI-features with clinical swelling, as this model takes into account that in every patient multiple joints were assessed.

To further support the results of our main findings in MTP-joints, 3 sub-analyses were performed. First, the relation for PE with MRI-detected inflammation was

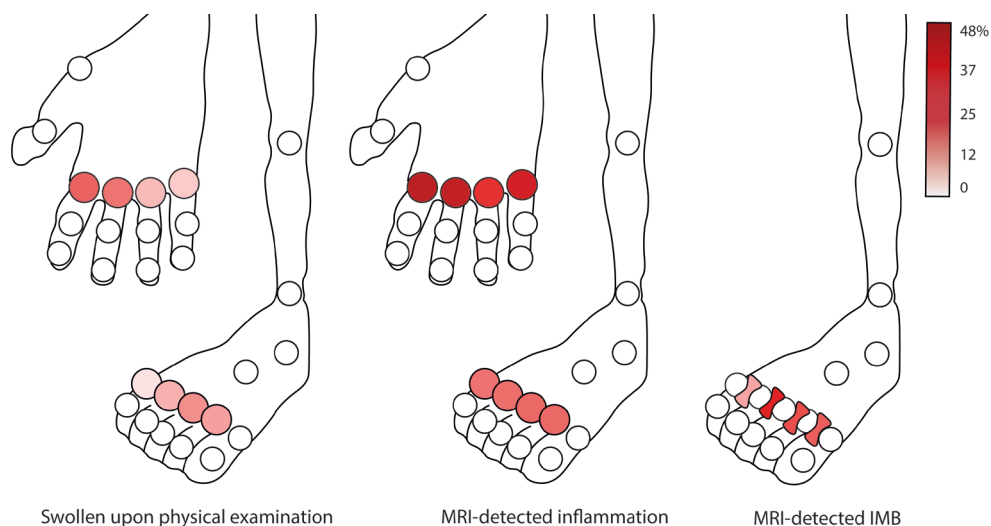


Figure 1. Frequency of a swollen joint upon physical joint examination, MRI-detected inflammation and intermetatarsal bursitis (IMB) per location for MTP(2-5)- and MCP(2-5)-joints in consecutive patients presenting with early arthritis. Physical joint examination was positive if two assessors independently scored the joint as swollen. MRI-detected inflammation was positive per joint if synovitis, tenosynovitis and/or osteitis were scored as present by two readers independently

evaluated in the subgroup of RA-patients. Next, we speculated that osteitis and in addition flexor tenosynovitis may not be palpable, as PE is performed at the dorsal side of MTP-joints. Therefore the frequency of concordance/discordance was studied excluding flexor tenosynovitis and osteitis from the definition of MRI-inflammation. Finally, non-swollen joints may be tender as a sign of 'subclinical' inflammation, to study this, analyses were repeated in joints that were tender, swollen joints were excluded from this analysis.

Results

Baseline characteristics

Baseline characteristics of the 441 patients are presented in Table 1. 73 patients (17%) had ≥ 1 swollen MTP-joint, MTP2 and MTP3 were most often swollen (Figure 1). 176 patients (40%) had MRI-detected inflammation at at least one MTP-joint.

Concordance and discordance of physical joint examination and MRI

Of all 1759 MTP-joints, 153 (9%) were clinically swollen (PE-positive) and 355 (20%) showed MRI-inflammation (MRI-positive). Combining the PE and MRI-scores re-

vealed that 1325 (75%) of all MTP-joints were PE-negative/MRI-negative (Figure 2A). The other concordant group was smaller: 73 (4%) of all MTP-joints were PE-positive/MRI-positive. 360 joints in total were discordant: of which 281 joints were PE-negative/MRI-positive (16% of all MTP-joints) and 79 were PE-positive/MRI-negative (5%).

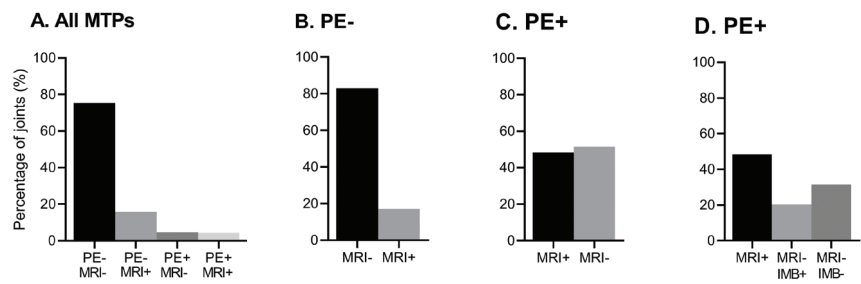


Figure 2. Concordance and discordance between clinical joint swelling at PE and findings at MRI, for all 1759 MTP-joints (A) and for non-swollen (B) and swollen MTP-joints (C, D) separately. The number of joints per group are as follows; PE-MRI- n=1325 joints, PE-MRI+ n=281, PE+MRI- n=79 and PE+MRI+ n=74 joints. A) Frequency of all 1759 MTP-joints per category of PE/MRI. B) 1606 non-swollen (PE-) MTP-joints. C) 153 swollen (PE+) MTP-joints. D) The same 153 PE+ joints as in Figure C, in addition to the frequency of MRI-inflammation the frequency of intermetatarsal bursitis (IMB) is presented in swollen joints that had no MRI-inflammation. MTP: metatarsophalangeal joints; PE: physical joint examination; PE-: not swollen; PE+: swollen; MRI: magnetic resonance imaging; MRI-: absence of MRI-detected inflammation defined as synovitis, tenosynovitis and osteitis; MRI+: presence of MRI-detected inflammation; IMB: intermetatarsal bursitis, either present (+) or absent (-)

Next, PE-positive and PE-negative joints were studied separately (Figure 2B,C). Of 1606 PE-negative joints, 83% were MRI-negative, 17% were MRI-positive, showing subclinical inflammation. Of all 153 PE-positive joints, 48% were MRI-positive, whereas 52% (79 joints) were MRI-negative.

Association between synovitis, osteitis and tenosynovitis and clinical joint swelling

Next we determined which of the MRI-features had the strongest association with joint swelling. In univariable analyses, synovitis, tenosynovitis and osteitis were all associated with joint swelling (Table 2). As these three features frequently co-occur, a multivariable GEE-analysis was performed that included all three variables. Here only tenosynovitis remained statistically associated with joint swelling (OR 3.19, 95%CI 1.6-6.3).

Relationship of IMB with clinical joint swelling

As we had observed that 52% of swollen MTP-joints (79 joints) showed no MRI-inflammation, we hypothesized that IMB could explain part of this discordance. IMB was scored in all patients, the frequency is given in Table 2 and shown per location in Figure 1. In joints that were negative for MRI-inflammation, IMB was more frequent in swollen joints than in non-swollen joints (OR 3.2, 95%CI 1.8-5.7, $P<0.001$) (Table 3). IMB alone explained 21% of all swollen joints (Figure 2D).

When considering all swollen MTP-joints ($n=153$), 48 (31%) could not be explained by MRI-detected inflammation or IMB and thus had no abnormality upon MRI (Figure 2D). MRI-examples of swollen MTP-joints are given in Figure 3.

Thereafter, we included IMB in the analysis assessing the association of MRI-findings with clinical joint swelling. Both in univariable and multivariable models IMB was associated with MTP-swelling, next to tenosynovitis (Table 2).

Concordance and discordance of PE and MRI at MCP-joints

The MCP-joints were studied for comparison; results are presented in Figures 1 and Figure S2 [Additional File 1]. Non-swollen MTP-joints showed less subclinical inflammation than non-swollen MCP-joints (18 vs. 34%, $P<0.001$). Swollen MTP-joints also showed less MRI-inflammation than swollen MCP-joints (48% vs. 88%, $P<0.001$). Finally, at the MCP-joints synovitis was the MRI-feature with the strongest association with joint swelling (OR 6.40, 95%CI 4.0-10.2) (Table S1).

Sensitivity analyses

Analyses were repeated in patients with RA ($n=157$). 22% had ≥ 1 swollen MTP-joint (Figure S3 and S4 [Additional File 1]). Subclinical inflammation was found in 29% of non-swollen MTP-joints, 51% of swollen MTP-joints had no MRI-inflammation. IMB was found in 54% of these swollen joints without MRI-inflammation (Table S2 [Additional File 1]).

We considered that osteitis and in addition flexor tenosynovitis may not be palpable, considering that PE is performed at the dorsal side of the foot. Therefore analyses on concordance and discordance were performed excluding osteitis and flexor tenosynovitis from the definition of MRI-inflammation. This yielded similar results as the main analyses (Figure S5 [Additional File 1]).

Finally, non-swollen joints may be tender as a sign of subclinical MRI-inflammation. Therefore analyses were repeated in joints that were tender, swollen joints were

excluded. Of non-tender joints, 85% were MRI-negative and 17% were MRI-positive. Of tender joints 33% were MRI-positive, 67% MRI-negative (Figure S6 [Additional File 1]). When also considering IMB, tender joints that were unexplained by MRI went from 67% to 43%.

Some characteristics of patients with swollen MTP-joints without MRI-findings

As mentioned, 31% of all swollen joints had no MRI-abnormality, these belonged to 19 patients. We speculated that these patients may have a higher BMI or possibly peripheral edema. The latter was not scored, therefore age was used as a rough proxy. Patients with swollen MTP-joints without MRI-findings had no difference in age or BMI than patients with swollen MTP-joints with MRI-findings (n=54) (age 54.8 versus 55.0 years, BMI 24.8 versus 25.5).

Discussion

The MTP-joints are a known preferential location of involvement in early arthritis. Nonetheless, in RA-outcome measures they are often ignored,(27) as for instance, the Disease Activity Score 28 (DAS28) excludes the feet. This may be due to several reasons, including feasibility, as taking shoes off costs time, but also due to the complexity of elaborate physical examinations.(28) Examination of MTP-joints is considered more challenging and perhaps less reliable.(6). As to the best of our knowledge there are no large studies on the relation between joint swelling and findings on MRI in the MTP-joints, we performed a large cross-sectional study in early arthritis to increase the understanding of the relationship between swelling upon PE with MRI-detected inflammation of the MTP-joints. We found that PE and MRI were mostly in agreement, as most joints were not swollen and had no MRI-detected inflammation. In other words, a negative joint examination largely corresponded to a lack of imaging inflammation. More unexpected, in swollen MTP-joints MRI-detected inflammation was also frequently absent. Thus while the common notion that PE of MTP-joints is difficult is perhaps true, our data revealed that this is not in the direction that most would expect, as our results indicate that PE of MTP-joints is perhaps sometimes too sensitive.

Subclinical inflammation was present in 17% of non-swollen MTP-joints. The relevance of subclinical inflammation of MTP-joints was assessed previously in two studies.(29,30) The first study analyzed hand- and foot-joints together, limiting

Table 2. Association of MRI-detected inflammation with physical joint examination per type of MRI-detected inflammation (synovitis, tenosynovitis, osteitis) and intermetatarsal bursitis for MTP-joints in early arthritis

	Swollen joints n (%)	Non-swollen arthritides n (%)	Univariable OR (95% CI)	Multivariable ¹ OR (95% CI)	Multivariable ² OR (95% CI)
Any MRI-detected inflammation*	74 (48)	281 (17)	4.42 (2.9-6.8)		
Synovitis	52 (34)	200 (12)	3.62 (2.3-5.8)	1.68 (0.8-3.5)	1.30 (0.6-2.6)
Tenosynovitis	49 (32)	140 (9)	4.94 (3.0-8.0)	3.19 (1.6-6.3)	2.21 (1.1-4.3)
Osteitis	31 (20)	117 (7)	3.20 (1.9-5.5)	1.55 (0.8-3.0)	1.5 (0.8-2.7)
Synovitis	52 (34)	200 (12)	3.62 (2.3-5.8)	1.68 (0.8-3.5)	1.30 (0.6-2.6)
Intermetatarsal bursitis	94 (61)	423 (26)	4.48 (2.8-7.1)		2.91 (1.8-4.8)

MRI: magnetic resonance imaging; MTP: metatarsophalangeal joints; n: number; OR: odds ratio, CI: confidence interval. *Defined by the presence of synovitis, tenosynovitis and/or osteitis. ¹Multivariable model including local synovitis, tenosynovitis and osteitis ²Multivariable model including local synovitis, tenosynovitis, osteitis and intermetatarsal bursitis

Table 3. Frequency of intermetatarsal bursitis (IMB) according to status at physical joint examination (PE) and MRI for all 1759 MTP-joints in early arthritis

	MRI+		MRI-	
	IMB+	IMB-	IMB+	IMB-
PE+, n (%)	63 (85)	11 (15)	31 (39)	48 (61)
PE-, n (%)	177 (63)	104 (37)	245 (18)	1080 (82)

PE: physical joint examination; PE+: swollen joints; PE-: non-swollen joints; MRI: magnetic resonance imaging; MRI+: positive for MRI-detected inflammation, defined by the presence of synovitis, tenosynovitis and/or osteitis; MRI-: negative for MRI-detected inflammation; IMB: intermetatarsal bursitis, either present (+) or absent (-).

the conclusions that can be drawn regarding the MTP-joints.(29) The second study found that osteitis but not synovitis of MTP-joints was associated with radiographic progression after 1 year.(30) Tenosynovitis at the MTP-joints was not assessed, its relevance for predicting radiographic progression remains a subject for future studies.

We studied IMB to explore whether it can explain part of the observed absence of MRI-inflammation in swollen MTP-joints. We acknowledge that no validated scoring method exists to score IMB, and scoring was done part of an exploratory analysis. Therefore reading was done by consensus rather than by two independent readers. Consensus reading may be necessary in the setting of preliminary findings, when the verification of the general validity of an initial observation is required,(31) as was the case in this study. However for determining the validity of an outcome-measure it is crucial to demonstrate the reliability of scoring between independent readers.(31,32) Validation of IMB-scoring according to the OMERACT Filter would be valuable.(32) Second, further evaluations on IMB in subsequent studies could include the association with RA, and within RA with long-term outcomes.

Another pathology in the forefoot is Morton's neuroma, this lesion originates from the neurovascular bundle and has no synovial lining. It was not included in this study on the relation with PE as it lies plantar to the deep transverse metatarsal ligament and the metatarsal heads.(15) In addition to its location, Morton's neuroma gives a distinct burning sensation. Therefore we assumed that clinicians would recognize Morton's neuroma as a different entity.

Statistically, joint swelling was independently associated with tenosynovitis and IMB in multivariable analyses, in contrast to synovitis. However tenosynovitis and synovitis often overlap; their collinearity may explain why synovitis was not statistically significant. For the clinician, it may be important to realize that swelling upon PE represents more than just synovitis, but that tenosynovitis and IMB can also be involved.

Surprisingly, 31% of all swollen MTP-joints had no MRI-abnormalities (Figure 3B). The origin of this swelling is speculative, possibly subcutaneous tissues (e.g. fat, peripheral edema) underlie the observed swelling. BMI was not associated but is also an incomplete proxy of fat at the forefeet. The joint swelling was also unlikely a simple measurement error as it was observed by two persons independently. Furthermore, joint evaluation was unlikely influenced by laboratory findings as these were not yet performed at the first visit at the outpatient clinic and GPs are discouraged to perform laboratory investigations according to national guidelines. (33) Notably swollen joints without MRI-detected abnormalities occurred more often at MTP-joints than MCP-joints, despite similar methodology of performing PE and similar scan protocols. All taken into consideration, we cannot explain the pathology underlying swollen MTP-joints without MRI-abnormality. The clinical relevance of this finding is unclear, and needs to be determined in longitudinal studies. Specifically, if long-term outcomes are different between swollen joints with and without MRI-abnormalities.

An important limitation of this study is the reproducibility of PE. Determination of joint swelling is notoriously difficult and poorly reproducible.(6,34) Variation between readers can be reduced by regular consensus exercises for swollen joint assessment,(35) such sessions were regularly held at our department. To further reduce reader-dependency we applied a stringent definition for a swollen joint, as it had to be observed by two assessors that independently evaluated the patient the same day. This increased the certainty of the presence of the feature, by reducing the chance of 'overscoring' any doubtfully swollen MTP-joint.

Deliberately, MTP1 was not included as it is also a predilection site for disease other than early arthritis, e.g. osteoarthritis and gout. As these degenerative diseases can also give MRI-detected inflammation that is not necessarily related to arthritis, MTP1 was excluded as it could hamper the comparison between findings on PE and MRI.

Disease activity is assessed by composite indices, like the DAS.(36) However for many treating physicians, the presence of swollen joints may carry substantial weight, regardless of whether a patient is in DAS remission. MRI-detected inflammation is associated with radiographic progression,(29) and the assumption is that MRI-detected inflammation underlies joint-swelling. The question rises whether swelling without underlying MRI-inflammation is clinically relevant, i.e. whether it leads to radiographic progression. Longitudinal studies are needed to determine the clinical relevance of MTP-swelling without inflammation, for instance by comparing radiographic progression of swollen MTP-joints with and without MRI-detected inflammation.

Conclusion

This is the largest study to date to compare PE with MRI in consecutively presenting early arthritis patients. A negative PE of the MTP-joints is reassuring, as MRI-detected subclinical inflammation is most often absent. Joint swelling of MTP-joints is traditionally interpreted as synovitis; we showed that pathologies underlying joint swelling at this location also include tenosynovitis and IMB, finally MTP-swelling remained unexplained by MRI in part of the joints. Validation studies are warranted. Subsequently longitudinal studies are required to determine the clinical relevance of joint swelling without underlying MRI-detected inflammation.

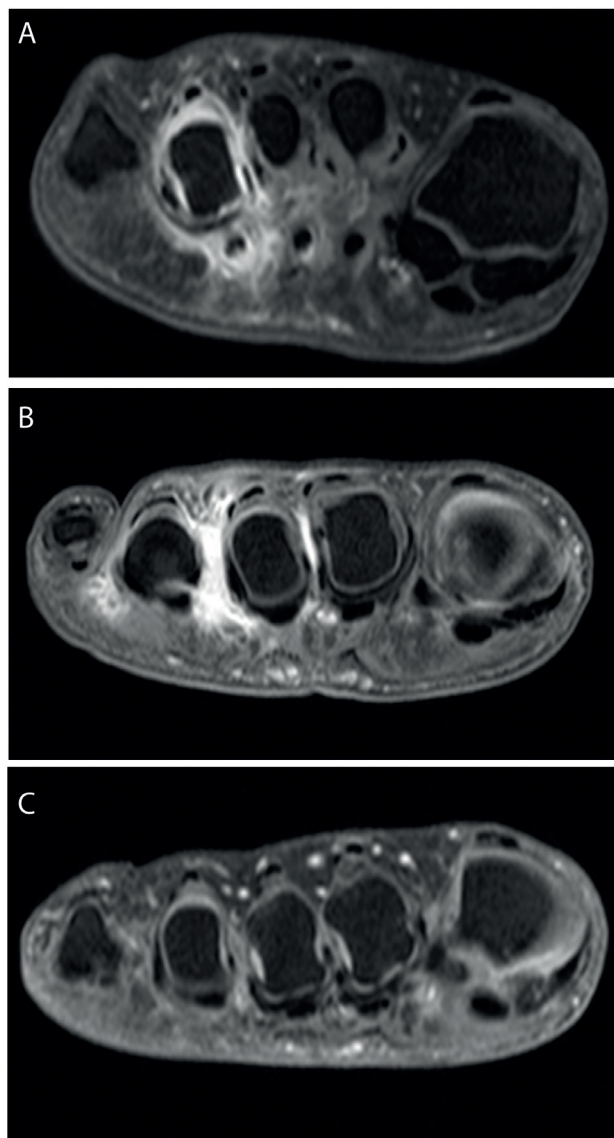


Figure 3. MRI-examples of MTP-joints that are swollen upon physical joint examination (PE) with MRI-detected inflammation (A), with intermetatarsal bursitis (B) and without any signs on MRI (C). A) Patient with a swollen MTP 4 upon PE and with MRI-detected synovitis and tenosynovitis at the same joint. B) Patient with swollen MTP 3 and 4, there is no MRI-detected synovitis, tenosynovitis or osteitis, there is intermetatarsal bursitis at the 2nd, 3rd and 4th intermetatarsal spaces. C) Patient with swollen MTP 2, 3 and 4 upon PE but no MRI-detected inflammation or intermetatarsal bursitis on MRI

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Supplementary data

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

Supplementary Table S1. Association of MRI-detected inflammation with physical joint examination per type of MRI-detected lesion (synovitis, tenosynovitis and osteitis) for MCP-joints

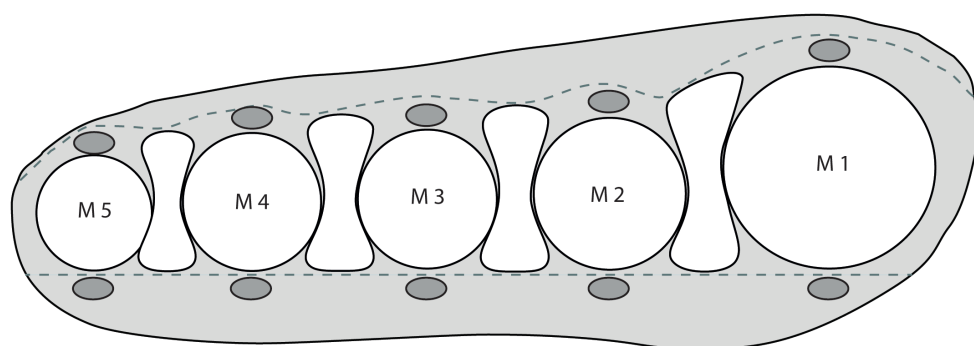
	Swollen joints	Non-swollen joints	Univariable	Multivariable ¹
	n (%)	n (%)	OR (95% CI)	OR (95% CI)
Any MRI-detected inflammation*	199 (88)	516 (34)	14.40 (9.2-22.6)	
Synovitis	184 (81)	395 (26)	12.50 (9.6-18.2)	6.40 (4.0-10.2)
Tenosynovitis	152 (67)	331 (22)	7.40 (5.3-10.4)	2.56 (1.7-3.9)
Osteitis	53 (24)	72 (5)	6.19 (4.1-9.4)	2.81 (1.8-4.3)

MRI: magnetic resonance imaging; MCP: metacarpophalangeal joints; n: number; OR: odds ratio, CI: confidence interval. *Defined by the presence of synovitis, tenosynovitis and/or osteitis. ¹Multivariable model including local synovitis, tenosynovitis and osteitis.

