ABSTRACT
Tenosynovitis is traditionally recognised at physical examination in patients with inflammatory rheumatic diseases, such as, e.g., psoriatic arthritis and (longstanding) rheumatoid arthritis (RA). The increasing use of sensitive imaging techniques (ultrasound, magnetic resonance imaging (MRI)) has recently revealed that subclinical tenosynovitis is prevalent in early RA and in patients in different phases of RA development (asymptomatic state, arthralgia, early arthritis). In this review, the recent findings on MRI-detected tenosynovitis and associations with RA development are highlighted, and an overview of the most reported inflamed tendon locations within the hand and wrist of patients in different disease phases is provided. The data presented show that tenosynovitis is one of the earliest inflammatory features in patients with imminent RA and associated with impairment of activities in daily life. The value of tenosynovitis as an outcome measure in RA is also discussed.

Introduction
Chronic inflammation of the synovium, resulting in inflammatory arthritis, is the hallmark of rheumatoid arthritis (RA). Joints are covered by a synovial membrane but they are not unique; tendon sheaths also have such a synovial lining. The synovial membrane covering joints and tendon sheaths generally consists of two layers, is responsible for synovial fluid production and has a role in the maintenance of the structural integrity of joints and tendons. Historically, inflammation of the joint lining has received much attention because of its central role in RA. In recent years, results of studies using imaging modalities such as magnetic resonance imaging (MRI) and ultrasound (US) suggest that the tenosynovial compartment is frequently inflamed in RA (1). In this review we will summarise the current knowledge on tenosynovitis by imaging with a focus on RA.

Anatomy
Tenosynovitis refers to inflammation of the synovial lining of the tendon sheaths. These sheaths are formed at locations where there is excessive movement or to bridge bends. However, most tendons in the body are short and without sheaths. For instance, not all tendons in the hand, wrist, and foot have such a sheath. In the hand at the flexor side, tendons sheaths are present at the level of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, whereas the extensor tendons do not have those sheaths at these locations (Fig. 1). The sheaths at the flexor side are reinforced by volar pulleys. Most tendons in the wrist have tendon sheaths but the flexor carpi ulnaris (compartment 1) lacks this as well. Whether there is a tenosynovial sheath at the flexors (plantar side) of the metatarsophalangeal (MTP) joints is less clear, but it is absent around the tendons at the extensor side of the MTP joints.

It is important to differentiate tenosynovitis (inflammation of the tenosynovial sheath) from tendinitis or enthesitis (the latter refers to inflammation located at the transition-site between tendon and bone) (2). Tenosynovitis can be detected with physical examination and can be caused by injury, overuse, strain, infection, or can be a symptom of an inflammatory rheumatic disease. De Quervain’s tenosynovitis, for instance, is a common tenosynovitis located at the thumb base that can be detected clinically using the Finkelstein's test. In addition, clinically evident tenosynovitis is a well-known manifestation of psoriatic arthritis, where tenosynovitis

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(in combination with arthritis and subcutaneous oedema) results in dactylitis. Tenosynovitis is also often found in patients with active, longstanding RA and predisposes to risk of tendon rupture if present for a prolonged period.

In addition to overt tenosynovitis, detailed imaging studies of wrist and MCP joints have revealed that subclinical tenosynovial inflammation is frequently present at the level of these joints in the early phases of RA, as will be reviewed below. Notably, MRI studies have even revealed contrast-enhancement around the extensor tendons of the MCP joints in patients with RA, a feature which has been labelled as peritendinitis because of the anatomic absence of a tendon sheath at this location. Similarly, contrast-enhancement has recently been observed at the level of the interosseous tendons in the hands of RA patients and also these tendons do not have sheaths (3). Peritendinitis of the extensor tendons at MCPs and of interosseous tendons can be present together with synovitis of MCP joints, however these lesions also occur without concomitant synovitis.

