Imaging detected tenosynovitis of metacarpophalangeal and wrist joints: an increasingly recognised characteristic of rheumatoid arthritis

E. Niemantsverdriet[1], A.H.M. van der Helm-van Mil[1,2]

[1]*Department of Rheumatology, Leiden University Medical Centre, Leiden;*
[2]*Department of Rheumatology, Erasmus University Medical Centre, Rotterdam, The Netherlands.*

Ellis Niemantsverdriet,
Annette H.M. van der Helm-van Mil,

Please address correspondence to:
Dr Ellis Niemantsverdriet,
Department of Rheumatology C1-R,
Leiden University Medical Center,
PO Box 9600,
Leiden 2300RC, The Netherlands.
E-mail: E.Niemantsverdriet@lumc.nl

Received on August 31, 2018; accepted in revised form on September 3, 2018.

Clin Exp Rheumatol 2018; 36 (Suppl. 114): S131-138.

Key words: tenosynovitis, magnetic resonance imaging, ultrasound, rheumatoid arthritis, arthralgia

Competing interests: none declared.

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

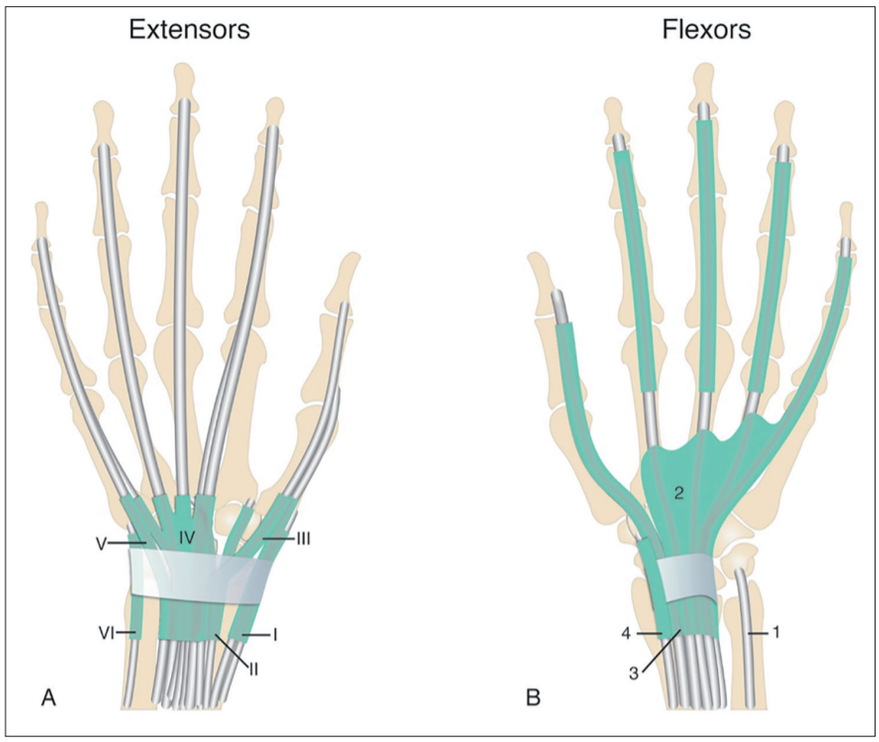

Fig. 1. Schematic illustration of the extensor and flexor tendons and tendon sheaths of the hand.
A: Dorsum side of the hand, including the six extensor compartments under the extensor retinaculum of the wrist (extensor pollicis brevis and abductor pollicis longus (I); extensor carpi radialis brevis and extensor carpi radialis longus (II); extensor pollicis longus (III); extensor digitorum communis and extensor indicus proprius (IV); extensor digiti quinti proprius (V); and extensor capri ulnaris (VI)).
B: Palmar side of the hand, including the four flexor compartments. The radial bursa contains the flexor pollicis longus tendon that extends to the thumb (compartment 3) and the ulnar bursa contains the 8 flexor tendons (flexor digitorum superficialis and profundus tendons, compartment 2) that extend distally to the fifth finger in the majority of cases. Between the carpal tunnel and the second, third, and fourth finger a gap exists in the tenosynovium. Those fingers have at the level of the MCP joints a separate tenosynovial coverage. The other two compartments, outside the carpal tunnel, are the flexor carpi ulnaris tendon (compartment 1) without a synovial sheath and is located ulnar to the carpal tunnel. Lastly, the flexor carpi radialis tendon (compartment 4) has a synovial sheath and is located radially to the tendons enclosed in the ulnar bursa. Modified from Nieuwenhuis *et al*., 2015 (31).

(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 vincula. 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-

ing tenosynovitis, and because it has been commonly used as a research tool in the field of RA, we will first review the current knowledge on MRI-detected tenosynovitis in wrist and hand joints of patients in different phases of RA as described by a EULAR taskforce (asymptomatic state, arthralgia, early arthritis, and RA) (15).