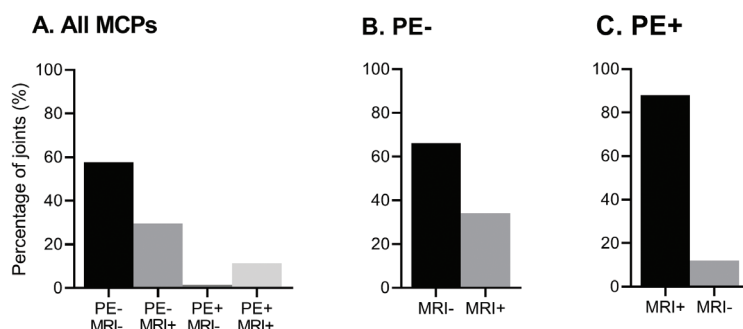
Supplementary Table S2. Frequency of intermetatarsal bursitis (IMB) according to status at physical joint examination (PE) and MRI in MTP-joints in 157 RA-patients

	MRI+		MRI-	
	IMB+	IMB-	IMB+	IMB-
PE +, n (%)	37 (93)	3 (8)	22 (54)	19 (46)
PE -, n (%)	113 (72)	44 (28)	138 (36)	249 (64)

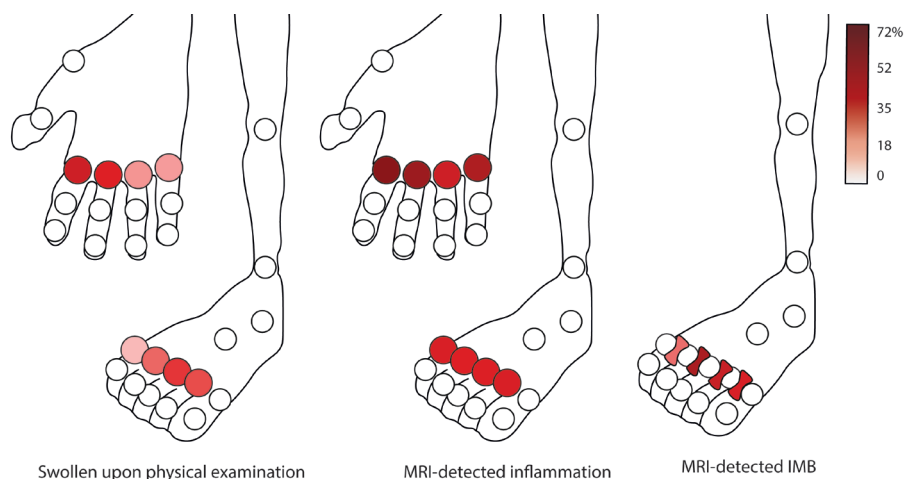
PE: physical joint examination: PE+: swollen joints; PE-: non-swollen joints; MRI: magnetic resonance imaging; MRI+: positive for MRI-detected inflammation, defined by the presence of synovitis, tenosynovitis and/or osteitis; MRI-: negative for MRI-detected inflammation; IMB: intermetatarsal bursitis, either present (+) or absent (-).



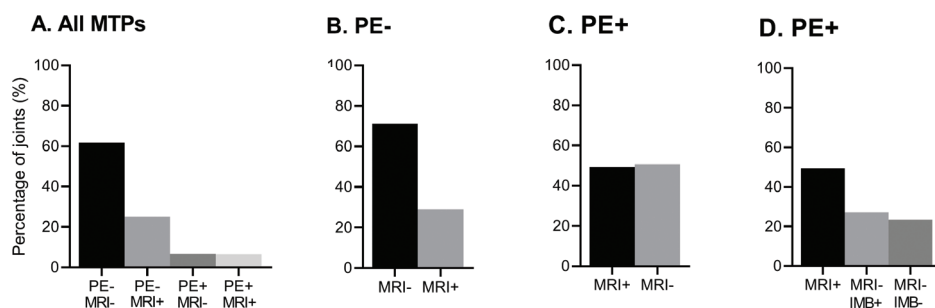
Supplementary Figure S1. Schematic illustration with coronal view of the forefoot at the metatarsal heads (M1-5) with intermetatarsal bursae in between. The intermetatarsal bursae are located between the metatarsal heads (M1-5). They are bound dorsally by the dorsal aponeurosis (dashed line dorsal of bursae) and plantarly by the deep transverse metatarsal ligament (dashed line plantar of bursae). Grey ovals represent the extensor and flexor tendons.



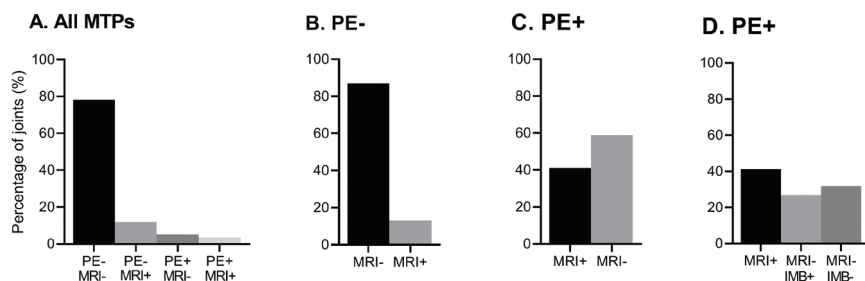
Supplementary Figure S2. Concordance and discordance between clinical joint swelling at PE and findings at MRI, for all 1750 MCP-joints (A) and for non-swollen (B) and swollen MCP-joints (C) separately. MCP: metacarpophalangeal joints; PE: physical joint examination; MRI: magnetic resonance imaging; MRI-: absence of MRI-detected inflammation defined as synovitis, tenosynovitis and osteitis; MRI+: absence of MRI-detected inflammation. The percentage of joints in each group are illustrated in the figure, the number of joint per group are as follows; PE-MRI- are n=1008 joints, PE-MRI+ n=516, PE+MRI- n=27 and PE+MRI+ n=199 joints.



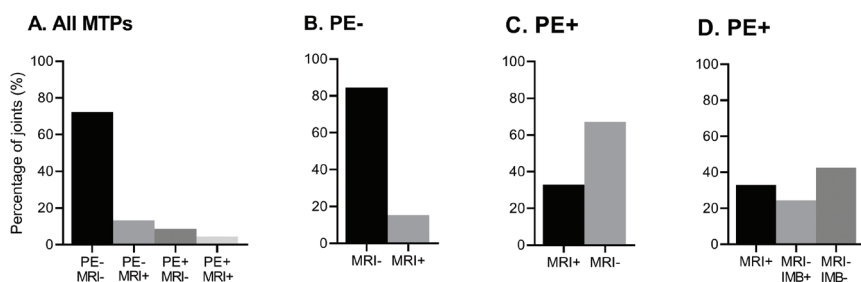
Supplementary Figure S3. Frequency of a swollen joint upon physical examination, MRI-detected inflammation and intermetatarsal bursitis (IMB) per location for MTP(2-5)- and MCP(2-5)-joints in 157 RA patients. RA was defined according to the clinical diagnosis and fulfilling the 2010 criteria during the first year of follow-up



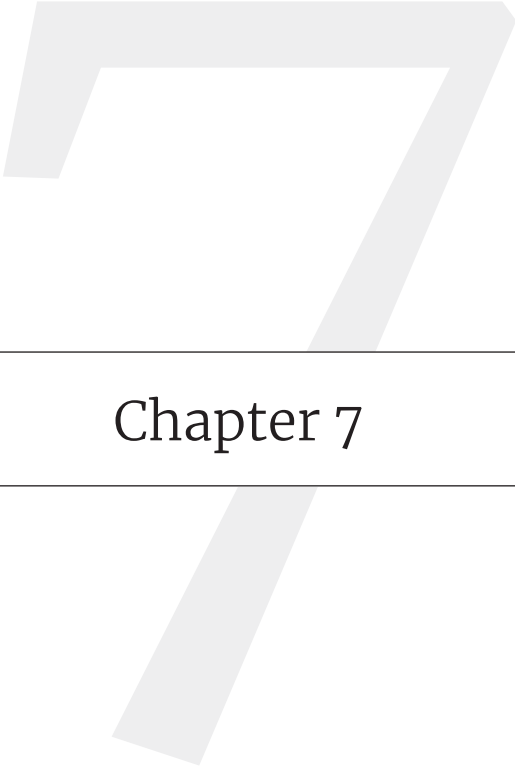
Supplementary Figure S4. Concordance and discordance between clinical joint swelling at PE and findings at MRI, for all 625 MTP-joints (A) and for non-swollen (B) and swollen MTP-joints (C, D) separately in 157 RA-patients. MTP: metatarsophalangeal joints; PE: physical joint examination; PE-: not swollen; PE+: swollen; MRI: magnetic resonance imaging; MRI-: absence of MRI-detected inflammation defined as synovitis, tenosynovitis and osteitis; MRI+: absence of MRI-detected inflammation; IMB: intermetatarsal bursitis, either present (+) or absent (-). RA was defined according to the clinical diagnosis and fulfilling the 2010 criteria during the first year of follow-up.



Supplementary Figure S5. Concordance and discordance between clinical joint swelling at PE and findings at MRI, for all 1759 MTP-joints (A) and for non-swollen (B) and swollen MTP-joints (C, D) separately when flexor tenosynovitis and osteitis were not included in definition of MRI-inflammation. MTP: metatarsophalangeal joints; PE: physical joint examination; PE-: not swollen; PE+: swollen; MRI: magnetic resonance imaging; MRI-: absence of MRI-detected inflammation defined as synovitis and/or extensor tenosynovitis; MRI+: absence of MRI-detected inflammation; IMB: intermetatarsal bursitis, either present (+) or absent (-).



Supplementary Figure S6. Concordance and discordance between joint tenderness at PE and findings at MRI, excluding swollen joints, given for all MTP-joints (A) and for non-tender (B) and tender MTP-joints separately (C, D). PE+ defined as tender upon physical joint examination. Swollen joints (n= 153) were excluded from this analysis. Tender joints were evaluated by one assessor.



Chapter 7

*Walking disabilities are associated with
tenosynovitis at the metatarsophalangeal joints:
A longitudinal MRI-study in early arthritis*

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Abstract

Objectives: The relationship between functional disability and MRI-inflammation has been studied for the hands, but has not been well established for the feet, even though walking-difficulties are common. Therefore we studied whether walking-difficulties were associated with MRI-inflammation at metatarsophalangeal(MTP)-joints in early arthritis patients, at diagnosis and during 24-months follow-up.

Methods: 532 consecutive patients presenting with early arthritis reported on presence and severity of walking-difficulties (HAQ-question 4a, scale 0-3), and underwent unilateral contrast-enhanced MRI of MTP(1-5)-joints at baseline. 107 patients had clinical and MRI-data at follow-up (4-, 12- and 24-months). MRI-inflammation (synovitis, tenosynovitis and osteitis) was scored in line with RAMRIS. At baseline the association of walking-disability with MRI-inflammation was assessed using regression. Longitudinally the association between a change in walking-disability with a change in MRI-inflammation was studied with linear mixed models.

Results: At baseline, 81% patients with walking-disabilities had MRI-inflammation at MTP-joints, versus 68% without walking-disabilities ($P<0.001$). Total MRI-inflammation (i.e. the sum of tenosynovitis, synovitis and osteitis) was associated with severity of walking disability ($P=0.023$, $P<0.001$). Studying the MRI-features separately, tenosynovitis, synovitis and osteitis were all univariable associated with severity of walking-disability ($P<0.001$, $P<0.001$ and $P=0.014$ respectively). Multivariable, the association was strongest for tenosynovitis. During follow-up a decrease in MTP-inflammation was associated with a decrease in walking-disability ($P=0.029$, $P=0.001$): in multivariable analyses only tenosynovitis was independently associated ($P=0.073$, $P=0.049$).

Conclusion: Of the different inflamed tissues in MTP-joints, predominantly MRI-detected tenosynovitis was associated with walking-disabilities. Likewise a reduction in tenosynovitis related to a decrease in walking-disabilities. This increases our understanding of the involvement of tenosynovitis in walking-disabilities in early arthritis.

Introduction

Rheumatoid arthritis (RA) is a disease that involves the small joints of the hands and feet. The focus in research, however, has primarily been on the hands,(1) though 80% of patients report disease-related foot-problems and 71% report walking-difficulties.(2) These difficulties have an important impact on the quality of life of patients that are often underestimated by clinicians,(3) and are associated with clinical factors such as inflammation, pain and duration of disease.(2,3)

Magnetic resonance imaging (MRI) is increasingly used in RA-research, as it sensitively detects inflammation, defined as tenosynovitis, synovitis and osteitis. The association between walking-difficulties and MRI-inflammation has not been fully explored for the forefoot. Two previous reports have included MRI-data of the metatarsophalangeal(MTP)-joints, however these were not contrast-enhanced, and tenosynovitis at the MTP-joints was not included.(4,5) Additionally, they were cross-sectional and thus did not study whether change in MRI-inflammation over time related to change in disability.

Therefore, with the aim to increase our understanding of the role of inflammation at the MTP-joints in functional disability, we set up a cross-sectional and longitudinal study in early arthritis patients to evaluate the association of walking-disabilities with MRI-inflammation, defined as tenosynovitis, synovitis and osteitis at the MTP-joints.

Patients and methods

Patients

Between June 2013 and July 2017, 604 consecutive patients newly presenting with clinical confirmed arthritis of ≥ 1 joint and a symptom duration < 2 years who were naïve to DMARDs were included in the Leiden Early Arthritis Cohort (EAC). The cohort is extensively described elsewhere.(6) In short, at baseline, 4-months, 12-months and yearly thereafter information was obtained from physical examination, laboratory tests, questionnaires including the Health Assessment Questionnaire (HAQ), and MRI. Included patients were treated in routine care.

Of 604 patients at baseline, 65 had missing HAQ-data and 7 had insufficient MRI-images. The remaining 532 were studied. A flowchart is presented in Supplement 1.

From August 2010 until February 2015, follow-up MRIs were performed in patients with the initial diagnosis of RA or undifferentiated arthritis (UA). From the 532 with complete baseline MRI and HAQ-data, follow-up MRI was available for 107 patients (Supplement 2).

The EAC was approved by the local medical ethics committee (approval number P10.108). Informed consent was obtained.

Assessment of walking disability

The HAQ is a well-validated, widely utilized questionnaire on functional disability that consists of 20 questions that cover different categories of functional activities,⁽⁴⁾ including two questions on walking: Question-4a: “are you able to walk outdoors on flat ground?” and question-4b: “are you able to climb up 5 steps?” They are answered as follows: 0=no difficulty, 1=some difficulty, 2=much difficulty, 3=unable to do. Question-4a was used as the primary measure of walking disability as walking outdoors on flat ground was assumed to importantly involve forefoot-mechanics. Question-4b was used as an alternative measure in a sub analysis, as climbing stairs was assumed to not only assess forefoot-, but also other joints such as ankle- and knee-mechanics. Data on walking-disability was available at baseline, 12 and 24 months. The HAQ also evaluates equipment-dependency, like walking-sticks. Equipment-dependency can be the result of disability in different domains, such as the knee or hip. To avoid the introduction of noise, equipment-dependency was therefore not incorporated in the analyses, although excluding this from the evaluation can potentially lead to an underestimation of the severity of walking-disability.

MRI

Unilateral contrast-enhanced MRI of the MTP(1-5)-joints of the more painful side, or the dominant side in case of symmetric symptoms, was performed with a 1.5T extremity MRI (General Electric, WI, USA). Baseline MRI was obtained ≤ 2 weeks after first presentation and before DMARD-initiation, follow-up MRI at 4, 12 and 24 months. MRIs were scored for tenosynovitis, synovitis, osteitis and erosions at MTP 1-5 in line with the RAMRIS, blinded from any clinical data, a detailed description is given in Supplement 3.⁽⁷⁻⁹⁾ Total MRI-inflammation was defined as the total sum of the semiquantitative scores of tenosynovitis (0-30), synovitis (0-15) and osteitis (0-30) at MTP-joints. Follow-up MRI was scored in known time-order. Reliability of scoring was excellent ($\text{ICC} \geq 0.92$). Additional information is given in Supplement 3&4.

Table 1. Association between MRI-detected inflammation at the MTP-joints and walking-disability at disease presentation in 532 early arthritis patients

Severity of walking-disability ^a	MRI-score, mean (SD) ^b			
	Univariable analyses			
	Disability +	Disability -	P (95% CI)	P-value
Total inflammation score ^c	4.6 (6.3)	2.7 (4.1)	0.023 (0.01-0.03)	<0.001
Tenosynovitis score	1.3 (2.2)	0.7 (1.4)	0.064 (0.03-0.1)	<0.001
Synovitis score	1.6 (2.1)	1.0 (1.5)	0.063 (0.03-0.1)	<0.001
Osteitis score	1.7 (3.2)	1.1 (2.1)	0.029 (0.02-0.05)	0.014
Erosion score	0.7 (1.1)	0.6 (0.9)	0.043 (-0.02-0.1)	0.18
Multivariable analysis: MRI features ^d				
Multivariable analyses: clinical features ^e				
	P (95% CI)	P-value	P (95% CI)	P-value
Total inflammation score ^c			0.015 (0.00-0.03)	0.014
Tenosynovitis score	0.042 (-0.02-0.09)	0.06	0.036 (0.00-0.07)	0.042
Synovitis score	0.026 (-0.02-0.08)	0.27		
Osteitis score	0.007 (-0.02-0.04)	0.66		
Presence of walking-disability ^f				
MRI-feature present: n (%) ^g				
Univariable analyses				
	Disability +	Disability -	OR (95% CI)	P-value
Total inflammation score ^c			1.06 (1.02-1.10)	0.005
Tenosynovitis score	1.15 (1.003-1.31)	0.045	1.15 (1.03-1.28)	0.017
Synovitis score	1.09 (0.93-1.27)	0.29		
Osteitis score	1.03 (0.94-1.12)	0.57		

^a Assessed using linear regression. ^b Mean score of MRI-feature in patients with walking disability (defined as HAQ 4a=0). ^c Total inflammation score is defined as the summed scores of tenosynovitis, synovitis and osteitis. ^d Multivariable analyses including MRI-detected tenosynovitis, synovitis and osteitis at the MTP-joints. ^e Multivariable analyses including swollen joint count, age at inclusion and CRP, performed separately for the total inflammation score and for tenosynovitis. Due to the risk of overfitting this multivariable analyses only included variables that were most importantly associated with walking-disability. ^f Dichotomous outcome, association assessed using logistic regression. ^g Presence of an MRI-feature in patients with (HAQ 4a=1) and patients without walking disability (HAQ 4a=0). SD: standard deviation; CI: confidence interval; OR: odds ratio

Statistical analysis

At baseline the association between walking-difficulties and total MRI-inflammation was assessed using linear regression with severity of walking-disability as outcome. Although erosions were expected to be infrequent at the time of diagnosis, they were also studied in relation to walking-disability. Next the association of tenosynovitis, synovitis and osteitis was assessed separately. Univariable and multivariable analyses were performed: multivariable analyses adjusted for the simultaneous presence of different types of MRI-inflammation, because these three features often co-occur, and in a separate analysis for the following clinical features: age, 66-swollen joint count (SJC) and CRP as they may associate with walking-disability and MRI-inflammation and to elucidate whether MRI-inflammation is associated with walking-disability regardless of the level of systemic and local inflammation (CRP and SJC respectively).(6,10). The analyses were repeated for the presence of walking-disability as a dichotomous outcome using logistic regression.

To assess whether a change in the severity of walking-disability was associated with a change in MRI-inflammation, linear mixed models (LMM) were used. First, the association was studied for total MRI-inflammation with walking-disability as the outcome. Subsequently, tenosynovitis, synovitis and osteitis were assessed separately. Also here analyses were performed univariable and multivariable, adjusting for the simultaneous presence of different types of MRI-inflammation, and for clinical features. LMM has the advantage that all patient-information, including those who had missing data, is used, as it assumes that missing outcomes can be estimated using available measurements.

RA-patients may have more severe inflammation, potentially influencing the relationship between walking-difficulties and MRI-inflammation. Therefore as a sub analyses, the analyses between walking-difficulties and MRI-inflammation at baseline and during follow-up were repeated in the subgroup of RA-patients (clinical diagnosis and fulfilment of 1987- or 2010-criteria at 2 weeks).

We prioritized walking-difficulties in the main analyses. As a sub analyses we analyzed whether MRI-inflammation at MTP-joints could possibly also be related to difficulty climbing stairs. Therefore analyses were repeated with difficulty climbing stairs as the outcome.

Results

Patient characteristics

Of 532 patients with baseline-data, mean age was 58 years, 60% was female and mean symptom duration was 10 weeks. Walking-disability was present in 202 patients (38%). This was comparable in the subgroup of patients that was studied longitudinally. Patient characteristics are presented in Supplement 2.