The vascular supply of tendons with or without a sheath differs. Tendons without sheaths, such as the extensor tendons at the level of MCP joints, are supplied with blood from the muscular origin and the paratenon (tissue filling the interstices of the fascial compartment in which a tendon is situated). Tendons in sheaths are less supplied with blood from their paratenon. However, at the flexor side of the fingers there is arterial supply via the vinculae (bands of connective tissue between tendon and bone). The vincular system consists of short and long vinculae. There is anatomic variation in distribution of the long vinculae; it differs between fingers and between persons (4).

**Imaging and measurements of tenosynovitis**

MRI provides excellent visualisation of bone and soft tissues, including tenosynovitis. To date, tenosynovitis is generally scored by the system developed by Haavardsholm et al. (5). This scoring system is an addition to the RA MRI score (RAMRIS), established by the Outcome Measures in Rheumatology in Clinical Trials (OMERACT) MRI in Arthritis Working Group (6). In 2017, the OMERACT RAMRIS scoring system was updated and it now includes tenosynovitis. In addition, some changes in methods consist of the inclusion of the assessment of flexor tendons at the level of the MCP joints, the exclusion of the flexor tendon carpi ulnaris (compartment 1) in the wrist, and changes in the definition of the semi-quantitative scores (0-3) (7).

Ultrasound can also detect tenosynovitis; scoring of tenosynovitis can be done by a system that is developed by the OMERACT US Task Force, an international collaborative group of musculoskeletal US (MSUS) experts (8). Six studies compared MRI- and US-detected tenosynovitis (9-12), of which a few used the OMERACT RAMRIS scoring system to score tenosynovitis (13, 14). These studies reported a high agreement between MRI- and US-detected tenosynovitis but the available data suggest that MRI was more sensitive in detecting tenosynovitis than US, and in addition, could better predict RA progression (9-11, 13, 14). Although some studies used the RAMRIS method to score MRIs, the US scoring system developed by OMERACT was not used in these studies. As well, the number of patients was relatively low (n<50). Therefore, larger studies comparing MRI and US (using the OMERACT scoring system) that investigate tenosynovitis, at both individual patient level and also at joint level, are needed to validate the reported results. As MRI appears to be more sensitive in detect-
Progression to RA
arthralgia that are suspicious for
Tenosynovitis in patients with
MRI-detected tenosynovitis.

Tenosynovitis in the asymptomatic population

Previous studies on MRI in symptom-free people from the general population have revealed that low-grade (grade 1) inflammation is more frequently present in asymptomatic people than was expected (16). This low-grade inflammation was generally absent in people <40 years of age and occurred more frequently at older age (>60 years). Bone marrow oedema (osteitis) and synovitis were quite often detected in people from the general population, whereas tenosynovitis at the MCP joints and wrist was infrequent. In older subjects (>60 years), flexor tenosynovitis was most frequently observed at the level of MCP-2 joints (6-12%) and in the extensor carpi ulnaris tendon of the wrist (compartment VI; 12%) (Table I, Figs. 2-3) (16). Another study performed in asymptomatic people reported that tendon sheath fluid was prevalent, but tenosynovitis may not have been truly assessed in this study as the MRI was performed without contrast-enhancement (17).

The reported association of tenosynovitis with age suggests that age should be considered when interpreting MRI for diagnostic purposes (18). In addition, although low-grade tenosynovitis is less prevalent in the general population than low-grade synovitis or bone marrow oedema (which may also reflect underlying osteoarthritis), it is preferred to include a control group of healthy subjects (19) or a reference atlas (20, 21) in observational MRI studies that aim to assess the diagnostic or prognostic value of MRI-detected tenosynovitis.

Tenosynovitis in patients with arthralgia that are suspicious for progression to RA

Subjects within the symptomatic phase that precedes the development of clinical arthritis and RA can be grouped as Clinically Suspect Arthralgia (CSA). The identification of CSA is based on pattern recognition by rheumatologists; for scientific studies homogeneity can be increased by using the EULAR definition of ‘arthralgia suspicious for progression to RA’ in addition to clinical expertise (22). In patients with CSA, bone marrow oedema and synovitis are more prevalent as inflammatory features on MRI than tenosynovitis (23).