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

		Symptom-free status		Arthralgia	Arthritis
Age (mean)		40-59	≥60	43	53-54
MCP extensors	2	0	0	4	15
	3	1	0	3	12
	4	0	0	3	11
	5	0	0	6	4
Flexors	2	1	6	10	22
	3	3	12	8	22
	4	3	6	6	8
	5	1	2	1	20
Wrist extensors	I	0	0	3	18
	II	0	0	2	18 - 20
	III	0	0	1	9
	IV	0	2	12	30 - 33
	V	0	0	1	12
	VI	9	12	8	20 - 39
Flexors	1	0	0	0	0
	2	0	0	1	15 - 44
	3	0	0	1	25
	4	0	2	0	5

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.

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 MCP2-4 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

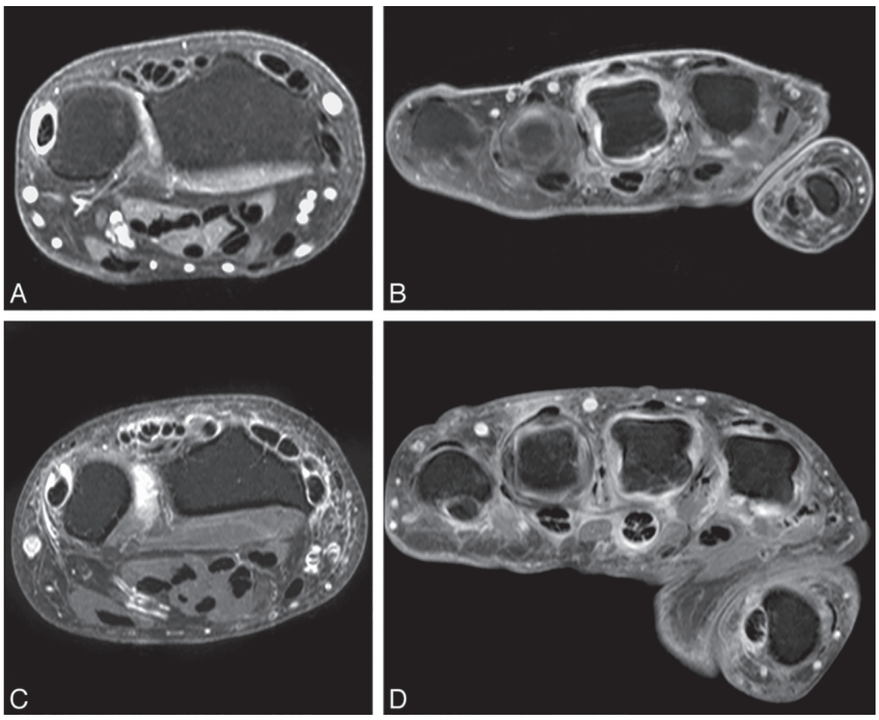

Fig. 2. Axial T1 post-gadolinium, fat-saturated magnetic resonance images (MRIs) at the level of the metacarpophalangeal (MCP) joints and wrist. MRIs of symptom-free control (**A**), a patient with clinically Suspect Arthralgia (CSA; **B**), and a patient with RA (**C-D**) are shown. In this symptom-free person a high tenosynovitis intensity is depicted at the extensor carpi ulnaris (A). In the CSA patient, synovitis and peritendinitis are pronounced at the MCP3 joint (**B**). The patient with RA has MRI-detected tenosynovitis in the extensor compartments of the wrist (**C**) and clear synovitis and tenosynovitis at the level of the MCP3 joint (**D**).

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 form 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.

Pathophysiological model of RA development					
Genetic risk factors	Environmental risk factors	Systemic autoimmunity	Symptoms without arthritis	Unclassified arthritis	RA
Clinically discernable phases of RA development					
Asymptomatic healthy controls			Clinically Suspected Arthralgia	Early RA	RA
Preferred tenosynovitis locations in phases of RA development					
MCP3 flexor Wrist compartment VI			MCP2, MCP3 flexors Wrist compartments IV +VI	MCP2, MCP3 flexors Wrist compartments IV, VI, 2, and 3	

Fig. 3. Pathophysiological, clinical, and preferred tenosynovitis locations in phases of RA development.

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 antirheumatic 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).

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.

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 clinical 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

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 1, 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.