Walking-disability and MRI-detected inflammation at baseline

Mean MRI-scores and the results from regression analyses are presented in Table 1. At baseline, more severe walking-disabilities were associated with more severe total MRI-inflammation ($P=0.023$, $P<0.001$). The severity of walking-disability was associated with tenosynovitis, synovitis and osteitis scores in univariable analyses ($P<0.001$, $P<0.001$ and $P=0.014$ respectively). In a multivariable analyses that included all three features, the effect size was largest for tenosynovitis ($P=0.042$, $P=0.060$). In a separate multivariable analyses the results for total MRI-inflammation and tenosynovitis were adjusted for clinical features (age, SJC and CRP): MRI-inflammation and tenosynovitis remained associated with walking-disability ($P=0.014$ and $P=0.005$ respectively). Walking-disability was not associated with erosion scores ($P=0.18$). In additional multivariable analyses the results for total MRI-inflammation and tenosynovitis were adjusted for clinical features and MRI-detected erosions that revealed similar results ($P=0.014$, $P=0.026$ for MRI-inflammation and $P=0.035$, $P=0.047$ for tenosynovitis, results not shown in table).

Next the association of the three inflammatory features was studied with the presence of walking-disability as a dichotomous outcome. This revealed similar results (Table 1).

Course of walking-disability and MRI-inflammation during 2 years of follow-up

Then we assessed whether a change in severity of walking-disability was associated with a change in MRI-inflammation during 2-years follow-up, presented in Figure 1 and Supplement 5. A decrease in total MRI-inflammation was associated with a decrease in walking disability ($P=0.022$, $P=0.019$). For the separate features a decrease in tenosynovitis and synovitis was associated with a decrease in walking disability ($P=0.001$ and $P=0.002$, respectively in univariable analyses), osteitis was not statistically significant ($P=0.058$). The association for tenosynovitis remained

in multivariable analysis adjusted for synovitis and osteitis ($P=0.073$, $P=0.049$), and when adjusted for clinical features ($P=0.091$, $P=0.002$). The analyses were repeated adjusted for baseline values, this revealed similar results (for MRI-inflammation ($P=0.024$, $P=0.014$) and for tenosynovitis ($P=0.069$, $P=0.034$)).

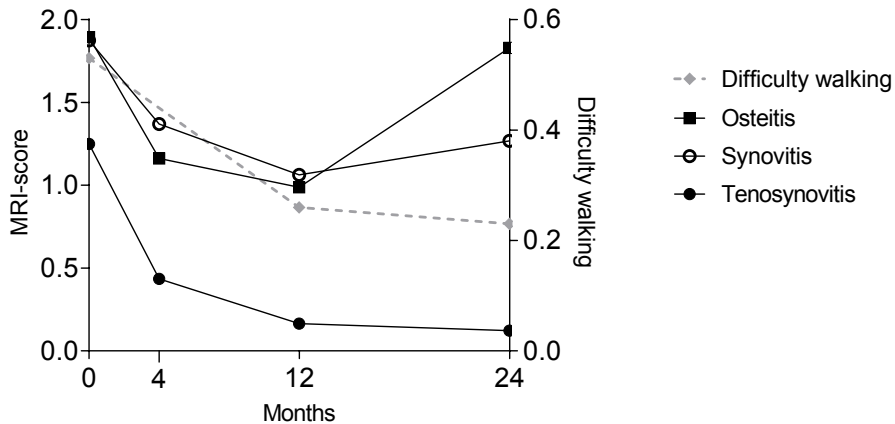


Figure 1. Difficulty walking and MRI-scores (both mean) for osteitis, synovitis and tenosynovitis during 24 months of follow-up. Difficulty walking was assessed by the Health Assessment Questionnaire (HAQ) question 4a: are you able to walk outdoors on flat ground? Patients answered on a scale from 0-3: 0= without difficulty, 1= with some difficulty, 2= with much difficulty, 3= unable to do. In univariable analyses a decrease in tenosynovitis and synovitis were associated with a decrease in walking disability ($P=0.001$ and $P=0.002$, respectively, see also Supplement 5). In multivariable analyses that included osteitis, synovitis and tenosynovitis, only the association for tenosynovitis remained ($P=0.073$, $P=0.049$). Follow-up MRI-data was available as follows: 107, 100, 80 and 41 patients at baseline, 4, 12 and 24 months respectively. Data on walking-difficulty was available for 107, 78 and 70 patients at baseline, 12 and 24 months respectively. The increase in osteitis score at 24 months is caused by missing data from patients with resolution of symptoms who were lost to follow-up at 24 months, while patients with more severe disease kept coming for follow-up (see also Supplement 10)

Sub analysis in RA-patients

As a sub analyses the association between walking-difficulties and MRI-inflammation at baseline was assessed in the subgroup of RA-patients ($n=192$), as RA-patients may have more severe inflammation that may influence the relationship between walking-difficulties and MRI-inflammation (Supplement 6). Indeed, walking-difficulties were more frequently present (46% vs. 38% of patients, presented in Supplement 2) and the total MRI-inflammation score was higher in RA-patients than in early arthritis patients with walking-disabilities (6.4 vs. 4.6, presented in Supplement 6). Similar results were observed as in the main analyses: multivariable the association only remained for tenosynovitis ($P=0.078$, $P=0.004$).

The effect of tenosynovitis remained when adjusted for clinical features ($P=0.054$, $P=0.015$).

Next we assessed whether a decrease in walking-difficulties was associated with a decrease in MRI-inflammation in the subgroup of RA-patients ($n=72$)(Supplement 7-8): this revealed similar results, multivariable the association only remained for tenosynovitis ($P=0.097$, $P=0.021$). The effect of tenosynovitis remained when adjusted for clinical features ($P=0.12$, $P<0.001$).

Sub analysis for difficulty climbing stairs and MRI-inflammation

Finally, the analyses at baseline were repeated with difficulty climbing stairs (HAQ4b) as the outcome (Supplement 9). Also here, the severity of walking-disability was associated with total MRI-inflammation score ($P=0.023$, $P<0.001$). In multivariable analysis with all three inflammatory features the effect was strongest for tenosynovitis ($P=0.045$, $P=0.045$).

Discussion

Walking disabilities were frequent, in our study 38% of early arthritis patients and 46% of RA-patients reported to have difficulties with walking. We aimed to increase our understanding of the role of inflammation at the MTP-joints in this disability, and observed that the severity of inflammation at MTP-joints as detected with MRI was associated with walking-disabilities at diagnosis. Interestingly, although univariable analyses revealed that synovitis, tenosynovitis and osteitis were associated with walking difficulties, and synovitis and tenosynovitis often co-occur (risk of collinearity in multivariable analyses), in multivariable analyses including the different inflammatory lesions tenosynovitis had the strongest association. This suggests that tenosynovitis does not only give walking difficulties because it co-occurs with synovitis, but that it also by itself can lead to walking difficulties in patients with early arthritis. The association of tenosynovitis with walking disability was also independent of regular measures of local and systemic inflammation (SJC, CRP). Finally, serial MRIs revealed that a decrease of MRI-inflammation was associated with a reduction in walking-disabilities and that also here the association was strongest for tenosynovitis. These results suggest that tenosynovitis at the level of MTP-joints importantly contributes to physical impairments.

These results add to the increasing evidence on the importance of tenosynovitis in early RA.(11) Most of this research, however, has focused on the hands,(1,4) also

regarding disability: In the hands tenosynovitis also had the strongest association. A recent study showed that of the three inflammatory MRI-features at the MTP-joints, tenosynovitis had the strongest association with early RA.(12) In this report tenosynovitis at both flexor and extensor tendons was associated with RA, and occurred in 31% and 28% of RA-patients respectively, of which the most common site was extensor tenosynovitis of MTP-1 that occurred in 20% of RA-patients. This is the first report to study MTP-tenosynovitis in respect to functional disability.

To the best of our knowledge no longitudinal studies on walking-disability in relation to imaging-detected inflammation exist in early disease. Previous studies have reported on the occurrence of walking-disabilities in established RA, where walking-disability remained moderate to severe during follow-up.(13) We have found a decrease in walking-disability from the moment of diagnosis until two years of follow-up. This decrease after diagnosis is most likely the result of treatment-initiation. Nonetheless after having observed that the severity of walking-disabilities is associated with the severity of tenosynovitis, it is confirmative to see that improvement in walking is associated with a reduction in tenosynovitis.

A limitation is that the HAQ is validated for integral use and not for the individual questions. Validated questionnaires that specifically study foot-related disability exist, like the Leeds Foot Impairment Score that more specifically studies impairment and activity limitation.(14) The relationship of imaging-detected MTP-inflammation in these different aspects of foot-disability would certainly be interesting and is a subject for further research.

MTP-1 is a predilection site for degenerative disease, and it is possible that part of the inflammation (synovitis, osteitis) at high age in MTP-1 is related to osteoarthritis. However it has also been reported that tenosynovitis at MTP-1 is RA-specific, and that involvement of MTP-1 is especially specific for RA in younger patients.(12,15) We therefore did not exclude MTP-1 from our analyses. Although radiographic information on osteoarthritis of MTP-1 was not systematically available, we did adjust for age in our analyses as osteoarthritis is mostly age-related.

Walking disabilities in established RA can be due to inflammation but also due to damage and joint deformity. We studied patients at first presentation to the outpatient clinic and found no relation between erosions and walking-disabilities. This is not surprising, as the prevalence of erosions, and thus the contribution to functional impairment, is low at disease onset.

Additionally to the studied MRI-features, interestingly, in the forefoot synovium-lined intermetatarsal bursae are present that can clearly be differentiated from tenosynovitis, synovitis and osteitis as they have no anatomical connection with MTP-joints and are surrounded bilaterally by the interosseous tendons.(16) Inflammation of these bursae, referred to as intermetatarsal bursitis, relates to clinical joint-swelling,(17) and may predict the development of foot-impairment in RA-patients.(13) How it relates to tenosynovitis, synovitis and osteitis in respect to disability is unknown.

In conclusion, in patients with arthritis we traditionally consider synovitis to be the cause of disability. We have illustrated that, additionally, tenosynovitis at the MTP-joints is an important feature that needs to be considered. Appreciating this role of tenosynovitis increases our understanding of walking-disabilities in patients with early arthritis, and of functional disability in RA-patients.

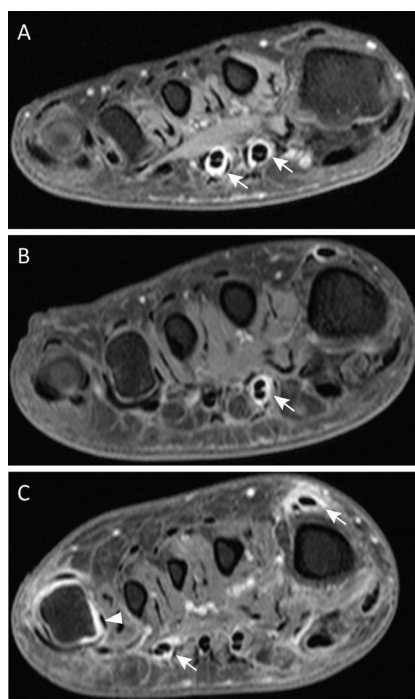


Figure 2. Examples of MRI-detected tenosynovitis (arrows) in the coronal plane. (A) Tenosynovitis of the common flexor digitorum at the 2nd and 3rd metatarsophalangeal (MTP)-joint, (B) tenosynovitis of the common flexor digitorum at the 2nd MTP-joint, and (C) tenosynovitis of the extensor hallucis longus and common flexor digitorum of the 4th MTP-joint with synovitis of MTP-5 (arrowhead)

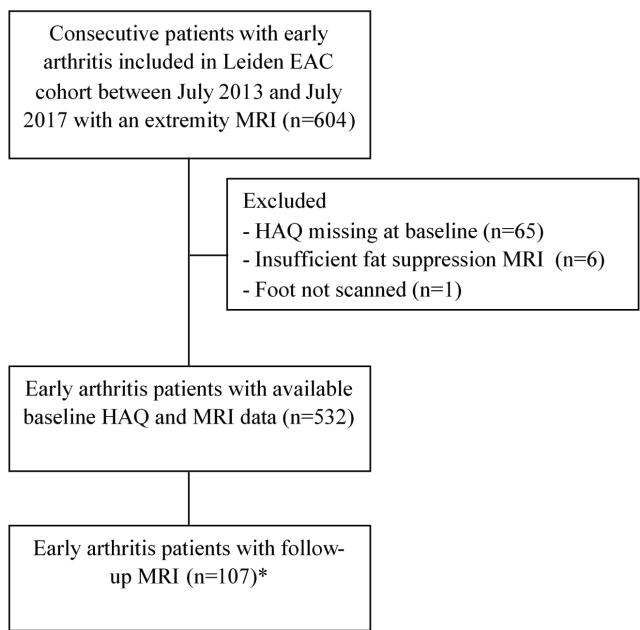
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Supplementary data

Supplementary methods are available at *Arthritis Care & Research* online.



Supplement 1. Supplementary Figure. Flowchart of patient selection *Patients with an initial clinical diagnosis of RA or UA included between August 2010 and February 2015 were eligible for repeated MRIs. Follow-up MRI-data was available as follows: 107, 100, 80 and 41 patients at baseline, 4, 12 and 24 months respectively. Data on walking-difficulty was available for 107, 78 and 70 patients at baseline, 12 and 24 months respectively. The baseline characteristics of patients with an initial clinical diagnosis of RA or UA with and without repeated MRI are presented Supplement 2.

Supplement 5. Association between MRI-detected inflammation at the MTP-joints and difficulty walking during 24 months of follow up

	Univariable analyses		Multivariable analysis: MRI features ^a		Multivariable analysis: clinical features ^b	
	P (95% CI)	P-value	P (95% CI)	P-value	P (95% CI)	P-value
Total inflammation score ^c	0.022 (0.004-0.402)	0.019			0.020 (0.001-0.038)	0.035
Tenosynovitis score	0.100 (0.042-0.158)	0.001	0.073 (0.00-0.126)	0.049	0.091 (0.034-0.15)	0.002
Synovitis score	0.076 (0.028-0.124)	0.002	0.034 (-0.037-0.105)	0.35		
Osteitis score	0.030 (-0.001-0.06)	0.058	0.008 (-0.028-0.045)	0.65		
Erosion score	-0.057 (-0.133-0.019)	0.14				

^a Multivariable analyses including MRI-detected tenosynovitis, synovitis and osteitis at the MTP-joints. ^b Multivariable analyses including swollen joint count, age at inclusion and CRP, performed separately for the total inflammation score and for tenosynovitis.

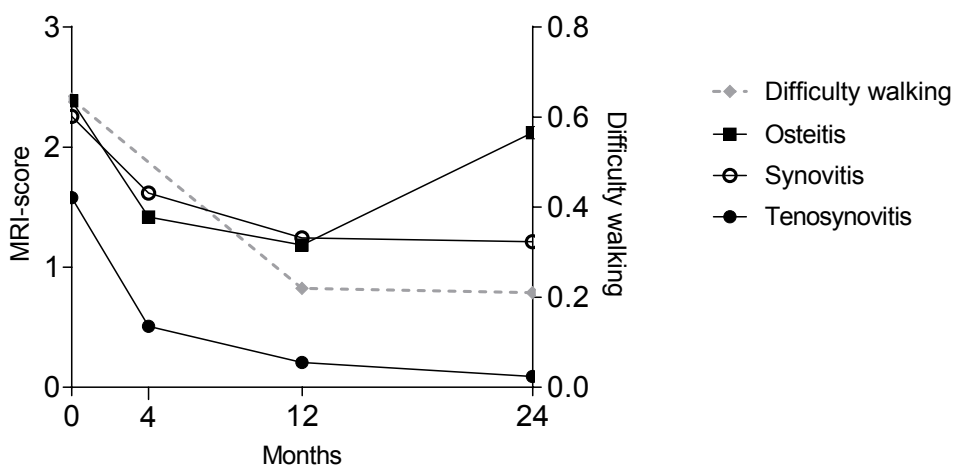
^c Total inflammation score is defined as the summed scores of tenosynovitis, synovitis and osteitis

Supplement 6. Association between MRI-detected inflammation at the MTP-joints and walking- disability at disease presentation in 192 RA-patients

	MRI-score, mean (SD)		Univariable analyses		Multivariable analysis: MRI features ^a		Multivariable analysis: clinical features ^b	
	Disability+	Disability-	P (95% CI)	P-value	P (95% CI)	P-value	P (95% CI)	P-value
Total inflammation score ^c	6.4 (6.8)	4.4 (5.3)	0.019 (0.003-0.035)	0.019			0.017 (0.000-0.033)	0.048
Tenosynovitis score	2.1 (2.8)	1.1 (1.7)	0.068 (0.026-0.110)	0.002	0.078 (0.025-0.132)	0.004	0.054 (0.010-0.098)	0.015
Synovitis score	2.1 (2.4)	1.6 (1.9)	0.037 (-0.009-0.082)	0.118	-0.028 (-0.096-0.040)	0.419		
Osteitis score	2.2 (3.4)	1.7 (3.0)	0.019 (-0.012-0.050)	0.239	0.015 (-0.023-0.053)	0.432		
Erosion score	0.7 (1.3)	0.7 (0.8)	0.014 (-0.078-0.106)	0.76				

^a Multivariable analyses including MRI-detected tenosynovitis, synovitis and osteitis at the MTP-joints. ^b Multivariable analyses including swollen joint count, age at inclusion and CRP, performed separately for the total inflammation score and for tenosynovitis.

^c Total inflammation score is defined as the summed scores of tenosynovitis, synovitis and osteitis.



Supplement 7. Supplementary Figure. Difficulty walking and mean MRI-scores for osteitis, synovitis and tenosynovitis during 24 months of follow-up in 72 patients with early RA. Difficulty walking was assessed by the Health Assessment Questionnaire (HAQ) question 4a: are you able to walk outdoors on flat ground? Patients answer on a scale from 0-3: 0= without difficulty, 1= with some difficulty, 2= with much difficulty, 3= unable to do. Of all MRI-features, in a multivariable analysis that included tenosynovitis, synovitis and osteitis, only a decrease in tenosynovitis was independently associated with a decrease in difficulty walking ($P=0.097$, $P=0.021$). RA was defined according to a clinical diagnosis at 2 weeks plus fulfilment of the 1987 or 2010 criteria.

Supplement 8. Association between MRI-detected inflammation at the MTP-joints and difficulty walking during 24 months of follow up in 72 patients with early RA

	Univariable analyses		Multivariable analysis: MRI features ^a		Multivariable analysis: clinical features ^b	
	P (95% CI)	P-value	P (95% CI)	P-value	P (95% CI)	P-value
Total inflammation score ^c	0.032 (0.01-0.05)	0.002			0.034 (0.014-0.054)	0.001
Tenosynovitis score	0.125 (0.06-0.19)	<0.001	0.097 (0.02-0.18)	0.021	0.12 (0.056-0.186)	<0.001
Synovitis score	0.089 (0.03-0.15)	0.002	0.043 (-0.04-0.13)	0.310		
Osteitis score	0.025 (-0.01-0.06)	0.143	-0.00 (-0.04-0.04)	0.993		

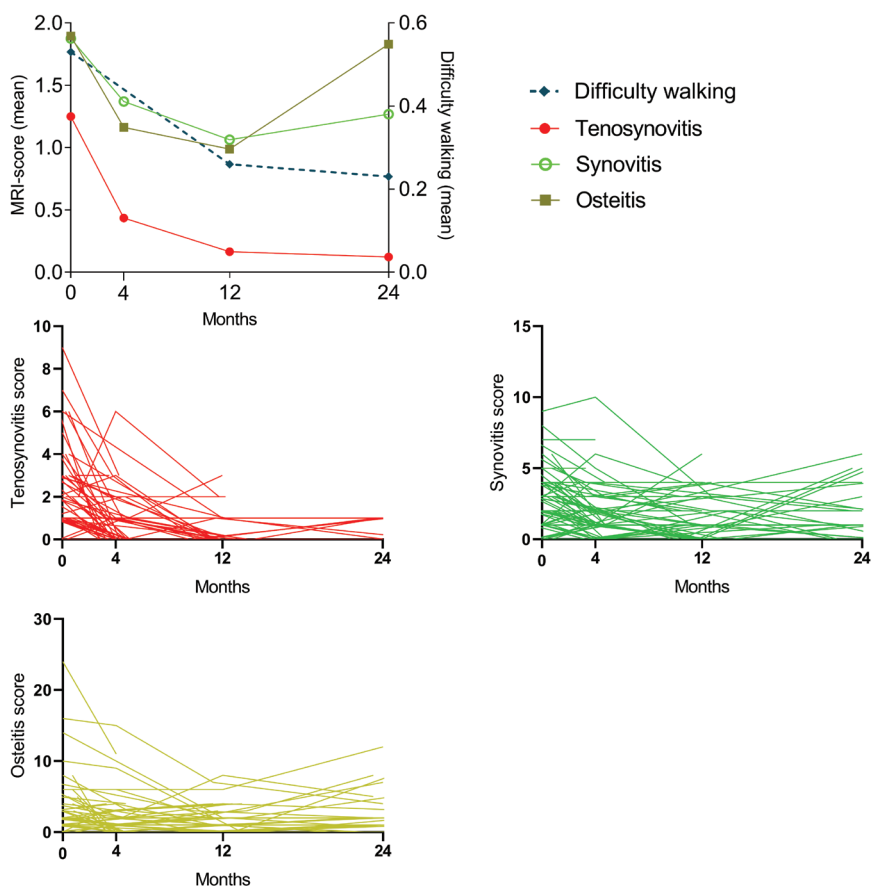
^a Multivariable analyses including MRI-detected tenosynovitis, synovitis and osteitis at the MTP-joints. ^b Multivariable analyses including swollen joint count, age at inclusion and CRP, performed separately for the total inflammation score and for tenosynovitis. ^c Total inflammation score is defined as the summed scores of tenosynovitis, synovitis and osteitis

Supplement 9. Association between MRI-detected inflammation at the MTP-joints and difficulty climbing stairs at disease presentation

	Univariable analyses		Multivariable analysis: MRI features ^a		Multivariable analysis: clinical features ^b	
	P (95% CI)	P-value	P (95% CI)	P-value	P (95% CI)	P-value
Total inflammation score ^c	0.023 (0.011-0.035)	<0.001			0.012 (0.00-0.025)	0.051
Tenosynovitis score	0.071 (0.035-0.105)	<0.001	0.045 (0.01-0.093)	0.045	0.033 (-0.003-0.069)	0.069
Synovitis score	0.067 (0.032-0.102)	<0.001	0.037 (-0.032-0.029)	0.179		
Osteitis score	0.025 (0.001-0.050)	0.143	-0.002 (-0.032-0.029)	0.900		
Erosion score	0.052 (-0.01-0.11)	0.121				

^a Multivariable analyses including MRI-detected tenosynovitis, synovitis and osteitis at the MTP-joints. ^b Multivariable analyses including swollen joint count, age at inclusion and CRP, performed separately for the total inflammation score and for tenosynovitis.