In patients with CSA, flexor MCP2 and wrist compartment IV tenosynovitis are the most frequent affected locations (Table I, Figs. 2-3). Although tenosynovitis is less frequent than synovitis and BME, tenosynovitis had the strongest association with progression to RA in longitudinal analyses (24). In addition, tenosynovitis scores had the strongest association with functional disability measured by the Health Assessment Questionnaire (HAQ) in this pre-arthritis phase; the association of tenosynovitis with functional impairments was stronger than that of synovitis and bone marrow oedema (25). Finally the presence of tenosynovitis in patients with CSA was associated with bone marrow density loss (26). Taken together, these results indicate that tenosynovitis is an early inflammatory feature that is predictive for future RA development and already causes functional impairments in the symptomatic phase preceding clinically apparent arthritis.

Tenosynovitis in early (undifferentiated) arthritis and RA

Subclinical inflammation can precede clinically detectable inflammatory arthritis. Another question is to what extent clinical joint swelling in patients with early clinically detectable arthritis is reflective of synovitis or tenosynovitis. An MRI study in patients with recent onset arthritis showed that synovitis and tenosynovitis were both independently associated with clinical joint swelling in the MCP joints and wrist, detected by physical examination (27). Low-grade (>1) tenosynovitis was present in 65% of swollen MCP joints and 78% of swollen wrist joints. In addition, low-grade tenosynovitis was also present in 13% of the non-swollen hand and in 41% of wrist joints of early arthritis patients. Similar frequencies were observed for MRI-detected synovitis. Preferential locations for tenosynovitis in early RA are the flexor tendons.

Table I. Overview of MRI-detected tenosynovitis in different phases of RA development.

<table>
<thead>
<tr>
<th>Age (mean)</th>
<th>Symptom-free status 40-59</th>
<th>Arthralgia ≥60</th>
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Tenosynovitis (%) detected in the flexor/extensor metacarpophalangeal (MCP) joints and wrist compartments in different phases of rheumatoid arthritis (RA) development; asymptomatic healthy controls [16], arthralgia [23], arthritis [30, 31]. Asymptomatic controls were divided into two groups based on age (>60 years and between 40-59 years). Mean age of arthralgia patients was 43 years and of arthritis patients the mean age was reported between 53-54 years.
of MCP2, MCP3, and the wrist extensor compartments IV, and VI, the flexor digitorum profundus and superficialis (compartment 2), and the flexor pollicis longus (compartment 3) (Table I, Figs. 2-3) (27-31).

As expected, MRI-detected tenosynovitis occurs more frequently in early RA and established RA patients compared to asymptomatic controls (18). Patients with RA also had higher scores for MRI-detected inflammation, including tenosynovitis, than early arthritis patients without RA (patients with other arthritides) (31, 32). Large observational cohorts (n=100) (31, 32) showed that RA patients could be differentiated from patients with other arthritides by higher tenosynovitis scores in the flexor tendons at MCP5, extensors at MCP2, MCP4, and extensor compartments I, II, and VI of the wrist. This association was independent of local synovitis (31). In smaller cohort studies (n<25) the opposite was found (33) or no difference between RA and other arthritides (34-36). Some observational studies in early RA showed that tenosynovitis scores decreased during disease progression (37-39), whereas two other studies with a relative low number of patients reported stable MRI-detected tenosynovitis scores (40, 41).

MRI-detected tenosynovitis in people presenting with undifferentiated arthritis is associated with RA development. This association of tenosynovitis was independent of other MRI inflammation measures, and also independent of age and other serological measures in blood (42). Other studies showed that tenosynovitis of flexor tendons was the most powerful predictor for early RA (43, 44). In here, tenosynovitis of the extensor carpi ulnaris (compartment VI) and flexor tendons of the second finger were significantly associated with progression to RA (45). Concerning the symptoms related to the presence of tenosynovitis in the disease phase of early arthritis; a recent study revealed that tenosynovitis was the only type of MRI-detected inflammation that was independently associated with functional disability as measured by HAQ scores (46). This was confirmed by another large data-set (n=200) (47).

So in early (undifferentiated) arthritis, MRI-detected tenosynovitis is the best predictor for RA development and associated with functional impairments in daily life.
Tenosynovitis data obtained from randomised clinical trials in RA

The data presented above were obtained from observational cohort studies. Tenosynovitis has also been assessed in a few randomised clinical trials.

Three clinical placebo-controlled trials with biological disease-modifying anti-rheumatic drugs (bDMARDs; etanercept or adalimumab) with or without methotrexate (MTX) revealed suppression of tenosynovitis, similar to the accompanying suppression of the other inflammatory pathologies (48-51); such studies also demonstrated the responsiveness of MRI-detected tenosynovitis as an outcome measure in trials. One of these trials also showed no decrease in tenosynovitis scores in the placebo group in contrast to the intervention group (50), further highlighting the responsiveness of tenosynovitis to treatment.

Positive significant correlations between tenosynovitis and disease activity score (DAS) 28, erythrocyte sedimentation rate and C-reactive protein have also been detected (50). Finally, analyses done on data from clinical studies showed that RA patients with remission, according to ACR/EULAR definitions, Simplified Disease Activity Index and Boolean criteria (52), showed lower levels of MRI-detected residual inflammation, including tenosynovitis, compared to patients without remission based on DAS28 scores (53-55).

Thus these trials revealed that tenosynovitis correlates with measures of inflammation, is responsive to therapy, and is present at lower scores in RA patients in remission.

Tenosynovitis detected by US

Because MRI is more sensitive in detecting inflammation than conventional radiographs and US (9-11, 13, 14, 45, 56), and has a higher reproducibility than US, it is commonly used in research settings. However, costs and accessibility may make MRI less feasible for the diagnostic process and follow-up of patients in clinical practice (16, 32, 57). Tenosynovitis has also been assessed by US in different studies.

The results of these studies are largely similar to the findings done with MRI. US-detected tenosynovitis at individual joint level showed that the MCP2, MCP3, and wrist compartment VI are the most affected locations in arthralgia and RA patients (58-63). Also US-detected tenosynovitis in patients with arthralgia or early arthritis has been shown predictive for RA development (58, 59).

Discussion

The studies reviewed here show that MRI-detected tenosynovitis is rare in asymptomatic individuals (except from tenosynovitis detected in compartment VI of the wrist and MCP3 in people aged ≥60). It is an early phenomenon in patients at risk for RA and is predictive for RA development, independent of synovitis and bone marrow oedema in different at risk phases. Furthermore both in arthralgia and early arthritis, tenosynovitis is independently associated with functional impairments in daily life (25, 46). Thus although tenosynovitis is mostly subclinical in early phases of RA (and therefore imaging modalities are needed for its detection) it is prognostically important and clinically relevant.

Based on the studies that have been published to date, it can be concluded that preferred locations are slightly different in different disease phases but there is also large overlap. Flexor tenosynovitis at MCP3 joints is the predominant location in asymptomatic people, and flexor tenosynovitis at the MCP2 and 3 joints are prevalent in arthralgia and (early) RA (Table I, Figs. 2-3). Within the wrist the extensor compartment VI is most frequent in asymptomatic controls, compartments IV and VI are most frequent affected in arthralgia patients, and extensor compartment IV and VI, flexor compartments 2 and 3 were frequently inflamed in early RA.

Although our understanding on subclinical tenosynovitis in the earliest phases of RA is increasing, there are also several questions that remain (Table II).