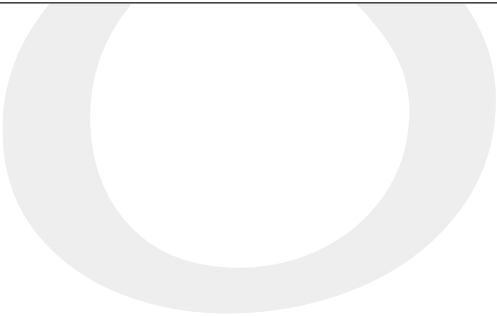
^c Total inflammation score is defined as the summed scores of tenosynovitis, synovitis and osteitis



Supplement 10. Supplementary Figure. Difficulty walking and MRI-scores (both mean) for osteitis, synovitis and tenosynovitis during 24 months of follow-up, including spaghetti plots. Difficulty walking was assessed by the Health Assessment Questionnaire (HAQ) question 4a: are you able to walk outdoors on flat ground? Patients answered on a scale from 0-3: 0= without difficulty, 1= with some difficulty, 2= with much difficulty, 3= unable to do. In univariable analyses a decrease in tenosynovitis and synovitis were associated with a decrease in walking disability ($P=0.001$ and $P=0.002$, respectively, see also Supplement 5). In multivariable analyses that included osteitis, synovitis and tenosynovitis, only the association for tenosynovitis remained ($P=0.073$, $P=0.049$). Follow-up MRI-data was available as follows: 107, 100, 80 and 41 patients at baseline, 4, 12 and 24 months respectively. Data on walking-difficulty was available for 107, 78 and 70 patients at baseline, 12 and 24 months respectively. The increase in osteitis score at 24 months is caused by missing data from patients with resolution of symptoms who were lost to follow-up at 24 months, while patients with more severe disease kept coming for follow-up, as is illustrated in the spaghetti plots.



Chapter 8



*What is the additional value of MRI of
the foot to the hand in undifferentiated arthritis
to predict rheumatoid arthritis development?*

Yousra Dakkak

Debbie Boeters

Aleid Boer

Monique Reijnierse

Annette van der Helm-van Mil

Abstract

Background: MRI-detected subclinical joint inflammation in hand-joints of patients with undifferentiated arthritis (UA) predicts progression to rheumatoid arthritis (RA). It is unknown if adding MRI of the foot increases predictive accuracy compared to the hand alone.

Methods: 1.5T-contrast-enhanced MRI of unilateral foot (MTP-1-5), and hand (MCP-2-5 and wrist) was performed in 123 patients presenting with UA (not fulfilling 2010 RA-criteria) and scored for bone marrow edema (BME), synovitis and tenosynovitis. Symptom-free controls (n=193) served as a reference for defining an abnormal MRI. Patients were followed for RA-development ≤ 1 -year, defined as fulfilling classification criteria or initiation of disease modifying anti-rheumatic drugs because of the expert opinion of RA. The added predictive value of foot-MRI to hand-MRI was evaluated.

Results: 52% developed RA. Foot tenosynovitis was predictive (OR 2.55, 95%CI 1.01-6.43), independent of BME and synovitis (OR 3.29, 95%CI 1.03-10.53), but not independent of CRP and number of swollen joints (OR 2.14, 95%CI 0.77-5.95). Hand tenosynovitis was also predictive independent of BME and synovitis (OR 3.99, 95%CI 1.64-9.69) and independent of CRP and swollen joints (OR 2.36, 95%CI 1.04-5.38). Adding foot tenosynovitis to hand tenosynovitis changed sensitivity from 72% to 73%, specificity from 59% to 54% and AUC from 0.66 to 0.64, the net reclassification index was -3.5.

Conclusion: MRI-detected tenosynovitis of the foot predicts progression to RA. However adding MRI of the foot does not improve predictive accuracy compared to MRI of the hand alone. In view of cost-reduction, performance of foot-MRI for prognostic purposes in UA can be omitted.

Introduction

In patients with rheumatoid arthritis (RA), early initiation of treatment with disease-modifying antirheumatic drugs (DMARDs) is associated with a better disease outcome.(1,2) The 2010 ACR/EULAR classification criteria have been developed to facilitate early classification of RA.(3) These criteria perform better in the early identification of anti-citrullinated protein antibody (ACPA)-positive RA, than in ACPA-negative RA.(4) This is explained by the fact that three of the six points required to fulfil the criteria can come from autoantibodies, and that in the absence of autoantibodies patients require >10 involved joints to be classified as RA.(5) Previously it may have been considered more important to identify ACPA-positive RA early, because of its association with a more destructive disease course. However with current treatment strategies the disease burden and functional status of ACPA-negative patients is similar to that of ACPA-positive patients,(6) underlining the equal relevance of early recognition of ACPA-negative RA.

Thus additional (bio)markers are needed to facilitate the early detection of RA and ACPA-negative patients in particular. Imaging is one of the tools that is being explored. Magnetic resonance imaging (MRI) is increasingly used in clinical trials in RA, as it is a sensitive tool to visualise inflammation as defined by synovitis, bone marrow edema (BME) and tenosynovitis.(7) The use of MRI in undifferentiated arthritis (UA) to predict the progression to clinical RA is recommended by EULAR(8); a recommendation that is supported by the findings of several studies in patients with UA that had RA development as outcome.(9,10) Advantages of MRI are its sensitivity and reproducibility, on the other hand MRI is costly and time-consuming. In order to achieve evidence-based and cost-effective use of MRI in the early detection of RA among patients presenting with UA, the optimal scan protocol needs to be examined. An important issue in this respect is whether imaging of the foot is of additional value to the hand, as it prolongs the scan-time and thereby costs.(11)

Two studies have performed MRI of metatarsophalangeal (MTP)-joints in UA-patients, in addition to MRI of wrists and metacarpophalangeal (MCP)-joints.(12,13) One study evaluated only BME of the MTP-joints (not synovitis and tenosynovitis). (12) The second study combined data of the hand and foot, but did not compare the predictive effect of the hand and foot separately.(13) In addition, both studies did not evaluate tenosynovitis in the foot, whilst in the hand tenosynovitis has shown to be the most predictive feature of inflammation by MRI.(13) Consequently,

the value of MRI-detected inflammation in the foot (synovitis, tenosynovitis or BME) in recognising UA-patients that will develop RA is still unknown. With the ultimate aim to arrive at an optimal protocol for MRI in UA, we aimed to assess whether MRI-detected inflammation of the foot is predictive for RA-development, and whether combining MRI-detected inflammation of the foot to that of the hand is of additional value.

Methods

Patients

Early arthritis cohort

The Leiden Early Arthritic Clinic (EAC) is a longitudinal inception cohort that includes patients with clinically confirmed arthritis of ≥ 1 joint and symptom duration < 2 years that are naïve to DMARDs. At baseline, questionnaires were completed, swollen joint counts were performed and serum samples were obtained. MRI scans were made at baseline, prior to the initiation of DMARDs, and were read later in time for research purposes only; results were not reported to patients or clinicians. At a second visit, two weeks after presentation, patients received their initial diagnosis. UA-patients did not fulfil the 2010 criteria and did not receive a diagnosis other than UA at the 2 weeks visit. Between June 2013 and March 2016, 447 consecutive patients presenting with early arthritis were included and underwent MRI. Of these patients, 123 were diagnosed with UA and were studied here (Figure 1).

Symptom-free volunteers

Previously it was shown that the predictive accuracy of MRI increased and the rate of false positive findings decreased, when features of low-graded inflammation as observed in the general population were used as reference.⁽¹⁴⁾ Therefore data from symptom-free controls (n=193) as described before were used as reference.⁽¹⁵⁾ In short, the volunteers 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.^[14] Data on synovitis and BME in MTP-joints were reported previously.⁽¹⁵⁾ For our current study, the presence of tenosynovitis of the flexor and extensor tendons at the level of the MTP-joints was also evaluated.

The study was approved by the local medical ethics committee. All participants signed informed consent.

MRI and scoring

Patients and symptom-free controls were scanned using the same protocol and scanner, a 1.5 Tesla(T) extremity MRI (General Electric, Wisconsin, USA). Unilateral scans were acquired of the MCP-joints (2-5), wrist and MTP-joints (1-5) of the most painful side or the dominant side, in case of equally severe symptoms and in the symptom-free volunteers. Gd-chelate contrast agent (gadoteric acid, Guerbet, Paris, France) (Gd) was administered intravenously at a standard dose of 0.1 mmol/kg. Sequences acquired were: coronal pre-contrast T1-weighted fast spin echo (T1) and coronal and axial post-contrast T1-weighted fast spin echo with frequency selective fat saturation (T1Gd) of the MCP-joints and wrist, and T1Gd in the coronal and axial plane of the MTP-joints. More details are provided supplementary. All scanned joints were scored for BME and synovitis according to the Outcome Measures in Rheumatology Clinical Trials Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (OMERACT-RAMRIS).(16) Tenosynovitis was scored according to Haavardsholm's score.(17) More details are provided supplementary. Each MRI was scored by two experienced readers, blinded to any clinical data. Intraclass correlation coefficients (ICCs) for the total inflammation scores were calculated to determine the reliability of the readers. All inter- and intrareader ICCs were ≥ 0.93 .

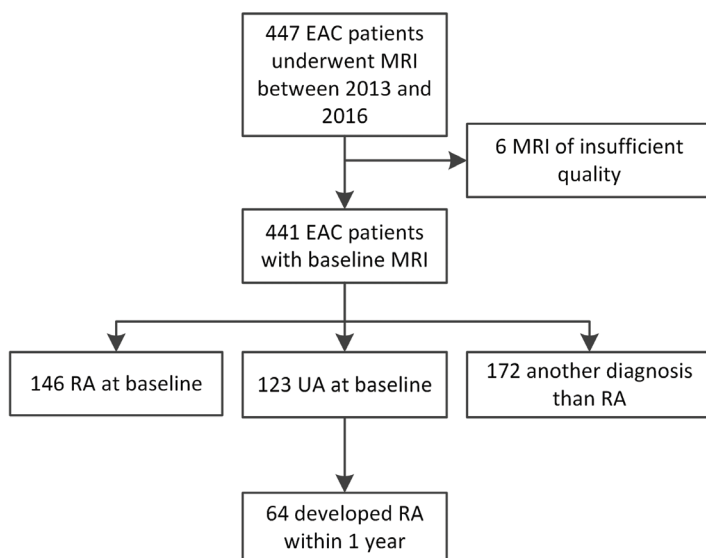


Figure 1. Flowchart. EAC: early arthritic cohort; MRI: magnetic resonance imaging; RA: rheumatoid arthritis; UA: undifferentiated arthritis

Table 1. Baseline characteristics of all undifferentiated arthritis-patients and those who progress to RA after one year and those who do not

	UA at baseline	RA after 1 year	no RA after 1 year	P- value
	N=123	N=64	N=59	
Clinical parameters				
Age, mean (SD)	57 (18)	59 (19)	55 (16)	0.29
Female, n(%)	73 (59)	40 (63)	33 (56)	0.46
Symptom duration, in weeks, median (IQR)	9 (4-27)	12 (6-30)	8 (3-21)	0.048
Swollen joint count, median (IQR)	2 (1-4)	3 (2-5)	1 (1-3)	<0.001
Presence of swollen joint foot, n (%)	25 (20)	12 (20)	13 (22)	0.65
Presence of swollen joint hand, n (%)	66 (54)	40 (63)	26 (44)	0.041
Presence of tender joint foot, n(%)	32 (26)	17 (27)	15 (25)	0.89
Presence of tender joint hand, n(%)	71 (58)	44 (69)	27 (46)	0.010
CRP, mg/L, median (IQR)	5 (3-14)	6 (3-16)	3 (3-9)	0.035
ACPA positive, n (%)	6 (5)	4 (7)	2 (3)	0.44
RF positive, n (%)	8 (7)	5 (8)	3 (5)	0.53
MRI features				
MTP 1-5				
Tenosynovitis, mean (SD)	0.6 (1.3)	0.8 (1.4)	0.4 (1.1)	0.075
Synovitis, mean (SD)	0.7 (1.0)	0.7 (1.0)	0.7 (1.1)	0.69
BME, mean (SD)	0.8 (1.4)	0.6 (0.9)	1.0 (1.7)	0.50
MCP 2-5				
Tenosynovitis, mean (SD)	1.4 (2.0)	2.0 (2.3)	0.8 (1.2)	<0.001
Synovitis, mean (SD)	1.6 (1.8)	2.1 (1.9)	1.1 (1.5)	0.001
BME, mean (SD)	0.6 (1.5)	0.6 (1.3)	0.7 (1.6)	0.85
Wrist				
Tenosynovitis, mean (SD)	2.4 (3.1)	3.2 (3.5)	1.5 (2.4)	0.006
Synovitis, mean (SD)	1.9 (2.1)	2.4 (2.3)	1.5 (1.8)	0.023
BME, mean (SD)	3.0 (5.2)	3.5 (5.8)	2.5 (4.5)	0.57

UA: undifferentiated arthritis; SD: standard deviation; IQR: interquartile range; CRP: c-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; MCP: metacarpophalangeal joint; MTP: metatarsophalangeal joint; BME: bone marrow edema. 66 swollen joint counts were performed. For the presence of a swollen or tender foot the presence of a swollen or tender MTP-joint was taken, respectively. For the presence of swollen or tender hand the presence of a swollen or tender MCP- or wrist-joint was taken, respectively. Differences between patients with and without progression to RA after 1 year were tested with chi-square test, t-test or Mann-Whitney U test as appropriate.

Outcome

The outcome was development of RA during one year follow-up. RA was defined as fulfilling the 2010 criteria and/or the initiation of DMARDs because of the clinical diagnosis of RA that represents the expert opinion of rheumatologists. Fulfilment of the 2010 criteria was not deemed necessary in the presence of a clinical diagnosis and start of DMARDs, as seronegative patients require >10 involved joints to fulfil the 2010 criteria; in case of a suspected (imminent) RA, patients were generally treated and progression towards acquiring >10 inflamed joints was hampered.

Analyses

For continuous scores the mean MRI-scores (BME, synovitis, tenosynovitis) of both readers were used. Next the MRI-scores were dichotomized by using the MRI findings of symptom-free persons as a reference. At joint level a score was considered abnormal for BME, synovitis or tenosynovitis if the scores of both readers at the same location was present in <5% of symptom-free persons of the same age category (18–40, 40–60, or >60 years), as described previously.⁽¹⁴⁾ At patient level, BME, synovitis and, tenosynovitis were considered present if ≥1 location was positive. The scores of MTP 1–5 were summed as ‘foot’, and MCP 2–5 and the wrist were summed together as ‘hand’.

Table 2. Frequencies of flexor and extensor tenosynovitis-scores at the MTP-joints of 193 healthy controls

	Tenosynovitis-score			
	0	1	2	3
Flexor tenosynovitis				
MTP	1192 (99.5%)	1 (0.5%)	-	-
MTP 2	192 (99.5%)	1 (0.5%)	-	-
MTP 3	192 (99.5%)	1 (0.5%)	-	-
MTP 4	193 (100%)	-	-	-
MTP 5	193 (100%)	-	-	-
Extensor tenosynovitis				
MTP 1	193 (100%)	-	-	-
MTP 2	193 (100%)	-	-	-
MTP 3	193 (100%)	-	-	-
MTP 4	192 (99.5%)	1 (0.5%)	-	-
MTP 5	193 (100%)	-	-	-

MTP: metatarsophalangeal joint. A dash ('-') indicates absence in healthy controls (0%).

Tenosynovitis data of the foot of symptom-free persons have not been studied before, in contrast to synovitis and BME.(15) Therefore we studied this in the symptom-free controls before analysing data of UA-patients.

Continuous MRI-data were compared between UA-patients with and without progression to RA with Mann-Whitney U-tests. Logistic regression analysis was used to assess the predictive value of MRI-detected inflammation in UA-patients. Multivariable analyses corrected for MRI-inflammation features and regularly used inflammatory markers (C-reactive protein (CRP) and swollen joint count). Test characteristics for the development of RA were calculated for the MRI-features and the net reclassification index (MRI of hand and foot combined versus hand alone) was determined.

Sub analyses were performed with initiation of DMARDs within one year as the outcome and thus not development of RA according to the classification criteria, next within the subgroup of UA-patients who were negative for rheumatoid factor (RF) and ACPA (n=110), with data for the flexor and extensor tendons of both the hand and foot separately, and with data for the MCP-joints and wrist separately (rather than summed together as the hand).

P-values less than 0.05 were considered significant. IBM SPSS v23.0 was used.

Results

Study population

Baseline characteristics are presented in Table 1. UA-patients had a mean age of 57, 59% were female, and they were mainly auto-antibody negative (95%). After one year follow-up, 64 patients (52%) had developed RA (6 received DMARDs and fulfilled classification criteria, 57 received DMARDs but did not fulfil the 2010-criteria and one fulfilled the criteria but did not receive DMARDs). Patients who developed RA had more swollen joints and a higher CRP as is presented in Table 1.

Continuous MRI scores

Continuous MRI scores are presented in Table 1. For the foot BME and synovitis scores were comparable in UA-patients who did and did not develop RA ($P=0.50$ and $P=0.69$ respectively); tenosynovitis scores were higher in patients that progressed to RA (mean score 0.8 versus 0.4), although the difference did not reach statistical significance ($P=0.075$).

Table 3. Results of logistic regression for RA development in undifferentiated arthritis patients

Patients with MRI-feature, n%		Univariable analyses		Multivariable analysis: types of MRI-inflammation ²		Multivariable analysis: presence of tenosynovitis adjusted for SJC and CRP ²	
RA	no-RA	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Foot (MTPs)¹							
Presence of							
Tenosynovitis	18 (29)	8 (14)	2.55 (1.01-6.43)	0.047	3.29 (1.03-10.53)	0.045	2.14 (0.77-5.95)
Synovitis	14 (22)	10 (17)	1.40 (0.57-3.45)	0.47	0.96 (0.30-3.10)	0.95	0.14
BME	6 (9)	11 (19)	0.44 (0.16-1.31)	0.14	0.33 (0.10-1.09)	0.068	
Hand (MCPs and wrist)¹							
Presence of							
Tenosynovitis	46 (72)	24 (41)	3.73 (1.76-7.91)	0.001	3.99 (1.64-9.69)	0.002	2.36 (1.04-5.38)
Synovitis	28 (44)	18 (31)	1.77 (0.84-3.72)	0.13	1.04 (0.41-2.67)	0.94	
BME	21 (33)	24 (41)	0.71 (0.34-1.49)	0.37	0.57 (0.25-1.29)	0.18	
Swollen joints, per joint			1.46 (1.20-1.79)	<0.001			
Elevated CRP			2.77 (1.23-6.23)	0.014			

¹ At joint level a score was considered abnormal for BME, synovitis or tenosynovitis if the scores of both readers at the same location was present in <5% of symptom-free persons of the same age category (18-40, 40-60, or >60 years). At patient level, BME, synovitis, tenosynovitis were considered present if ≥1 joint of foot or hand respectively was positive. ²Multivariable analyses was performed for the foot and for the hand separately. SJC: swollen joint count (66 swollen joint counts were performed); CRP: C-reactive protein; RA: rheumatoid arthritis; OR: odds ratio; CI: confidence interval; MTP: metatarsophalangeal joint; MCP: metacarpophalangeal joint; BME: bone marrow edema.

Studying the frequency of tenosynovitis at MTP-joints in symptom-free persons for different age categories, revealed tenosynovitis never occurred in >5% of patients (Table 2). Thus, the presence of tenosynovitis at the foot was always considered abnormal.

Prediction of RA development within one year for UA-patients

Then MRI-features of UA-patients were dichotomized according to a cut-off based on findings in symptom-free controls as described in the methods and is done previously.(14) Results of univariable logistic regression are depicted in Table 3. Of all MRI-features of the foot, only tenosynovitis was associated with RA-development, as it occurred in 29% of patients that progressed to RA and in 14% of those that did not (OR 2.55, 95% CI 1.01-6.43). Tenosynovitis regularly co-occurred with synovitis and BME, as is illustrated by Supplementary Figure 1. Therefore, a multivariable analysis was performed for all three types of inflammation of the foot. Tenosynovitis predicted the outcome independently of local BME and synovitis of the foot (OR 3.29, 95% CI 1.03-10.53). In a multivariable analysis that adjusted tenosynovitis for CRP and swollen joint count, the OR for tenosynovitis was 2.14 (95% CI 0.77-5.95).

The test characteristics of tenosynovitis of the foot to identify RA-patients were as follows: sensitivity 29%, specificity 86%, positive predictive value (PPV) 69%, negative predictive value (NPV) 53% and area under the curve (AUC) 0.58 (Table 4). An example of MRI-detected tenosynovitis of the foot is shown in Figure 2.

Additional value of MRI of the foot over the hand

Since at the foot level the association of an abnormal MRI with the development of RA was the strongest for tenosynovitis, further analyses were confined to tenosynovitis. To answer the question whether imaging of the foot is of additional value to imaging the hand, first the value of MRI of the hand was assessed. Of all MRI-features at the hand, tenosynovitis was the only predictor for the outcome (OR 3.73, 95% CI 1.76-7.91), as was previously shown.(13) This effect was independent of local BME and synovitis (OR 3.99, 95% CI 1.64-9.69) and also independent of clinical inflammatory markers (OR 2.36, 95% CI 1.04-5.38) (Table 3).