It is surprising that contrast enhancement is also observed at the level of the extensor tendons at the MCP joints (‘peritendinitis’), since tendon sheaths are lacking at these locations; the cause of this signal remains to be determined. The same goes for the recently observed peritendinitis of the interosseous tendons, which was present in up to 18% of patients with established RA and was absent in controls (3). These findings pose questions on the origin of tenosynovitis/peritendinitis at these locations. It could be considered as ‘overgrowth’ of synovitis in the tendon compartment, however the sole presence of peritendinitis without concomitant synovitis suggests that this explanation is insufficient. Presumably, it is also a feature of the systemic nature of RA. Further research is needed on the development and origin of this peritendinitis.

Another unsolved question is the order in which the different tissues of the joints become inflamed during the onset of RA. One hypothesis suggests that RA is a primary bone marrow disease, known as the ‘inside-out hypothesis’, with osteitis preceding synovitis and tenosynovitis. Alternatively, the ‘outside-in hypothesis’ presumes that inflammation of the synovium (of the lining and within the tendon sheaths) precedes osteitis (64, 65). The latter hypothesis fits the murine data in which tenosynovitis was the first inflammatory event/phenomenon of induced

Table II. Overview of the research agenda.

- Determine the anatomy of tendon sheath at the flexor site of MTP joints. Do these tendons have a sheath?
- Determine the biologic nature of peritendinitis at the extensor sites of MCP joints and interosseous tendons.
- Determine the order at which different tissues in the joint become inflamed using longitudinal studies with serial imaging.
- Determine the correlation of MRI and US at tendon level using OMERACT RAMRIS and US scoring methods, respectively.
- Determine the value of MRI- or US-detected tenosynovitis in disease monitoring.
- Evaluate if MRI- or US-detected tenosynovitis can be used as outcome measures in clinical trials.
Imaging detected tenosynovitis of MCP and wrist joints / E. Niemantsverdriet & A.H.M. van der Helm-van Mill

arthritis in mice (66). The observation that tenosynovitis is predictive of RA development may also fit with the latter hypothesis. Large observational studies with serial MRIs (or US) performed prior to the development of clinically apparent arthritis, are needed to determine which hypothesis is correct.

MRI is more sensitive but US is more accessible at many centers for routine clinical management. Further studies at the level of individual joints are necessary to determine to what extent US can replace MRI in the detection of tenosynovitis. Possibly the correlation is better for tendons that are located more superficially, whereas inflammation around tendons that are located more deeply may be less reliably assessed by US, due to lack of acoustic window. It should be noted that in contrast to the incorporation of the scoring protocol for MRI, flexors compartments I, 3, 4, extensor compartment I, III, and V in the wrist are not included in the OMERACT scoring system for US, which is due to the proximity of radial arteries that can produce Doppler artefacts or because of frequent variability in level of differentiation into distinct tendon slips and consequent anisotropy (8).

The current EULAR recommendations concerning the use of imaging modalities does not include imaging-detected tenosynovitis (67). This absence may reflect the recent interest in tenosynovitis in RA and the fact that the recommendations have been formulated in 2013. Future studies should prove whether the implementation of tenosynovitis could be of added value when the EULAR imaging recommendations will be updated.

A final issue on the research agenda (Table II) is to determine if imaging-detected tenosynovitis is a relevant outcome measure for clinical trials. The first trials in patients with classified RA have revealed that tenosynovitis is responsive. However, other criteria could be taken into account and also earlier disease phases should be considered. This is especially important for future trials that will be done in pre-clinical phases of the disease and that may consider to include the assessment of tenosynovitis.

Conclusion

Studies using imaging modalities have revealed that tenosynovitis is often present at the level of wrist and MCP joints in patients with imminent RA. Its presence is mostly subclinical, hence not discernible with physical examination, but it associated with impairment of activities in daily life and can be considered as a predictive marker for RA development. In conclusion, studies performed in the last few years have revealed the importance of a hitherto virtually unknown characteristic of RA.

More research is needed to fully appreciate the importance of tenosynovitis in the onset of RA and in its value in disease monitoring and as outcome measure.

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