Tenosynovitis of the hand had a sensitivity of 72%, specificity of 59%, PPV of 66%, NPV of 66% and AUC of 0.66 for the identification of RA-patients, as is presented in Table 4. To evaluate if scoring tenosynovitis of the foot is of additional value, the test characteristics of hand and foot combined were calculated. This resulted in a

comparable sensitivity of 72% and 73%, at the cost of a decrease in specificity from 59 to 54% and a change in AUC from 0.66 to 0.64 (Table 3). The net reclassification index was -3.5 (as is illustrated in Supplementary Table 1).

Sub analyses

We repeated the analyses for the association between tenosynovitis at the foot for UA-patients who received DMARDs within 1 year, although they did not fulfil the 2010 classification criteria ($n=57$). The OR for the association of tenosynovitis was 2.76 (95%CI 1.12-6.82) in univariable analyses, and 2.96 (95%CI 0.97-9.01) in multivariable analyses corrected for local BME and synovitis (Supplementary Table 2).

The association between tenosynovitis at the foot and RA-development was also studied in the UA-patients who were negative for RF and ACPA ($n=110$), as it has been suggested that MRI may be most helpful in the ACPA-negative subgroup. (13) Then the OR of tenosynovitis at the MTP-joints was 2.06 (95% CI 0.78-5.40) in univariable analyses, and 2.62 (95% CI 0.79-8.68) when corrected for local BME and synovitis (Supplementary Table 3).

In the main analyses inflammation at the flexor and at the extensor tendons were summed. It was also assessed whether the predictive value of foot tenosynovitis differed between the two sides (Supplementary Table 4). The effect remained present for the flexor side (22% versus 9% of patients, OR 3.09, 95% CI 1.04-9.20), but not for the extensor side (14% versus 9% of patients, OR 1.80, 95% CI 0.57-5.72).

It was observed that tenosynovitis at the hand level had a larger effect size (OR 3.73, 95% CI 1.76-7.91) than that of the foot (2.55, 95% CI 1.01-6.43)(Table 1). Thus far, in the analyses of the hand, tenosynovitis of the wrist and MCP-joints was summed. To explore whether the fact that more tendons were scored in the hand (yielding a higher chance of MRI-positivity), explained this finding, we repeated the analyses for the MCP-joints and wrist separately and compared the MCP- and MTP-joints (Supplementary Table 5). The predictive effect of tenosynovitis of the MCP-joints remained present (OR 3.64, 95% 1.68-7.91), also after correction for other MRI-inflammatory features and after correction for CRP and swollen joints (OR 3.61, 95% CI 1.50-8.65 and OR 2.64, 95% CI 1.14-6.16 respectively). This was in contrast to the results of tenosynovitis of the MTP-joints (OR 2.14, 95%CI 0.77-5.95) (Table 3). This suggests that tenosynovitis of hand joints is truly stronger associated with RA-development than tenosynovitis of foot joints.

Finally we wondered if the lack of an additive effect of foot-MRI to hand-MRI is based on the concurrent presence of foot tenosynovitis and hand tenosynovitis. Indeed we observed that 3% of UA-patients had foot tenosynovitis without hand tenosynovitis, whereas 60% of UA-patients had foot tenosynovitis as well as hand tenosynovitis.

Table 4. Test characteristics of the MRI-features in patients with UA for RA development

	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Foot (MTPs)						
Tenosynovitis	29 (19-41)	86 (75-93)	69 (50-83)	53 (43-63)	57 (48-65)	0.58
Synovitis	22 (14-34)	83 (72-91)	58 (39-76)	50 (40-60)	52 (43-60)	0.53
BME	9 (4-19)	81 (70-89)	35 (17-59)	45 (36-55)	44 (35-53)	0.45
Any Inflammation	38 (27-50)	68 (55-78)	56 (41-70)	50 (39-61)	52 (43-61)	0.53
Hand (MCPs and wrist)						
Tenosynovitis	72 (60-81)	59 (47-71)	66 (54-76)	66 (53-77)	66 (57-74)	0.66
Synovitis	44 (32-56)	69 (57-80)	61 (46-74)	53 (42-64)	56 (47-65)	0.57
BME	33 (23-45)	59 (47-71)	47 (33-61)	45 (34-56)	46 (37-54)	0.46
Any Inflammation	77 (65-85)	36 (25-48)	56 (46-66)	58 (42-65)	57 (48-65)	0.56
Hand or foot						
Tenosynovitis	73 (62-83)	54 (42-66)	64 (52-74)	65 (51-77)	64 (55-72)	0.64
Synovitis	48 (37-60)	59 (47-71)	56 (43-69)	51 (40-63)	54 (45-62)	0.54
BME	39 (28-51)	47 (35-60)	45 (32-58)	42 (31-54)	43 (35-52)	0.43
Any Inflammation	78 (67-86)	24 (15-36)	53 (43-62)	50 (33-67)	52 (43-61)	0.51

PPV: positive predictive value; NPV; negative predictive value; AUC: area under the curve; MTP: metatarsophalangeal joint; MCP: metacarpophalangeal joint; BME: bone marrow edema. Any Inflammation is defined as the presence of BME, synovitis and/or tenosynovitis. Values are depicted with their corresponding 95% confidence intervals between brackets.

Discussion

The presence of MRI-detected inflammation has been shown to be predictive for RA development in patients with UA and the use of MRI in the diagnostic process of RA has been advocated by the EULAR.(8,12,13). However, the value of MRI of the foot has not been studied thoroughly. Therefore, we assessed the added benefit of MRI of the foot to MRI of the hand. We observed that of all features of MRI-detected inflammation (BME, synovitis and tenosynovitis) in the foot, tenosynovitis was the only feature to predict progression to RA, consistent with the hand. However, presence of tenosynovitis in the foot did not have additional value to tenosynovitis in the hand in detecting patients who progressed to RA.

Although MRI-detected tenosynovitis in the foot had a high specificity (86%), and was thus an infrequent occurrence in the group of patients that did not develop RA, it had a low sensitivity (29%). Therefore, scanning the foot instead of the hand is not advisable as the majority of the patients that will progress to RA will remain undetected.

As RA is a disease characterized by inflammation of the small joints of hands and feet(18), the negative finding on the added value of foot-MRI may be unexpected. A presumable explanation is that the foot is less affected in UA. UA is, as shown, a population that is mostly autoantibody negative. The notion that ACPA-negative patients have a lower frequency of foot involvement is supported by a recent finding done at symptom level in patients with arthralgia suspicious for progression to RA; ACPA-negative patients less often had symptoms in lower extremities than ACPA-positive patients.(19) In the UA-patients studied here, the frequency of foot involvement at joint examination was lower than hand involvement (lower number of tender and swollen joints) (Table 1), and also MR-detected tenosynovitis of the feet was less frequent than in the hand (21% versus 57% on group level). More importantly, only 3% of the UA-patients had MTP tenosynovitis without concomitant hand tenosynovitis (Supplementary Table 1). Thus although tenosynovitis of the foot was associated with the development of RA, it occurs infrequent without hand tenosynovitis, and this may explain why MRI of the foot is not of added benefit.

An absence of added benefit for foot-MRI has been observed in different disease phases. MRI-detected erosions of the foot were not of added value to MRI-detected erosions of the hand in identifying RA-patients with erosive progression,

and in a trial MRI-detected erosions and synovitis of the foot did not have much additional value to MRI of the hands in evaluating MRI-detected improvement in different treatment arms.(20,21)

This is the first study in UA reporting on the predictive value of tenosynovitis at the MTP-joints. The finding in the foot that, of all inflammatory features, tenosynovitis is most predictive for RA development is in line with previously published findings on tenosynovitis in the hand.(13) Our study also newly reports on the absence of tenosynovitis in MTP-joints in symptom-free persons from the general population. This highlights the relevance of tenosynovitis as an early phenomenon in RA-development.(22)

Tenosynovitis was defined as inflammation present at either the flexor or the extensor tendon of the joint, similar as was done in a previous study evaluating tenosynovitis at the level of MCP-joints.(23) For MCP-joints it is known that the flexor tendons have a tendon sheath, whereas the extensor tendons do not and inflammation detected around this tendon may better be named peritendinitis (23) The anatomy with respect to the presence and extent of tendons sheaths at the flexor and extensor tendons at the MTP-joints is less clear and defined differently in anatomic atlases, but there seems to be agreement on the absence of a sheath at the extensor side. Although also here peritendinitis may be a better term for the signal at the extensor site, for reasons of simplicity we kept the naming 'tenosynovitis' for the signal intensity observed around the tendons at MRI. Nonetheless the anatomy and the nature of tendon inflammation at the MTP-joints are subject of further studies.(11)

The development of RA was used as outcome. This was defined as fulfilling the 2010 criteria and/or as start of DMARDs by rheumatologists based on their clinical expertise. The latter was considered an outcome without the fulfilment of the 2010 criteria, as these criteria are difficult to fulfil for patients without auto-antibodies, as >10 involved joints are required and initiated DMARDs may hamper the progression to fulfilment of RA classification criteria. Indeed in our data, most patients that were treated did not achieve sufficient points over time to fulfil the 2010 criteria. We cannot exclude that this resulted in a frequency of RA development that is higher than would have been observed if patients were not treated and the natural course would have been observed. This could have resulted in overdiagnosis of RA and could have diluted our results leading to an underestimation of the obtained effects for MRI-inflammation. However, this probably has not affected the results on the additive value of foot-MRI in UA.

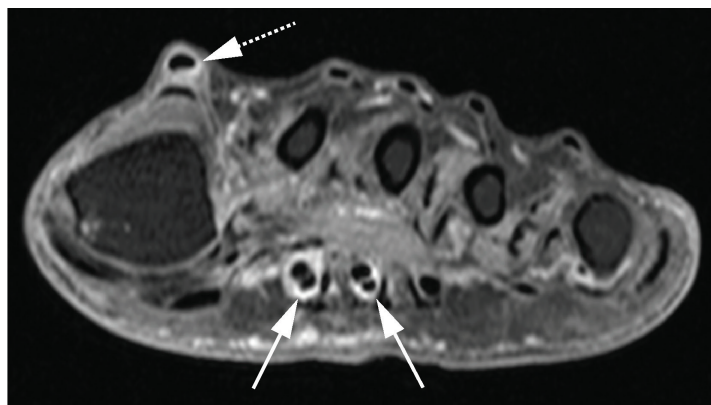


Figure 2. Example of tenosynovitis in patient with undifferentiated arthritis who developed RA. The axial image portrays tenosynovitis at the flexor of metatarsophalangeal(MTP)-2 and -3 (arrows with line) and the extensor of MTP-1 (arrow with dotted line)

Excluding the foot from the MRI-protocol saves time. We used a 1.5T MSK scanner and deletion of the foot saves 10 minutes of a total protocol of 45 minutes. A 3T MRI is more often used, here deletion of the foot and scanning according to our protocol would roughly save 10 minutes from the total time of 30 minutes, saving a third of the scanning time and thereby reducing costs.

Conclusion

Patients with UA are mostly auto-antibody-negative, in these patients MRI-detected tenosynovitis of the foot associates with an increased risk to develop RA. However, MRI of the foot does not have additive predictive value to MRI of the hand. This contributes to evidence based scanning protocols in UA, and may reduce costs, as MRI of the foot can be omitted when MRI of the hand is made.

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Supplementary data

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

Supplementary Table 1: Reclassification of patients by adding MRI-detected tenosynovitis of the foot to that of the hand with RA-development after one year as an outcome

	RA within 1 year		
	no RA	RA	Total
MRI of hand			
- No tenosynovitis	35	18	53
- Tenosynovitis	24	46	70
MRI of hand and foot			
- No tenosynovitis in hand or foot	32	17	49
- Tenosynovitis in hand or foot	27	47	74
Total	59	64	123

The hand is defined as MCP 2-5 or the wrist, the foot is defined as MTP 1-5. By adding MRI-detected tenosynovitis of the feet to that of the hand the net proportion of reclassifications was 3.3% ((3+1)/123). The net increase in correct classifications was 1.6% (1/64), the net increase in incorrect classifications was 5.1% (3/59). Thus the net reclassification index was -3.5 (1.6-5.1).

Supplementary Table 2. Results of logistic regression with initiation of DMARDs as the outcome in undifferentiated arthritis patients

Patients with MRI-feature, n%		Univariable analyses		Multivariable analysis: types of MRI-inflammation ²		Multivariable analysis: presence of tenosynovitis adjusted for SJC and CRP ²	
RA	no-RA	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Foot (MTPs) ¹							
Presence of							
Tenosynovitis	17 (30)	9 (14)	2.76 (1.12-6.82)	0.028	2.96 (0.97-9.01)	0.056	2.28 (0.81-6.42)
Synovitis	14 (25)	10 (15)	1.87 (0.76-4.61)	0.18	1.47 (0.46-4.67)	0.52	0.12
BME	5 (9)	12 (18)	0.43 (0.14-1.31)	0.14	0.27 (0.08-0.97)	0.045	
Hand (MCPs and wrist) ¹							
Presence of							
Tenosynovitis	44 (77)	26 (39)	5.21 (2.36-11.49)	<0.001	5.24 (2.10-13.09)	<0.001	3.33 (1.39-7.97)
Synovitis	27 (47)	19 (29)	2.23 (1.06-4.69)	0.035	1.19 (0.46-3.04)	0.72	0.007
BME	19 (33)	26 (39)	0.77 (0.37-1.61)	0.49	0.57 (0.24-1.32)	0.19	
Swollen joints, per joint			1.47 (1.21-1.78)	<0.001			
Elevated CRP			3.96 (1.74-9.00)	0.001			

¹At joint level a score was considered abnormal for BME, synovitis or tenosynovitis if the scores of both readers at the same location was present in <5% of symptom-free persons of the same age category (18-40, 40-60, or >60 years). At patient level, BME, synovitis, tenosynovitis were considered present if ≥1 joint of foot or hand respectively was positive. ²Multivariable analyses was performed for the foot and for the hand separately. DMARD: disease modifying antirheumatic drug; SJC: swollen joint count (66 swollen joint counts were performed); CRP: C-reactive protein; OR: odds ratio; CI: confidence interval; MTP: metatarsophalangeal joint; MCP: metacarpophalangeal joint; BME: bone marrow edema.



Supplementary Table 3. Results of logistic regression for RA development in undifferentiated arthritis patients who are antibody negative

Patients with MRI-feature, n%		Univariable analyses		Multivariable analysis: types of MRI-inflammation ²		Multivariable analysis: presence of tenosynovitis adjusted for SJC and CRP ²	
RA	no-RA	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Foot (MTPs)¹							
Tenosynovitis	14 (26)	8 (15)	2.06 (0.78-5.40)	0.14	2.62 (0.79-8.68)	0.12	1.89 (0.64-5.56)
Synovitis	11 (20)	9 (16)	1.31 (0.49-3.46)	0.59	1.19 (0.34-4.16)	0.79	
BME	5 (9)	11 (20)	0.40 (0.13-1.24)	0.11	0.27 (0.075-1.01)	0.051	0.25
Hand (MCPs and wrist)¹							
Tenosynovitis	41 (75)	23 (42)	4.08 (1.81-9.15)	0.001	3.36 (1.67-11.37)	0.003	2.64 (1.07-6.48)
Synovitis	25 (46)	17 (31)	1.86 (0.85-4.06)	0.12	1.02 (0.38-2.75)	0.96	0.034
BME	17 (31)	22 (40)	0.67 (0.31-1.47)	0.32	0.55 (0.23-1.31)	0.18	
Swollen joints, per joint		1.57 (1.26-1.97)		<0.001			
Elevated CRP		3.23 (1.36-7.72)		0.008			

110 patients with undifferentiated arthritis (UA) were selected who were negative for both rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA). ¹On patient level a score was considered present or abnormal for BME, synovitis or tenosynovitis if, according to both readers, the score was present in <5% at the same location of symptom-free controls of the same age category. ²Multivariable analyses was performed for the foot and for the hand separately. SJC: swollen joint count (66 swollen joint counts were performed); CRP: C-reactive protein; OR: odds ratio; CI: confidence interval; MTP: metatarsophalangeal; MCP: metacarpophalangeal joint; BME: bone marrow edema.

Supplementary Table 4. Results of logistic regression for RA development in undifferentiated arthritis for the extensor and flexor tendons separately

Patients with MRI-feature, n%		Univariable analyses		Multivariable analysis: adjusted for local BME and synovitis ²		Multivariable analysis: adjusted for SJC and CRP ²	
RA	no-RA	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
MTP 1-5¹							
Extensor tendon	9 (14)	1.80 (0.57-5.72)	0.32	2.03 (0.56-7.30)	0.28	1.60 (0.45-5.74)	0.47
Flexor tendon	14 (22)	3.09 (1.04-9.20)	0.043	4.14 (1.03-16.68)	0.046	2.11 (0.64-7.01)	0.22
MCP 2-5¹							
Extensor tendon	13 (20)	2.75 (0.92-8.27)	0.071	3.21 (0.84-12.34)	0.090	2.00 (0.57-7.00)	0.28
Flexor tendon	26 (41)	3.80 (1.60-9.05)	0.003	3.17 (1.29-7.78)	0.012	2.54 (1.00-6.50)	0.051

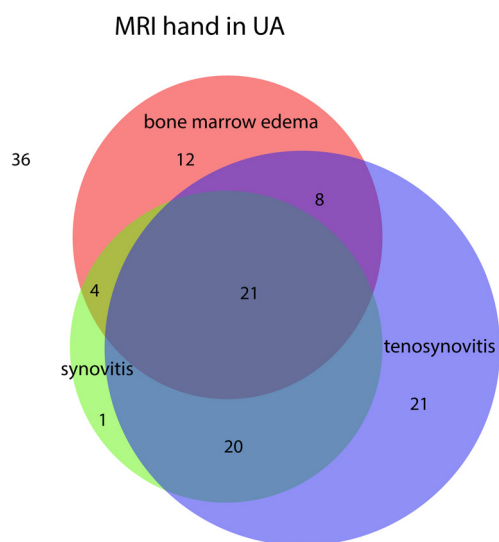
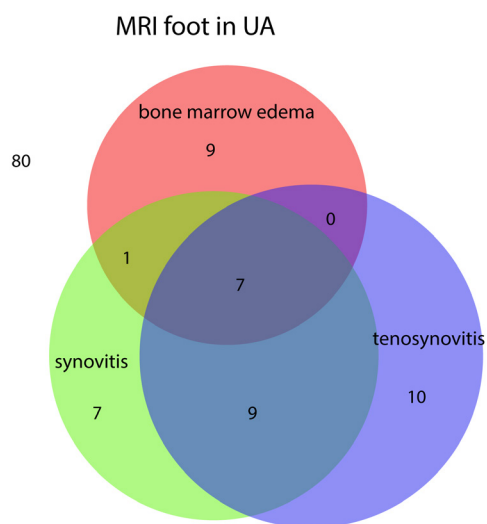
¹At joint level a score was considered abnormal for BME, synovitis or tenosynovitis if the scores of both readers at the same location was present in <5% of symptom-free persons of the same age category (18-40, 40-60, or >60 years). At patient level, BME, synovitis, tenosynovitis were considered present if ≥1 joint of foot or hand respectively was positive. ²Multivariable analyses was performed for the MTPs and MCPs separately. MRI: magnetic resonance imaging; RA: rheumatoid arthritis; BME: bone marrow edema; SJC: swollen joint count (66 swollen joint counts were performed); CRP: C-reactive protein; OR: odds ratio; CI: confidence interval; MTP: metatarsophalangeal; MCP: metacarpophalangeal joint.



Supplementary Table 5. Results of logistic regression for RA development in undifferentiated arthritis, for MRI-features at metacarpophalangeal and wrist joint separately

	Patients with MRI-feature, n%		Univariable analyses		Multivariable analysis: presence of local BME synovitis and tenosynovitis ²		Multivariable analysis: presence of tenosynovitis adjusted for SJC and CRP ²	
	RA	no-RA	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
MCPs¹								
Tenosynovitis	34 (53)	14 (24)	3.64 (1.68-7.91)	0.001	3.61 (1.50-8.65)	0.004	2.64 (1.14-6.16)	0.024
Synovitis	22 (34)	12 (20)	2.05 (0.91-4.65)	0.085	1.61 (0.58-4.47)	0.36		
BME	9 (14)	13 (22)	0.58 (0.23-1.48)	0.25	0.34 (0.11-1.03)	0.056		
Wrist¹								
Tenosynovitis	36 (56)	19 (32)	2.71 (1.30-5.65)	0.008	2.60 (1.19-5.69)	0.017	1.45 (0.62-3.35)	0.39
Synovitis	14 (22)	8 (14)	1.79 (0.69-4.63)	0.23	1.27 (0.42-3.86)	0.68		
BME	17 (27)	15 (25)	1.06 (0.47-2.38)	0.89	0.84 (0.34-2.09)	0.71		

¹At joint level a score was considered abnormal for BME, synovitis or tenosynovitis if the scores of both readers at the same location was present in <5% of symptom-free persons of the same age category (18-40, 40-60, or >60 years). At patient level, BME, synovitis, tenosynovitis were considered present if ≥1 joint of foot or hand respectively was positive. ² Multivariable analyses was performed for the MCPs and wrist separately. OR: odds ratio; CI: confidence interval; MCP: metacarpophalangeal joint 2-5; BME: bone marrow edema.



Supplementary Figure 1. Frequencies of concomitant presence of MRI-detected inflammation for the foot and hand. The foot is defined as MTP 1-5, the hand is defined as MCP 2-5 or the wrist. UA: undifferentiated arthritis.



Summary and discussion

Summary

RA is a disease that involves the small joints of both the hands and the feet. The focus in RA research has, however, primarily been on involvement of the hands.(1) Therefore, in this thesis we aimed to increase our understanding of involvement of the MTP-joints in patients with early arthritis and RA. Since this is a broad aim, throughout the thesis collaborations with the departments of Radiology and with the department of Anatomy and Embryology were necessary.

MRI is increasingly utilized in RA research. The RAMRIS is developed and validated as a standardized outcome measure regarding MRI-scoring of the hands. It assesses various outcome measures: joint inflammation, measured by synovitis, tenosynovitis and osteitis (also referred to as bone marrow edema), and structural damage, measured by erosions and joint space narrowing. In chapter 2 a systematic literature search was performed to study if there is currently enough evidence to conclude the application of the RAMRIS MRI-scoring of the MTP-joints is valid. This was done according to the OMERACT Filter criteria of Truth (Face, Content and Construct validity), Discrimination (test-retest reliability, ability to discriminate in trials, longitudinal construct validity and thresholds of meaning) and Feasibility.(2) The available evidence was limited, as only 13 studies were included in the review. Limited evidence was only available for osteitis and erosions, that suggested that construct validity was present; i.e. that these features were related to, among others, imaging and symptoms. For the three remaining MRI-features, synovitis, tenosynovitis and joint space narrowing, no conclusions could be drawn regarding construct validity as data was lacking. Regarding discrimination and feasibility, data for all MRI-features was lacking. We concluded the review with a research agenda for the further validation of MRI of the forefeet. Some points from this research agenda were addressed in the remainder of this thesis.

Reliability of scoring is an important aspect of Discrimination and was assessed in chapter 3. MRI-data of MTP-joints were compared to data from wrist- and MCP-joints. The following aspects were studied: inter- and intrareader reliability for patients with arthritis, and also for patients with clinically suspect arthralgia. In addition the reliability of change scores were evaluated for patients with RA. Intraclass correlation coefficients (ICC) were determined and were generally good to excellent for patients with arthritis: interreader ICCs ≥ 0.80 and intrareader ICCs ≥ 0.84 , change-score ICCs ≥ 0.90 . A pitfall of ICCs is that they are sensitive to a lack of variability among samples subjects. Therefore other indicators of reliability were

included: Bland-Altman plots and the smallest detectable change. These indicated that there was no systematic bias nor large measurement error. To further support our results, the reliability of the RAMRIS applied to the wrist- and MCP-joints was studied and was found to be equally reliable. Therefore applying the RAMRIS to the MTP-joints was found to be reliable for both status and change scores. Finally, data from patients with clinically suspect arthralgia supported the good inter- and intrareader reliability. This data was included as the focus in rheumatology is shifting from established RA to earlier forms of disease, including clinically suspect arthralgia. Previously, the reliability of status scores of osteitis, synovitis and erosions as well as change score of erosions in MTPs have been published and were found to be excellent.(3,4) Our study is the first to look at the reliability of scoring tenosynovitis at the MTP-joints and in addition to include change scores. Our results, supported by the results from previous studies, show that scoring synovitis, tenosynovitis, osteitis and erosions at the MTP-joints is reliable. Joint space narrowing was not included, as it was not yet part of the RAMRIS at the start of the study. These results are encouraging for the use of MRI of the MTP-joints in trials.

As part of Face and Content validity it is important that MRI is able to capture the intended pathophysiological feature. In the case of tenosynovitis, the pathophysiological feature is the synovial sheath surrounding the tendons. Previous MRI studies of the hands have shown that tenosynovitis at the MCP-joints and wrist is an early phenomenon in patients with RA.(5) Regarding the MTP-joints, the prevalence of inflammation of the tendons and its association with RA are unknown. In addition, and perhaps more surprising, anatomic literature leaves it undetermined whether tendons at these joints actually possess a synovial sheath, and thus it is unclear whether inflammation at these tendons can actually be referred to as tenosynovitis. Therefore in chapter 4 two studies were performed: an anatomic and an MRI-study. For the first we collaborated with the department of Anatomy and Embryology to anatomically study whether a synovial tendon sheath is actually present at the flexor and extensor tendons at the MTP-joints. Therefore, 14 forefeet of donated bodies were examined macroscopically: all extensor and flexor tendons crossing MTP-joints demonstrated sheaths surrounding tendons. Microscopy confirmed that this was indeed a synovial sheath. Next, in the MRI-study, 157 consecutive patients presenting with early RA, 284 patients with other arthritides and 193 healthy controls were studied. MRI of MTP 1-5 joints were scored for tenosynovitis at flexor and extensor tendons, and in addition also for synovitis and osteitis. MRI-detected tenosynovitis occurred in 42% of RA patients,

compared to 22% of other arthritides and only 2% of healthy controls. MRI-detected tenosynovitis was therefore associated with RA, also when corrected for synovitis and osteitis, and also when in addition corrected for swollen joint counts, CRP and ACPA. Thus, tendons at MTP-joints have a synovial sheath, of which inflammation can thus be referred to as tenosynovitis, and, similar to tenosynovitis in the hands, tenosynovitis at the MTP-joints was identified as a feature of RA, independent of local synovitis and osteitis.

In the forefoot, besides bone and tendons, other tissues that can be found are the synovium-lined intermetatarsal bursae, the neurovascular bundle and the subcutis.(6) There have been some reports on the involvement of these lesions in established RA,(7-10) however they have not been studied systematically. In chapter 5 therefore we studied the forefoot from a different perspective: instead of studying inflammation of the joints and tendons according to the scoring systems that were developed to score RA-inflammation (RAMRIS and Haavardsholm), we reviewed the complete images from a radiological point of view. . We started by exploring anatomic literature focused on the inter- and submetatarsal spaces. In anatomic literature there was no mention of these spaces, nor the structures that lie in it, however previous MRI- and anatomic studies have characterized these regions.(6,11) In the four intermetatarsal spaces we studied the following lesions: intermetatarsal bursitis, i.e. inflammation of the intermetatarsal bursae, and Morton's neuroma that arises from the neurovascular bundle, presumably upon irritation followed by inflammation. The subcutis was divided into five submetatarsal spaces, one under each metatarsal head. Here, two types of lesions were defined: submetatarsal bursitis and diffuse submetatarsal alterations. The lesions were scored for presence. In addition, as previous studies in healthy controls suggested that the size of the lesion may be relevant, the three lesions that were well demarcated (i.e. intermetatarsal bursitis, Morton's neuroma and submetatarsal bursitis) were measured in the transverse and dorsoplantar planes. For this study we used the same participants as described in chapter 4. We found that intermetatarsal bursitis, Morton's neuroma and submetatarsal bursitis were associated with RA, diffuse submetatarsal alterations was not. The three lesions that were associated with RA often co-occurred, therefore a multivariable analyses was performed where we found the lesions to be associated with RA independent of each other. In additional multivariate analyses they were also associated with RA independent of age, gender, BMI, local MRI-inflammation (i.e. synovitis, tenosynovitis and osteitis at the MTP-joints) and structural abnormalities in the forefeet. Finally, regarding the size of the lesions there was large overlap

between the three groups. Therefore no cut-off for RA could be determined with high sensitivity and specificity. Thus, the presence of intermetatarsal bursitis, Morton's neuroma and submetatarsal bursitis were identified as early features of RA, their size was not discerning.

Next, as a measure of construct validity, the relation between MRI-detected inflammation and physical examination as a clinical outcome was assessed in chapter 6. The relationship between physical joint examination and MRI-detected inflammation in early inflammatory arthritis has mostly been studied in the hands. However, physical examination of MTP-joints is considered difficult and for these joints this relationship is unknown. Therefore the concordance of physical examination with MRI-inflammation in MTP-joints was studied. Besides classic MRI-inflammation (synovitis, tenosynovitis and osteitis), intermetatarsal bursitis was also studied. The synovial lining of intermetatarsal bursae may enlarge and fill with fluid upon inflammation and become palpable. Additionally, the MCP-joints were included as a comparison. 441 patients with early arthritis were included whom all underwent physical joint examination by two independent assessors and MRI of their MTP- and MCP-joints. We showed that in non-swollen MTP-joints MRI-detected inflammation was infrequent. Thus, non-swollen MTP-joints are reassuring. Swollen MTP-joints, however, appeared to have a heterogeneous origin. Next to synovitis, also tenosynovitis importantly contributed to joint swelling. However, 52% of the swollen MTP-joints showed none of these classic inflammatory features: 21% of this was explained by intermetatarsal bursitis, whereas in 31% of swollen MTP-joints no abnormality was detected by MRI. Additionally, the relation between physical examination and MRI was different for the MTP- and MCP-joints, as in MCP-joints swelling was most frequently observed with the classic inflammatory MRI-features, as expected. Thus while the common notion that physical examination of MTP-joints is difficult is perhaps true, our results indicate that physical examination of MTP-joints is perhaps sometimes too sensitive.

Disability might be a more important outcome for patients than clinical joint swelling. Walking difficulties are common in RA-patients, and have an important impact on their quality of life.⁽¹²⁾ Therefore in chapter 7 the association between MRI-detected inflammation and walking disability was studied at the time of diagnosis and during 2 years of follow-up in 532 patients with early arthritis. We observed that walking disabilities had an association with inflammation, and most importantly with tenosynovitis at MTP-level. Moreover, a decrease in walking-disabilities was associated with a reduction in MRI-inflammation, and also this

association was strongest for tenosynovitis. Thus, although in patients arthritis is traditionally considered to be the cause of disability, these results suggest that tenosynovitis at the level of MTP-joints contributes significantly to physical impairments. This finding increases our understanding of the involvement of tenosynovitis in walking-disabilities in early arthritis.

In chapter 4 we show that MRI-detected tenosynovitis at the MTP-joints was associated with early RA at disease presentation. We know from previous studies that MRI-detected inflammation of the hand is predictive for RA-development in the early phases of disease.(13,14) In chapter 8 we aimed to study whether MRI-detected inflammation of the forefoot was also predictive, and if so, which MRI-feature was most important. In addition, data of MRI-inflammation in the hand was added, and for feasibility we studied whether combining MRI of the foot and the hand was of additional value in recognizing patients who progressed to RA. For this we studied 123 patients presenting with undifferentiated arthritis (UA); i.e. patients that did not fulfil the 2010 criteria, and that did not receive a diagnosis other than UA at their two weeks visit. The outcome was the development of RA during one year follow-up, defined as fulfilling the 2010 criteria and/or the initiation of DMARDs because of the clinical diagnosis of RA. MRI-data from symptom-free controls were used as a reference; MRI-inflammation was only considered positive if it was rare in healthy controls, defined as present in <5% of age-matched healthy controls. This was done to increase predictive accuracy of MRI by decreasing the rate of false-positive findings.(15) We observed that MRI-detected inflammation at the MTP-joints, and MRI-detected tenosynovitis at the MTP-joints in particular, was predictive for RA development. Tenosynovitis at the MCP-joints was also predictive for RA-development, with a stronger effect size than MTP-tenosynovitis (OR 3.73, 95%CI 1.76-7.91 versus OR 2.55, 95%CI 1.01-6.43). Adding data of foot-MRI to hand-MRI led to an increase in correct classification of RA-development of 1.6%, however there was also a 5.1% increase in incorrect classifications. Thus, performing MRI of the foot in addition to MRI of the hand did not increase the predictive performance. The reason behind this was that 60% of UA patients had combined foot and hand tenosynovitis and only 3% of UA patients had MTP-tenosynovitis without concomitant hand tenosynovitis. Based on these results we concluded that foot MRI does not have to be added to hand MRI, which saves scan time and thereby costs.

Discussion

In this thesis we aimed to increase our understanding of involvement of the forefoot in patients with early RA. In order to achieve this, we started off from what is known from the literature. Since the rheumatologic field mostly focuses on the hands, the RAMRIS was developed as a tool to evaluate MRI-detected inflammatory and destructive changes in the hands.(16) A logical step towards understanding involvement of the forefoot, therefore, was to apply the RAMRIS to MRI of the forefoot. A small amount of MRI-studies previously measured inflammation at the MTP-joints using the RAMRIS. These MRI-studies, however, had some limitations. They were generally small (≤ 30 RA patients), did not include information at joint level, did not compare findings of RA-patients to that of patients with other arthritides in order to determine the specificity of findings, and/or did not assess tenosynovitis.(17-22) In addition, simply applying the RAMRIS to the forefoot could be considered unfair, as the method was only validated for the hand, and not for the forefoot. We cannot assume that findings in the hand can be directly extrapolated to the feet. Therefore, a prior question that needed to be addressed was whether the RAMRIS was actually a valid outcome measure in these joints. Thus, this thesis started with a systematic literature review. Herein we concluded that the validity of applying the RAMRIS to the MTP-joints was insufficient on most aspects, and a future research agenda was determined. To answer to this research agenda, MRI-studies of the forefoot are necessary, but also, more fundamentally, anatomic studies are warranted, to reveal whether tendons at the MTP-joints possess a synovial sheath. As anatomy may help us to better interpret our MR-images, this in turn can help us to better understand the disease of the patient.

We were surprised to learn that anatomic literature was incomplete regarding structures in the forefoot. Besides anatomic literature, which are the books known to every medical student, for more recent advancements made in the field one can also look at anatomic studies that are published in journals. It may not be obvious for the treating physician that also in the field of anatomy advances can still be made. Then again, it may not be surprising that, as we bring into view progressively finer detail through advanced imaging, we expose new structures that pose questions on how to interpret what can be seen. For understanding these fine details, merely studying the anatomic literature may give an incomplete picture. One must dig deeper to understand what one sees.

In line with this, it is important to realize that every person looks at matters from his

or her own perspective. We started this thesis defining classic MRI-inflammation as synovitis, tenosynovitis and osteitis, because that is how it is commonly defined: in MRI-studies of hands but also in the small amount of MRI-studies available of the forefeet.(17-22) Along the way, we realized that in the foot perhaps there is more than just these three classic features. At first, when interpreting MRI of the forefoot, we stuck to our own rheumatologic perspective. Signals visible on the MRI that could not be defined as classic MRI-inflammation were waved off as mere 'noise'. We only came to the realization that these signals might be relevant when we studied the relationship between physical examination and MRI-inflammation in chapter 6. We were surprised to find that 52% of swollen MTP-joints showed no classic inflammatory features on MRI. Skeptic of these numbers, we went through the images, and noticed that in some cases there was actually a clear signal visible between the joints, in the intermetatarsal spaces. This led to a literature search. Soon we realized that these intermetatarsal spaces house synovium-lined bursae(6,11) and that inflammation of these bursae had been described in patients with established RA in ultrasound studies.(9,10) Additionally, the literature described other lesions in the forefoot; submetatarsal bursitis, intermetatarsal Morton's neuroma, and even more diffuse submetatarsal alterations in the subcutis.(23-25) Submetatarsal bursitis and Morton's neuroma have previously been described in RA (7,8) and in healthy controls(24,26). Diffuse submetatarsal alterations in the subcutis have been described in healthy controls, but not in RA.(26) Therefore we decided to revise the MR-images to systematically study these lesions in relation to physical examination. Furthermore, we extended our research by also studying the lesions in relation to RA in chapter 3. Thus, by including the complete MRI information and changing the way we looked at MRI-images already scored for MRI-inflammation, our interpretation of the images changed and the additional lesions became visible. This eventually led to a better understanding of the physical examination of the MTP-joints, and, more importantly, it helped us to better understand the structures involved in the forefoot in early RA.

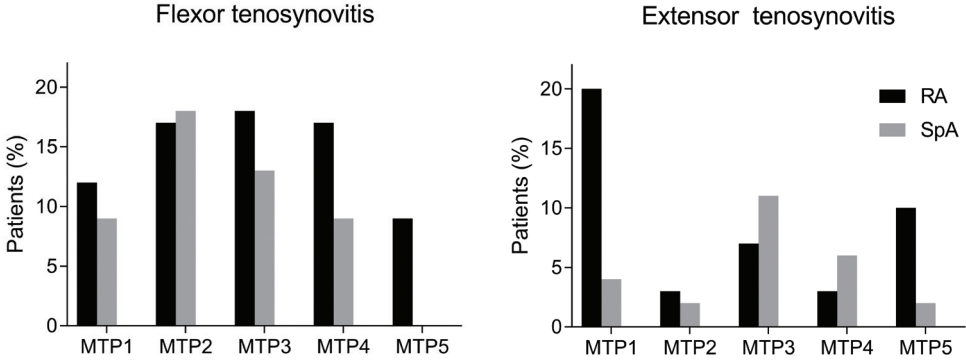
Our primary aim was to better understand the involvement of the forefoot in RA. It may seem odd that in order to achieve this we also included data from the hands, as was done in chapter 3, 6 and 7. However, since most research up to this point has focused on the hands,(1) we felt that including data of the hands could strengthen the results of the forefoot. Research requires validation, data on the hands may help to achieve this. Especially considering that the data of the hands was taken under the same circumstances as the data from the feet: from the

same patients, undergoing physical examination by the same physicians and both extremities were scanned with a similar MRI-protocol. In chapter 3 scoring of the MTP-joints was equally reliable as the MCP-joints, which came as a reassurance. In chapter 7, MRI-detected tenosynovitis at the MTP-joints was predictive for the progression from UA to RA, similar to MRI-detected tenosynovitis in the hands. (27) In line with this, in chapter 2 we found that tenosynovitis at the MTP-joints was associated with RA, similar to a previous publication of tenosynovitis in the hands.(5) Remarkably, chapter 6 underlines the relevance of including the hands as comparison to the feet, not because the feet were similar to the hands, but this time because they were different: the relationship between physical joint examination and MRI-inflammation turned out to be different for the MTP- and MCP-joints. At the MCP-joints absence of joint swelling was related to absence of MRI-inflammation, and swelling was correlated with classic inflammatory MRI-features. This finding was reassuring: the relation between physical examination and MRI at MCP-joints was as expected. The data of the MTP-joints, however, showed a different relation, and revealed that physical examination of MTP-joints was sometimes perhaps too sensitive: swollen MTP-joints often revealed no MRI-inflammation. For clinicians this may seem unexpected. While most clinicians would agree that physical examination of MTP-joints is difficult,(28) most would probably expect to see inflammation in joints that are not swollen, and would certainly not expect inflammation to be absent in swollen joints. Unexpected results may question the credibility and methodology of research. Adding the reassuring data of the hands may help to refute these arguments.

Besides the comparison of data of the feet to that of the hands, this thesis also focused on the inclusion of control groups. To study the association of MRI-detected lesions for RA, not only healthy individuals/volunteers were used as a control group, but also patients who presented to the rheumatologist with arthritis other than RA. This is a clinically more relevant control group, as these are the type of patients that rheumatologists in clinical practice would want to differentiate patients with RA from.(29) Adding data from healthy controls served to analyse whether these findings could be considered normal or not, and as an extra step in the validation of the results. Nevertheless, despite the use of different control groups in this thesis, and the comparisons made between hands and feet, external validation of our results is necessary.

From this thesis, it is clear that tenosynovitis at the MTP-joints is an important aspect of RA-involvement in the forefoot. We have shown that tenosynovitis at

MTP-joints is associated with RA compared to other arthritides. It is important to note that psoriatic arthritis (PsA) is a disease that is known for the occurrence of tendinitis at the insertion sites especially of larger tendons, such as the Achilles tendon, referred to as enthesitis. In our studies, patients with this disease were included as part of the 'other arthritides' group, but we have not specifically studied how tenosynovitis at the MTP-joints compared between RA-patients and PsA-patients. To briefly touch upon this subject in this discussion, we hereby include a histogram, that is analogous to figure 4 in chapter 4: on the left the frequencies of flexor tenosynovitis and on the right of extensor tenosynovitis are portrayed.



The histograms illustrate that tenosynovitis at MTP-joints occurs more frequently in PsA than in the overall 'other arthritides' group as was presented in chapter 4. The contrast between RA and PsA is therefore not as strong. However, in general tenosynovitis at MTP-joints does occur more frequently in RA- than in PsA-patients, especially flexor and extensor tenosynovitis at MTP-1 and 5. Thus tenosynovitis at the MTP-joints is perhaps more a feature of RA, a disease of the synovium, than of PsA, that is characterized by enthesitis. It would be interesting to study this in more detail in future studies, and to also include tenosynovitis of the hands.

Structural damage depicted by conventional radiography is considered the gold standard for imaging in RA.(30) Regarding these radiographs, the predictive value of hand and foot images alone are of limited value; combining the two provides better diagnostic performance for RA.(31,32) As the focus in RA is shifting towards early treatment, the recognition of early disease is increasingly important. In these early phases conventional radiography is not sensitive, therefore more advanced

imaging such as MRI is gaining importance.(30) A previous study found that MRI-detected erosions in both hand and feet were not predictive for the development of RA.(33) In a different study MRI-detected inflammation in the hands, however, did contribute to the identification of patients who will develop RA.(27) We therefore wondered in chapter 7 whether adding MRI of the foot could be of additional benefit. Contradictory to what is known from radiographs, adding MRI of the feet did not improve the predictive accuracy: in terms of feasibility excluding the foot from the MRI-protocol would save time and reduce costs. These results were also found in the phase of clinically suspect arthralgia.(34) This finding might seem contradictory however it could be explained by the fact that in the majority of patients with MRI-detected inflammation at the MTP-joints, specifically tenosynovitis, was also present in the hands. This does not mean that the feet are unimportant, because tenosynovitis at MTP-joints was predictive for the development of RA, however it highlights that the hands are more often involved. We can also conclude this from the other chapters throughout the thesis: in chapter 4 we found MRI-detected tenosynovitis at MTP-joints in 41% of patients with RA, while a previous study found MRI-detected tenosynovitis at the hands in 65% of patients with RA.(5) In addition, in chapter 6 is shown that swelling upon physical joint examination was also more frequent in the hands than the feet: 30% of patients had swelling of an MCP-joint vs. 17% of an MTP-joint, a pattern that is similar to a previous observation.(35)

Therefore, it is perhaps not so strange that the literature is focused on the hands. Even the most important measure of disease activity, the Disease Activity Score (DAS), has been transformed to the DAS28 that omits joint examination of the feet.(36) In order to consider this further, perhaps a distinction between group and patient level is important. In trials, the effects of treatment are studied on group level. As the majority of patients with RA will indeed have complaints of the hands, it may not be a big problem if the study neglects the lower extremities. However, for the individual patient with isolated inflammation of the feet, neglecting the lower extremities may potentially lead to undertreatment. Indeed, previously the DAS28 was found to be inferior to the DAS, as residual activity in foot-joints was found despite remission according to the DAS28.(37) Therefore, in clinical practice, the DAS28 must be used with caution.(37) This underlines the difference between research and clinical practice. It is important to note that the aim of this thesis was to understand involvement of RA in the forefoot. It does not necessarily encourage the use of MRI of the feet in daily clinical practice. The question arises, whether we can conclude from our data, especially in chapter 7, that performing MRI of the

feet, at least for research purposes, can be omitted. As we learned from chapter 2 there are many aspects that are important to consider. For example, inflammation at the MTP-joints may respond differently to treatment of the MCP-joints; however this is as of yet unknown and should be subject of subsequent studies. Therefore data from clinical trials are necessary to be able to study how inflammation at the MTP-joints respond to treatment, and perhaps to compare this to inflammation at the MCP-joints.

In short, based on this thesis we learned that:

- To better understand disease, sensitive imaging is performed. To better understand these images, we are at times forced to go back to studying the human body.
- Synovitis in the rheumatoid foot affects more than just the joints: tendon-sheaths and intermetatarsal bursae also have a synovial lining and are often inflamed due to involvement in disease
- Secondary lesions without a synovial lining can be found in the rheumatoid foot: submetatarsal bursae and Morton's neuroma.
- The tendon sheaths of the forefoot are almost never inflamed in healthy controls
- Results of the hands cannot be directly extrapolated to the feet: as in the foot additional structures can be involved and it is unknown whether these respond differently to treatment, if at all
- In RA, the feet are less often involved than the hands. MRI of the feet, at group level, can possibly be omitted. However for the individual patient, omitting examination of the feet may potentially lead to undertreatment.

Future perspectives

This brings us to our future perspectives. Regarding the research agenda that was formulated in chapter 2 that concerned MRI-detected inflammation (synovitis, tenosynovitis and osteitis) and structural damage (erosions and joint space narrowing), we were unable to answer all questions. In addition, new questions can be posed regarding the inter- and submetatarsal lesions. Of these lesions, intermetatarsal bursitis is the only primary lesion, as it can be found in naturally occurring synovial intermetatarsal bursae, as opposed to Morton's neuroma and submetatarsal bursitis that are secondary in nature. Intermetatarsal bursitis also

had the highest sensitivity for RA. Therefore intermetatarsal bursitis is perhaps the most interesting to include in future studies. A future research agenda might include:

Regarding classic MRI-features (i.e. synovitis, tenosynovitis, osteitis, erosions, joint space narrowing):

- Does MRI-detected subclinical joint inflammation at the MTP-joints predict radiographic progression?
- What is the clinical relevance of MTP-swelling without MRI-detected inflammation? Is radiographic progression or the development of MRI-detected erosions different for swollen MTP-joints with and without MRI-detected inflammation?
- What is the value of MRI of MTP-1? How does inflammation of MTP-1 in RA relate to other arthritides?
- What is the validity of MRI of the MTP-joints in established RA
- How do these MRI-features at the MTP-joints change over time, how does treatment influence this? How does this relate to change in other instruments, such as symptoms, physical examination, conventional radiography? Preferably studied in the controlled environment of clinical trials.
- Regarding joint space narrowing no data at the MTP-joints is as of yet available, thus all aspects require validation
- How do the MRI-features at the MTP-joints relate to auto-antibodies in patients with RA?
- How does tenosynovitis at MTP- and MCP-joints in RA compare to tenosynovitis in psoriatic arthritis?

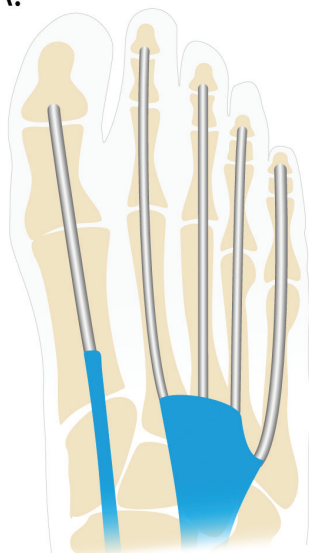
Regarding intermetatarsal bursitis, it is striking that so little is known about a lesion that is so frequently present in patients with RA. Therefore for intermetatarsal bursitis an extensive future research agenda can be made:

- What is the best MRI-protocol to visualize intermetatarsal bursitis?
- Can intermetatarsal bursitis be scored reliably?
- How does intermetatarsal bursitis relate to other clinical parameters or to radiographic progression?
- How does intermetatarsal bursitis relate to classic MRI-detected features on joint level? Are the features associated with each other?

- How does intermetatarsal bursitis relate to auto-antibodies in patients with RA?
- What is the diagnostic value of determining the presence of intermetatarsal bursitis?
- Can intermetatarsal bursitis predict the development of RA in patients with undifferentiated arthritis?
- Is intermetatarsal bursitis present in the earliest phases of disease, i.e. in clinically suspect arthralgia? Can it predict the development of clinically apparent inflammatory arthritis?
- How does intermetatarsal bursitis change over time? Does it respond to treatment?
- How does change in intermetatarsal bursitis relate to change in other instruments, such as symptoms, physical examination, conventional radiography?

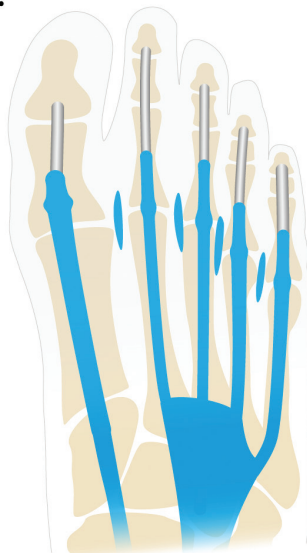
Finally, a last remark to conclude this thesis: changing one's perspective leads to discoveries that were in front of us all this time. Importantly, collaborations with the departments of radiology and anatomy were necessary to achieve this. By doing this, throughout this thesis, the way we appreciate RA in the forefoot has changed. The image below illustrates this: Image (A) illustrates the way we viewed the forefoot in RA prior, and image (B) after the studies that have been performed as part of this thesis.

A.



Before

B.



After

A: Dorsal view of the forefoot illustrating tenosynovium proximal of the MTP-joints, B: Dorsal view of the forefoot illustrating that the tenosynovium of the extensor tendons extends distally past the MTP-joints, in addition there are synovial bursae between the metatarsal heads.

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Nederlandse samenvatting

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Reumatoïde artritis (RA) is een auto-inflammatoire ziekte die zich kenmerkt door ontsteking van met name de kleine synoviale gewrichten van de handen en voeten. In het reumatologische onderzoeksveld gaat de meeste aandacht echter uit naar onderzoek van de handen. Daarom was het doel van deze thesis om beter begrip te krijgen van de betrokkenheid van de kleine voetgewrichten, de metatarsofalangeale (MTP)-gewrichten in de vroege fase van RA, dat wil zeggen op het moment dat een patiënt zich voor het eerst bij de reumatoloog presenteert vanwege artritis. Om deze brede vraagstelling te kunnen beantwoorden, is er vanuit de afdeling reumatologie samengewerkt met de afdelingen Radiologie en Anatomie en Embryologie.

MRI wordt steeds vaker ingezet in het reumatologisch onderzoeksveld. De RA-MRI-score (RAMRIS) is ontwikkeld en gevalideerd als een gestandaardiseerde uitkomstmaat voor het scoren van MRI van de handen. Door middel van deze score kunnen verschillende soorten ontsteking worden gemeten: synovitis, tenosynovitis en osteitis. Tenosynovitis kenmerkt zich door een ontsteking van de synoviale schede rondom pezen. Osteitis, ook wel bekend als beenmergoedeem, is een infiltratief proces in het botweefsel nabij een synoviaal gewricht. Tevens kan door middel van de RAMRIS schade worden gemeten door het scoren van erosies en gewrichtsspleetversmalling. In hoofdstuk 2 hebben we een systematische literatuuronderzoek uitgevoerd om nader te bestuderen of er genoeg bewijskracht is om de RAMRIS op de MTP-gewrichten toe te passen. Dit hebben we gedaan aan de hand van de OMERACT Filter criteria: 'Truth', 'Discrimination', en 'Feasibility'. Truth oftewel waarheid, bepaald of hetgeen wat gemeten wordt overeen komt met wat men daadwerkelijk wilt meten. Dit wordt bepaald aan de hand van Face, Content en Construct validiteit. Face en content validiteit zijn veelal subjectieve parameters die aan de hand van consensus wordt bepaald, terwijl construct validiteit wordt bepaald door bijvoorbeeld de MRI-variabele te vergelijken met een andere uitkomstmaat, zoals echo, histologisch onderzoek of symptomen. Discrimination wordt o.a. bepaald door de betrouwbaarheid waarmee een variabele gemeten kan worden, en de mate waarin een variabele verandering over tijd kan laten zien. Feasibility, oftewel haalbaarheid bekijkt hoe makkelijk toepasbaar het betreffende onderzoek in de praktijk kan worden toegepast. Al met al bleek uit het systematische literatuuronderzoek dat er weinig bekend was over het toepassen van de RAMRIS op de MTP-gewrichten. Er waren maar 13 studies die voldeden aan de inclusiecriteria. Hieruit bleek dat construct validiteit

aanwezig was voor osteitis en erosies, maar dat voor de overige variabelen (synovitis, tenosynovitis en gewrichtsspleetvermalling) er onvoldoende bewijs was om hier een conclusie over te trekken. Voor discriminatie en haalbaarheid was er onvoldoende data voor alle MRI-variabelen. Het onderzoek werd daarom afgesloten met een uitgebreide onderzoeksagenda. Bovendien bleek dat voor face en content validiteit voor tenosynovitis aanvullend anatomisch onderzoek vereist was om nader te onderzoeken of de pezen nabij de MTP-gewrichten een synoviaal beklede peesschede hebben. Enkele van de punten hieruit zullen in het vervolg van de thesis aan bod komen.

Betrouwbaarheid van het scoren is een belangrijk onderdeel van Discriminatie, en werd nader onderzocht in hoofdstuk 3. Hiervoor werd MRI-data van de MTP-gewrichten vergeleken met data van de handen (pols en metacarpofalangeale (MCP)-gewrichten). De inter- en intralezers betrouwbaarheid werden bepaald voor patiënten met vroege artritis, maar ook bij patiënten met artralgie die klinisch verdacht was voor het ontstaan van artritis (clinically suspect arthralgia – CSA). Tevens werd de betrouwbaarheid bepaald voor de verandering van de scores over de tijd. Hiervoor werden intraclass correlation coefficients (ICC) uitgerekend als maat om deze betrouwbaarheid weer te geven. De interlezer ICC-scores waren ≥ 0.80 , de intralezer ICCs ≥ 0.84 , en de ICCs voor verandering over tijd ≥ 0.90 . Deze ICCs waren al met al goed tot excellent. Als een andere maat voor de betrouwbaarheid werden tevens Bland-Altman plots gemaakt, en voor de verandering over tijd werd de kleinste detecteerbare verandering (smallest detectable change, SDC) bepaald. Hieruit kwam naar voren dat er geen systematische bias was en geen grote metingsfouten. Om de resultaten kracht bij te zetten werden de uitslagen van de MTP-gewrichten vergeleken met de pols- en MCP-gewrichten: de resultaten van de MTP-gewrichten bleken even betrouwbaar. We concludeerden daarom dat het scoren van de MTP-gewrichten door middel van de RAMRIS betrouwbaar is. Uit de CSA-data kwamen dezelfde resultaten. Dit is van belang omdat in het reumatologisch onderzoeksveld de aandacht verschuift van vroege RA naar steeds eerdere fases van de ziekte, inclusief CSA. Een eerdere studie had al gekeken naar de betrouwbaarheid van het scoren van osteitis, synovitis en erosies, en een andere studie naar de verandering over tijd van erosies. Onze studie kijkt voor het eerst naar de betrouwbaarheid van het scoren van tenosynovitis bij de MTP-gewrichten, en de verandering over tijd van de overige scores. Aansluitend op de eerdere onderzoeken hebben wij aangetoond dat het scoren van synovitis, tenosynovitis, osteitis en erosies bij de MTP-gewrichten betrouwbaar is. Dit is een belangrijke steen waarop de rest van deze

thesis verder zal bouwen. Gewrichtsspleetversmalling was geen onderdeel van deze studie, omdat bij aanvang van de studie deze variabele nog geen onderdeel was van de RAMRIS.

Voor 'Face' en 'Content' validiteit is het belangrijk dat de MRI het onderliggende pathofysiologische kenmerk weergeeft. In het geval van tenosynovitis, is het pathofysiologische kenmerk ontsteking van de synoviale bekleding van de peesschede die zich rondom de pees begeeft, oftewel de synoviale peesschede. Eerdere MRI-studies van de handen hebben laten zien dat tenosynovitis bij de MCP-gewrichten en pols een vroeg kenmerk is van RA. Met betrekking tot de MTP-gewrichten is er weinig bekend over tenosynovitis: de frequentie waarin inflammatie alhier te zien is, alsmede de associatie met RA zijn onbekend. Bovendien, en wellicht meer onverwacht, is dat het vanuit de anatomische literatuur onduidelijk is of de pezen nabij de MTP-gewrichten überhaupt een synoviaal beklede peesschede hebben. Het is daarmee dan ook onbekend of een ontsteking rondom de pezen een tenosynovitis zou betreffen. Daarom hebben we in hoofdstuk 4 twee onderzoeken uitgevoerd: een anatomisch en een MRI-onderzoek. Voor het eerste onderzoek hebben we samengewerkt met de afdeling Anatomie en Embryologie om te onderzoeken of er een synoviale peesschede bij de flexor en extensorpezen nabij de MTP-gewrichten aanwezig was. Hiervoor werden 14 voorvoeten van aan de wetenschap gedoneerde lichamen macroscopisch onderzocht: er bleek bij alle extensor en flexorpezen macroscopisch een peesschede aanwezig te zijn. Microscopisch werd bevestigd dat het hierbij inderdaad gaat om een synoviale bekleding van deze peesscheden. Vervolgens werden in een MRI-onderzoek 157 achtereenvolgende patiënten die zich presenteerden met vroege RA, 284 die zich presenteerden met artritis met een andere diagnose (de zogeheten 'andere artritiden' groep) en 193 gezonde vrijwilligers onderzocht. Zij ondergingen allen MRI van MTP 1-5, die werd gescored op tenosynovitis, synovitis en osteitis. 42% van de RA-patiënten bleken tenosynovitis te hebben, vergeleken met 22% van de andere artritiden en 2% van de gezonde vrijwilligers. Tenosynovitis bleek derhalve geassocieerd te zijn met RA, ook nadat het gecorrigeerd werd voor de aanwezigheid van synovitis en osteitis, en bij aanvullende correcties voor gezwollen gewrichten, CRP en ACPA antistoffen. Concluderend: pezen nabij de MTP-gewrichten hebben een synoviaal beklede peesschede, die, vergelijkbaar met tenosynovitis bij de kleine handgewrichten een vroege feature van RA zijn, onafhankelijk van lokale synovitis en osteitis.

In de voorvoet zijn, behalve botten en pezen, ook andere weefsels aanwezig, zoals

de synoviaal beklede bursae, de neurovasculaire bundel en de subcutis. Uit oudere literatuur blijkt dat deze betrokken kunnen zijn in patiënten met langer bestaande RA, alhoewel dit niet systematisch bestudeerd is. In hoofdstuk 5 hebben we daarom de voorvoet vanuit een ander anatomisch perspectief bestudeerd: in plaats van vanuit het perspectief van de gewrichten, kijkt dit hoofdstuk naar de voorvoet vanuit het perspectief van de inter- en submetatarsale ruimtes. Hiervoor werden, wederom, eerst de anatomische boeken geconsulteerd: helaas werden deze ruimtes hierin niet genoemd. Er bleken gelukkig wel enkele anatomische studies te zijn die deze regio's uitgebreid hadden gekarakteriseerd. In de vier intermetatarsale ruimtes kunnen de intermetatarsale bursae worden aangetroffen, alsmede de neurovasculaire bundel, van waaruit het Morton's neuroom zich kan ontwikkelen. In de subcutis worden de vijf submetatarsale ruimtes aangetroffen, één onder elk metatarsale kopje. Hierin worden twee type laesies onderscheiden: de submetatarsale bursitis en een laesie die zich kenmerkt door een diffusere aankleuring: de diffuse submetatarsale alteraties. Hoofdstuk 5 legt de nadruk met name op de bursitiden: de intermetatarsale en submetatarsale bursitis. Echter, de Morton's neuroom en de diffuse submetatarsale alteraties werden meegescored. Hiervoor werd dezelfde populatie onderzocht als in hoofdstuk 4. De laesies werden gescored op aanwezigheid, daarnaast werden de transversale en dorsoplantaire diameters van de inter- en submetatarsale bursitis en Morton's neuroom opgemeten. De diameter van de diffuse submetatarsale alteraties werden niet bepaald omdat deze laesie per definitie geen scherpe grenzen heeft. Uit de analyses bleek dat zowel intermetatarsale als submetatarsale bursitis en Morton's neuroom geassocieerd waren met RA. Uit multivariabele analyses bleek dat deze associatie onafhankelijk van elkaar was, als ook onafhankelijk van leeftijd, geslacht, BMI en lokale MRI-inflammatie (synovitis, tenosynovitis en osteitis bij de MTP-gewrichten). Tenslotte bleek de grootte van de laesies weinig onderscheidend vermogen te hebben: er kon geen afkap-punt worden bepaald voor RA met voldoende behoud van sensitiviteit en specificiteit.

In hoofdstuk 6 werd als maat voor construct validiteit de relatie tussen MRI-inflammatie en lichamelijk onderzoek als klinische uitkomstmaat onderzocht. Het gewrichtsonderzoek van de MTP-gewrichten wordt vaak als moeilijk beschouwd. De concordantie en discordantie van het lichamelijk onderzoek met MRI werden bepaald. Behalve de klassieke MRI-inflammatie, d.w.z. synovitis, tenosynovitis en osteitis, werd intermetatarsale bursitis ook bestudeerd. De synoviale bekleding van deze bursae kan door inflammatie namelijk vergroten en palpabel worden. Tevens werden de relatie tussen het gewrichtsonderzoek en MRI van de MCP-gewrichten

meegenomen ter vergelijking. 441 patiënten met vroege artritis werden onderzocht. Allen ondergingen gewrichtsonderzoek van de MTP- en MCP-gewrichten door twee onafhankelijk onderzoekers. We toonden aan dat niet gezwollen MTP-gewrichten geruststellend waren, omdat deze veelal geen MRI-inflammatie hadden. Echter, gezwollen MTP-gewrichten, hadden een heterogene origine. Behalve synovitis, leverde tenosynovitis een belangrijk bijdrage aan gewrichtszwelling. Desalniettemin bleek dat 52% van de gezwollen MTP-gewrichten geen van deze inflammatoire features toonden: hiervan kon 21% verklaard worden door intermetatarsale bursitis, de resterende 31% van de gezwollen MTP-gewrichten had echter geen verklaring voor de zwelling op MRI. Deze relatie was duidelijk anders voor de MTP- dan voor de MCP-gewrichten. Gezwollen MCP-gewrichten hadden, zoals verwacht, in het merendeel van de gevallen inflammatie. Dus, alhoewel ons onderzoek het algemene begrip dat het gewrichtsonderzoek van de MTP-gewrichten moeilijk is bevestigt, is dit wellicht niet de kant op waarin de meesten het zouden verwachten. Onze resultaten suggereren dat het gewrichtsonderzoek van de MTP-gewrichten wellicht te sensitief is.

Voor patiënten zijn beperkingen wellicht een belangrijkere uitkomstmaat dan gewrichtszwelling, daar dit een belangrijkere impact heeft op de kwaliteit van leven. Daarom werd in hoofdstuk 7 de associatie tussen MRI-inflammatie en moeilijkheden bij het lopen onderzocht, zowel voor 532 patiënten met vroege artritis op baseline, als voor 107 patiënten met 2 jaar follow-up. We zagen hierbij dat moeilijkheden bij het lopen geassocieerd waren met MRI-inflammatie, met name met tenosynovitis bij de MTP-gewrichten. Tevens was een afname in loopproblemen geassocieerd met een reductie in MRI-inflammatie. Ook deze associatie was het sterkste voor tenosynovitis. Alhoewel in patiënten met artritis meestal wordt gedacht dat synovitis de belangrijkste invaliderende factor is, hebben wij aangetoond dat tenosynovitis een belangrijke bijdrage levert aan de lichamelijke beperkingen die patiënten ervaren.

In hoofdstuk 4 zagen we dat tenosynovitis bij de MTP-gewrichten geassocieerd was met RA op het moment dat patiënten zich voor het eerst presenteerden met artritis. Uit eerder onderzoek weten we dat MRI-inflammatie van de handen geassocieerd is met het ontwikkelen van RA in de vroegere fases van de ziekte. In hoofdstuk 8 onderzochten we of MRI-inflammatie bij de MTP-gewrichten voorspellend was voor het ontwikkelen van RA. MRI-inflammatie van de handen werd ook onderzocht, om te kunnen beantwoorden of MRI van de voeten toegevoegde waarde had boven MRI van de handen (in het kader van Feasibility, oftewel haalbaarheid).

123 patiënten met ongedifferentieerde artritis, dat wil zeggen patiënten die niet voldeden aan RA-classificatie criteria van 2010 en die bij hun 2 weken visite geen diagnose anders dan ongedifferentieerde artritis kregen, werden een jaar lang gevolgd. De uitkomst was het ontwikkelen van RA binnen dat jaar, gedefinieerd als het voldoen aan de 2010 criteria en/of starten met de behandeling met disease modifying anti-rheumatid drugs (DMARDs) dankzij de klinische diagnose van RA. De MRI-data van gezonde vrijwilligers werd als referentie gebruikt; MRI-inflammatie werd alleen als positief beschouwd als deze zeldzaam was in gezonde vrijwilligers, dat wil zeggen als het aanwezig was in <5% van gezonde vrijwilligers in dezelfde leeftijdscategorie. We vonden dat MRI-inflammatie, en met name tenosynovitis, voorspellend waren voor het ontwikkelen van RA. Tenosynovitis nabij de MCP-gewrichten was ook voorspellend, met een sterkere effectgrootte dan MTP-tenosynovitis (OR 3.73, 95%CI 1.76-7.91 versus OR 2.55, 95%CI 1.01-6.43). Het toevoegen van MRI van de voeten bij MRI van de handen gaf een toename in correcte classificaties van RA met 1.6%, maar er was ook een 5.1% toename in foutieve classificaties. MRI van de voeten bovenop MRI van de handen had dus geen toegevoegde waarde in het verbeteren van de voorspellende waarde. Dit kwam doordat 60% van de patiënten MTP-tenosynovitis had samen met hand-tenosynovitis. Maar 3% van de patiënten had MTP-tenosynovitis zonder hand-tenosynovitis. We concludeerden derhalve dat MRI van de MTP-gewrichten geen toegevoegde waarde had bovenop MRI van de handen. Dit helpt om scantijd, en dus kosten te besparen.

Discussie

10

Het doel van deze thesis was om het inzicht in de betrokkenheid van de kleine voetgewrichten in de vroege fase van RA te vergroten, met behulp van sensitieve imaging (MRI), klinische parameters, en anatomie. We begonnen met een literatuuroverzicht. In het reumatologische veld is de RAMRIS een belangrijke tool in de evaluatie van inflammatie en destructie die te zien zijn op de MRI van de handen. Een logische stap om betrokkenheid van de MTP-gewrichten te vergroten is om in eerste instantie te kijken of de RAMRIS toegepast kan worden op MRI van de MTP-gewrichten. Slechts een handvol onderzoeken pasten de RAMRIS toe op MRI van de voeten. Deze studies hadden limitaties; zij waren veelal klein (<30 patiënten), vergeleken de MRI-waarden in RA niet met een controlegroep om de specificiteit van de bevindingen te kunnen weergeven, en tenosynovitis bij de MTP-gewrichten bleek nog niet eerder onderzocht te zijn. Een belangrijke primaire vraag

bleek derhalve of de RAMRIS überhaupt wel een valide uitkomstmaat is voor de MTP-gewrichten. Ons literatuuronderzoek in hoofdstuk 2 gaf antwoord op deze vraag. Hieruit bleek dat het toepassen van de RAMRIS op de MTP-gewrichten in de meeste aspecten van de validiteit ontoereikend was. We sloten het hoofdstuk daarom af met een overzicht van de vragen die nog beantwoord dienden te worden. Om deze vragen te beantwoorden zijn MRI-studies nodig, maar ook meer fundamentele anatomische onderzoeken om nader te bepalen of de pezen nabij de MTP-gewrichten een synoviale schede hebben. Door beter begrip van de anatomie kunnen we de beelden van de MRI beter interpreteren waardoor we uiteindelijk beter inzicht krijgen in de ziekte van de patiënt.

Tot onze verbazing bleek de kennis die wij uit de anatomische tekstboeken haalden incompleet was met betrekking tot de anatomische structuren in de voorvoet. Behalve deze tekstboeken, kan voor meer recente anatomische kennis worden gekeken naar gepubliceerde onderzoeken. De clinicus realiseert zich wellicht niet dat er ook in de anatomie nog vooruitgang kan worden geboekt en er alsmaar nieuwe inzichten worden verkregen. Alhoewel dit wellicht niet zo verrassend is, aangezien we door steeds sensitievere imaging het menselijk lichaam steeds gedetailleerder kunnen bekijken. Deze details vragen om interpretatie, waar nieuwe anatomische studies bij kunnen helpen, zoals het geval was in hoofdstuk 4.

Belangrijk hierbij is de realisatie dat een ieder zaken vanuit zijn eigen perspectief bekijkt. Zo startte wij deze thesis met de volgende definitie van 'klassieke' MRI-inflammatie: synovitis, tenosynovitis en osteitis, omdat de literatuur van MRI van de handen dat op deze manier definieert. Echter, gaandeweg realiseerden wij ons dat er in de voorvoet wellicht meer inflammatoire features zijn dan alleen deze drie. Aanvankelijk scoren we de MRIs vanuit een reumatologisch perspectief: signaal wat niet onder de klassieke MRI-features viel werd opzij gezet als 'ruis'. We kwamen pas tot de realisatie dat deze ruis relevant zou kunnen zijn toen we onderzoek deden naar de relatie tussen lichamelijk onderzoek en MRI in hoofdstuk 6. Het verbaasde ons dat 52% van de gezwollen MTP-gewrichten geen klassieke MRI-inflammatie toonde. Sceptisch gingen wij opnieuw door de beelden, waarbij wij zagen dat er in sommige gevallen wel degelijk een duidelijk signaal zichtbaar was tussen de MTP-gewrichten in de intermetatarsale ruimtes. We doken opnieuw de literatuur in, waarbij we ons al snel realiseerde dat er in deze intermetatarsale ruimtes bursae zitten met een synoviale bekleding. Inflammatie van deze laesies bleek ook al eerder beschreven te zijn in een echo-onderzoek in patiënten met langer bestaande RA. We kwamen in de literatuur nog andere laesies tegen

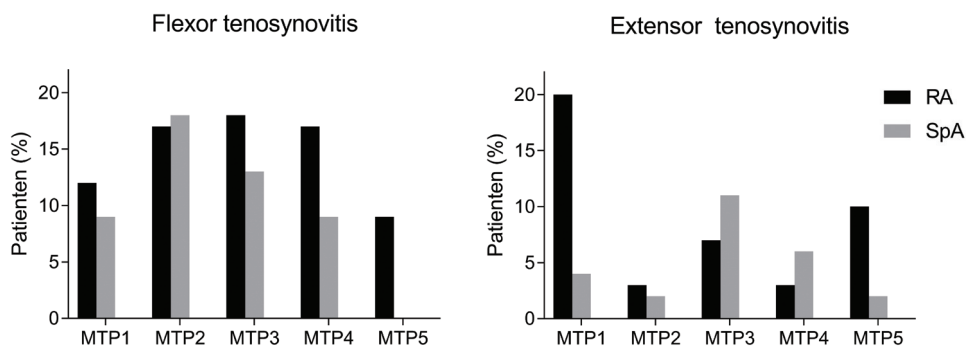
zoals submetatarsale bursitis, Morton's neuroom in de intermetatarsale ruimte en diffuse submetatarsale alteraties in de subcutis. Ook submetatarsale bursitis en Morton's neuromen bleken beschreven te zijn in RA. Diffuse submetatarsale alteraties in de subcutis waren beschreven in gezonde vrijwilligers, maar niet in RA. We besloten hierop om de MRIs te herzien, ditmaal vanuit een ander perspectief: dat van de laesies in de inter- en submetatarsale ruimtes. We onderzochten de relatie met het lichamelijk onderzoek, omdat daar de zoektocht naar deze laesies was begonnen, maar ook in relatie met RA in hoofdstuk 3. Het veranderen van ons perspectief, en op een andere manier naar de MRIs te kijken die we al uitgebreid hadden gescored, leverden ons interessante nieuwe bevindingen op. Hierdoor kregen we een beter begrip in het gewrichtsonderzoek van de MTP-gewrichten, maar ook een beter begrip in welke structuren in de voorvoet betrokken zijn in vroege RA.

Door de thesis heen hebben we in hoofdstukken 3, 6 en 7 data van de handen meegenomen, om beter begrip te krijgen in de data van de voorvoet. Omdat er in de literatuur meer bekend was over de handen, besloten wij deze data mee te nemen om de data van de voorvoet kracht bij te zetten. Validatie is een belangrijke voorwaarde voor onderzoek, data van de handen zou kunnen helpen om dit te bereiken, met name omdat de MRI-data van de handen onder dezelfde omstandigheden als de data van de voorvoet was verkregen: dezelfde patiënten, die hetzelfde lichamelijk onderzoek door dezelfde artsen ondergingen en waarbij beide extremiteiten gescand werden volgens hetzelfde MRI-protocol. In hoofdstuk 3 bleek dat het scoren van de MTP-gewrichten even betrouwbaar was als het scoren van de MCP-gewrichten, wat als een geruststelling kwam. In hoofdstuk 7 bleek tenosynovitis bij de MTP-gewrichten een voorspellende factor te zijn voor de ontwikkeling van RA in patiënten met ongedifferentieerde artritis, vergelijkbaar met tenosynovitis nabij de handgewrichten. In hoofdstuk 6 bleek dat de relatie van het gewrichtsonderzoek met MRI anders was voor de MTP-gewrichten dan de MCP-gewrichten. Voor de MCP-gewrichten was de afwezigheid van gewrichtszwelling geassocieerd met de afwezigheid van MRI-inflammatie, en de aanwezigheid van zwelling met de aanwezigheid van MRI-inflammatie. Dit kwam als een geruststelling, omdat dit patroon verwacht werd. De data van de MTP-gewrichten toonde echter een andere relatie, waarbij het gewrichtsonderzoek soms wellicht te sensitief bleek: gezwollen MTP-gewrichten toonden vaak geen MRI-inflammatie. Deze uitslag is wellicht onverwacht. Alhoewel de meeste klinici het gewrichtsonderzoek van de MTP-gewrichten wellicht moeilijk vinden, zouden deze wellicht verwachten dat de relatie omgekeerd zou zijn: d.w.z. dat niet

gezwollen gewrichten inflammatie toonden. Door deze onverwachte resultaten zou men vraagtekens kunnen zetten bij de methodologie van het onderzoek. Door het toevoegen van de geruststellende resultaten van de MCP-gewrichten, kunnen deze vragen weerlegd worden.

Behalve het toevoegen van data van de handen, focuste deze thesis zich ook op het includeren van controlegroepen. Om de associatie van MRI met RA goed te kunnen onderzoeken, werden niet alleen gezonde vrijwilligers onderzocht als een controlegroep, maar ook patiënten die zich met artritis presenteerden en uiteindelijk een andere diagnose dan RA kregen. Dit is een klinisch relevante groep, omdat dit de patiënten zijn waarvan reumatologen de patiënten met RA van willen onderscheiden. De data van de gezonde vrijwilligers is relevant omdat dit helpt te onderscheiden of een bevinding normaal is. Desondanks het gebruik van de verschillende controlegroepen en de vergelijking tussen handen en voeten, is externe validatie van onze bevindingen geïndiceerd.

Uit deze thesis blijkt dat tenosynovitis bij de MTP-gewrichten een belangrijk onderdeel is van RA-betrokkenheid van de voorvoet. We toonden aan dat tenosynovitis bij de MTP-gewrichten geassocieerd was met RA vergeleken met andere artritiden. Het is belangrijk om te noemen dat artritis psoriatica (PsA) een ziekte is die zich kenmerkt door tendinitis bij de insertieplek van de grotere pezen, zoals de Achillepees, ook wel bekend als enthesitis. In onze studies waren patiënten met PsA onderdeel van de 'andere artritiden' controlegroep, maar patiënten met PsA en RA zijn niet 1 op 1 met elkaar vergeleken. We willen daar in deze discussie kort wat aandacht aan besteden. In het histogram hieronder, dat analoog is aan figuur 4 in hoofdstuk 4, is links de frequentie van flexor tenosynovitis, en rechts de frequentie van extensor tenosynovitis te zien in patiënten met RA (in het zwart) en PsA (grijs).



Uit deze histogrammen blijkt dat tenosynovitis nabij de MTP-gewrichten vaker voorkomt bij patiënten met PsA dan patiënten met andere arthritiden in hoofdstuk 4. Het contrast tussen RA en PsA is derhalve niet zo duidelijk. In het algemeen geldt dat tenosynovitis bij de MTP-gewrichten vaker voorkomt in RA dan in patiënten met PsA, met name flexor en extensor tenosynovitis van MTP 1 en 5. Concluderend is tenosynovitis bij de MTP-gewrichten wellicht toch meer een RA feature, een ziekte die zoals gezegd zich kenmerkt door synoviale ontsteking, dan PsA, een ziekte die zich kenmerkt door enthesitis. Het is interessant om deze relatie verder uit te werken in vervolgstudies, en om daarbij ook data van tenosynovitis van de handgewrichten mee te nemen.

Gewrichtsschade, gedefinieerd als erosies en gewrichtsspleetversmalling, zoals zichtbaar op conventionele röntgenfoto's zijn de gouden standaard voor imaging in RA. Echter, de predictieve waarde van röntgenfoto's van alleen handen of voeten zijn beperkt: door de twee te combineren neemt de diagnostische waarde voor RA toe. In RA-onderzoek ligt de focus in toenemende mate op het steeds vroeger behandelen van de ziekte, waarbij het ook steeds belangrijker wordt om deze ziekte vroeg op te sporen. In deze vroege fases zijn röntgenfoto's niet sensitief, waardoor meer geavanceerde imaging zoals MRI meer aandacht krijgt. Uit een eerder onderzoek bleek dat erosies op MRI van handen en voeten niet voorspellend waren voor het ontwikkelen van RA. Uit een ander onderzoek bleek dat MRI-inflammatie van de handen wel voorspellend was. In hoofdstuk 7 onderzochten we of MRI van de voeten toegevoegde waarde had. Tegenstrijdig met wat we weten van röntgenfoto's, bleek dit geen toegevoegde waarde te hebben, maar juist te resulteren in meer vals positieve uitslagen. In het kader van 'feasibility' kan met het achterwege laten van MRI van de voorvoet tijd en geld bespaard worden. Een verklaring voor deze bevinding was dat als er sprake was van tenosynovitis bij de MTP-gewrichten, er eigenlijk nagenoeg ook altijd sprake was van tenosynovitis bij de handgewrichten. Dit betekent niet dat de voeten onbelangrijk zijn, tenosynovitis bij de MTP-gewrichten was namelijk wel voorspellend, echter het benadrukt dat de handen vaker zijn aangedaan. Een zelfde conclusie kan worden getrokken aan de hand van andere hoofdstukken in deze thesis. In hoofdstuk 4 vonden we dat 41% van de RA-patiënten tenosynovitis bij de MTP-gewrichten had, terwijl een eerdere publicatie vond dat 65% van de RA-patiënten tenosynovitis bij de handgewrichten had. Uit hoofdstuk 6 blijkt dat gezwollen handgewrichten vaker voorkomen dan gezwollen voetgewrichten: 30% versus 17% van patiënten met vroege artritis hebben zwelling van het een of ander.

Daarom is het wellicht niet verassend dat de literatuur de nadruk legt op betrokkenheid van de handen in RA. Zelfs de belangrijkste maat van ziekte-activiteit, de Disease Activity Score (DAS), is getransformeerd naar de DAS28, waarbij het gewrichtsonderzoek van de voeten achterwege wordt gelaten. Onderscheid tussen groep- en patiënten-niveau is hierin belangrijk. In onderzoeken worden behandel-effecten op groepsniveau onderzocht. De meerderheid van patiënten met RA zullen inderdaad klachten van de handen hebben, en daarom is het voor het belang van de studie wellicht niet of minder erg als de voetgewrichten niet mee worden onderzocht. Echter, voor de individuele patiënt met geïsoleerd inflammatie van de voeten, leidt het negeren van de onderste extremiteit potentieel tot onderbehandeling. Zo blijkt dat de DAS28 inferieur is aan de DAS, omdat ondanks het bereiken van DAS28-remissie patiënten ziekteactiviteit aan de voeten bleken te houden. Daarom moet in de klinische praktijk de DAS28 met voorzichtigheid worden gebruikt. Dit benadrukt het onderscheid tussen onderzoek en klinische praktijk. Het is belangrijk om te benadrukken dat het doel van deze thesis is om beter begrip te krijgen in de betrokkenheid van RA in de voorvoet. Het heeft niet als doel om MRI van de voeten in de dagelijkse klinische praktijk aan te moedigen. Het is de vraag of we, op basis van de resultaten van met name hoofdstuk 7 kunnen concluderen dat MRI van de voeten, met name voor onderzoek doeleinden, achterwege kan worden gelaten. Uit hoofdstuk 2 blijkt dat er meerdere aspecten belangrijk zijn om te overwegen. Het is onbekend hoe inflammatie van de MTP-gewrichten reageert op behandeling, en of dit anders is dan inflammatie in de handen. Data uit klinische trials zijn belangrijk om hier conclusies over te kunnen trekken.

Kort samengevat heeft deze thesis ons geleerd dat:

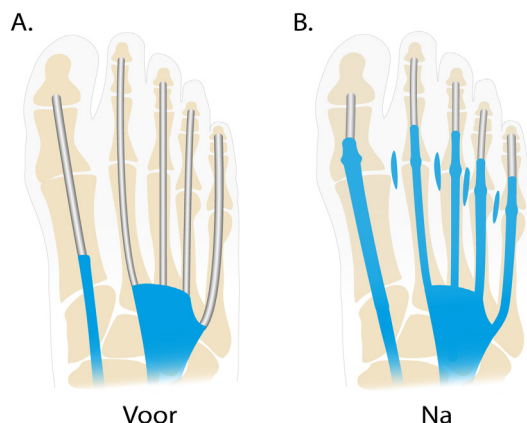
- Om ziekte beter te kunnen begrijpen wordt sensitieve beeldvorming verricht. Om deze beeldvorming beter te begrijpen zijn we soms genooddaakt om de anatomie beter uit te zoeken
- Synovitis in de reumatische voet uit zich in meer dan alleen ontsteking van het gewricht: peesscheden en intermetatarsale bursae hebben ook een synoviale bekleding die vaak ontstoken zijn door ziekte-betrokkenheid
- Secundaire laesies zonder synoviale bekleding worden ook gevonden in de reumatische voet: submetatarsale bursae en Morton's neuroom.
- De synoviale peesschede in de voorvoet zijn bijna nooit ontstoken in gezonde vrijwilligers
- Onderzoeksresultaten van de handen kunnen niet direct geëxtrapoleerd

worden naar de voeten: in de voorvoet kunnen additionele structuren betrokken zijn, en het is onbekend of deze reageren op behandeling

- In RA zijn de kleine voetgewrichten minder vaak aangedaan dan de kleine handgewrichten. MRI van de voeten kan, op groepsniveau, waarschijnlijk achterwege worden gelaten. Echter, voor de individuele patiënt kan het achterwege laten van een gewrichtsonderzoek van de voeten potentieel tot onderbehandeling lijden.

Dit brengt bij onze toekomstperspectieven. Niet alle vragen uit hoofdstuk 2 zijn in deze thesis beantwoord. Daarnaast zijn er ook nieuwe vragen bijgekomen met betrekking tot de inter- en submetatarsale laesies. Van deze laesies is de intermetatarsale bursitis de enige primaire laesies die ontstaan uit een van nature synoviaal beklede intermetatarsale bursa. Deze laesie had tevens de hoogste sensitiviteit voor RA. Dit maakt de intermetatarsale bursa wellicht de meest interessante laesie om in de toekomst nader te bestuderen.

Tot slot nog een laatste opmerking om deze thesis mee af te sluiten. Verandering van mens' perspectief kan interessante nieuwe bevindingen opleveren. Voor deze thesis waren samenwerkingen met de afdelingen Radiologie en Anatomie en Embryologie essentieel. Dit heeft uiteindelijk geleid tot een andere kijk op de reumatische voet. Waarbij in het plaatje hieronder A weergeeft hoe de anatomische kennis van de voorvoet was, en B hoe wij voorstellen dat deze is aan de hand van de verrichte studies.



A: Dorsaal aanzicht van de voorvoet waarbij het tenosynovium proximalal van de MTP-gewrichten eindigt. B: Dorsaal aanzicht van de voorvoet waarbij het tenosynovium tot distal van de MTP-gewrichten reikt, bovendien zijn er synoviale bursae tussen de metatarsale kopjes.



Appendices

Curriculum vitae

List of publications

Dankwoord

Curriculum vitae

Yousra Dakkak werd op 13 juli 1989 geboren in Amsterdam. In 2007 behaalde zij haar VWO diploma aan het Berlage Lyceum te Amsterdam.

Nadien startte zij met de opleiding Geneeskunde aan de Vrije Universiteit te Amsterdam. Zij sloot haar studie af met het oudste co-schap op de afdeling interne geneeskunde van het Waterlandziekenhuis te Purmerend. In januari 2015 werd het artsexamen behaald.

Hierna startte zij met haar eerste baan als arts-assistent in het Spaarne Gasthuis te Hoofddorp, aanvankelijk 6 maanden bij de afdeling cardiologie, gevolgd door 1 jaar bij de interne geneeskunde.

In maart 2017 startte zij haar promotieonderzoek 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 Academisch Medisch Centrum te Amsterdam. In dit kader is zij sinds mei 2019 gestart met de vooropleiding interne geneeskunde in hetzelfde centrum.

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Dakkak YJ, Wouters W, Matthijssen XME, Reijnierse M, van der Helm-van Mil AHM. Walking disabilities are associated with tenosynovitis at the metatarsophalangeal joints: A longitudinal MRI-study in early arthritis. *Arthritis Care Res (Hoboken)*. 2020 Sep 22. doi: 10.1002/acr.24452. Online ahead of print.

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Dankwoord

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