References

1. BOTTE MJ: Surgical anatomy of the hand and upper extremity. 2003: Lippincott Williams & Wilkins.
2. SCHETT G, LORIES RJ, D'AGOSTINO MA *et al*.: Enthesitis: from pathophysiology to treatment. *Nat Rev Rheumatol* 2017; 13: 731-41.
3. ROWBOTHAM EL, FREESTON JE, EMERY P, GRAINGER AJ: The prevalence of tenosynovitis of the interosseous tendons of the hand in patients with rheumatoid arthritis. *Eur Radiol* 2016; 26: 444-50.
4. BYWATERS EGL: Lesions of Bursae, Tendons and Tendon Sheaths. *Clin Rheum Dis* 1979; 5: 883-925.
5. HAAVARDSHOLM EA, OSTERGAARD M, EJBJERG BJ, KVAN NP, KVIEN TK: Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study. *Ann Rheum Dis* 2007; 66: 1216-20.
6. OSTERGAARD M, PETERFY C, CONAGHAN P *et al*.: OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. *J Rheumatol* 2003; 30: 1385-6.
7. OSTERGAARD M, PETERFY CG, BIRD P *et al*.: The OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging (MRI) Scoring System: Updated Recommendations by the OMERACT MRI in Arthritis Working Group. *J Rheumatol* 2017; 44: 1706-12.
8. NAREDO E, D'AGOSTINO MA, WAKEFIELD RJ *et al*.: Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. *Ann Rheum Dis* 2013; 72: 1328-34.
9. XU H, ZHANG Y, ZHANG H, WANG C, MAO P: Comparison of the clinical effectiveness of US grading scoring system vs MRI in the diagnosis of early rheumatoid arthritis (RA). *J Orthop Surg Res* 2017; 12: 152.
10. WAKEFIELD RJ, O'CONNOR PJ, CONAGHAN PG *et al*.: Finger tendon disease in untreated early rheumatoid arthritis: a comparison of ultrasound and magnetic resonance imaging. *Arthritis Rheum* 2007; 57: 1158-64.
11. NAVALHO M, RESENDE C, RODRIGUES AM *et al*.: Bilateral evaluation of the hand and wrist in untreated early inflammatory arthritis: a comparative study of ultrasonography and magnetic resonance imaging. *J Rheumatol* 2013; 40: 1282-92.
12. BACKHAUS M, KAMRADT T, SANDROCK D *et al*.: Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. *Arthritis Rheum* 1999; 42: 1232-45.
13. SARAN S, BAGARHATTA M, SAIGAL R: Diagnostic accuracy of ultrasonography in detection of destructive changes in small joints of hands in patients of rheumatoid arthritis: a comparison with magnetic resonance imaging. *J Assoc Physicians India* 2016; 64: 26-30.
14. AMMITZBOLL-DANIELSEN M, GLINATSI D, TORP-PEDERSEN S *et al*.: Tenosynovitis evaluation using image fusion and B-flow - a pilot study on new imaging techniques in rheumatoid arthritis patients. *Ultraschall Med* 2017; 38: 285-93.
15. GERLAG DM, RAZA K, VAN BAARSEN LG *et al*.: EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. *Ann Rheum Dis* 2012; 71: 638-41.
16. MANGNUS L, VAN STEENBERGEN HW, REIJNIERSE M, VAN DER HELM-VAN MIL AH: Magnetic resonance imaging-detected features of inflammation and erosions in symptom-free persons from the general population. *Arthritis Rheumatol* 2016; 68: 2593-602.
17. AGTEN CA, ROSSKOPF AB, JONCZY M, BRUNNER F, PFIRRMANN CWA, BUCK FM: Frequency of inflammatory-like MR imaging findings in asymptomatic fingers of healthy volunteers. *Skeletal Radiol* 2018; 47: 279-87.
18. NIEUWENHUIS WP, MANGNUS L, VAN STEENBERGEN HW *et al*.: Older age is associated with more MRI-detected inflammation in hand and foot joints. *Rheumatology* (Oxford) 2016; 55: 2212-9.
19. PARODI M, SILVESTRI E, GARLASCHI G, CIMMINO MA: How normal are the hands of normal controls? A study with dedicated magnetic resonance imaging. *Clin Exp Rheumatol* 2006; 24: 134-41.
20. CONAGHAN P, BIRD P, EJBJERG B *et al*.: The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the metacarpophalangeal joints. *Ann Rheum Dis* 2005; 64 (Suppl 1): i11-21.
21. EJBJERG B, MCQUEEN F, LASSERE M *et al*.: The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the wrist joint. *Ann Rheum Dis* 2005; 64 (Suppl. 1): i23-47.
22. VAN STEENBERGEN HW, ALETAHA D, BEAART-VAN DE VOORDE LJ *et al*.: EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. *Ann Rheum Dis* 2017; 76: 491-6.
23. VAN STEENBERGEN HW, VAN NIES JA, HUIZINGA TW, BLOEM JL, REIJNIERSE M, VAN DER HELM-VAN MIL AH: Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI. *Ann Rheum Dis* 2015; 74: 1225-32.

24. VAN STEENBERGEN HW, MANGNUS L, REIJNIERSE M, HUIZINGA TW, VAN DER HELM-VAN MIL AH: Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. *Ann Rheum Dis* 2016; 75: 1824-30.
25. TEN BRINCK RM, VAN STEENBERGEN HW, MANGNUS L *et al*.: Functional limitations in the phase of clinically suspect arthralgia are as serious as in early clinical arthritis; a longitudinal study. *RMD Open* 2017; 3: e000419.
26. MANGNUS L, VAN STEENBERGEN HW, REIJN-IERSE M, KALVESTEN J, VAN DER HELM-VAN MIL A: Bone mineral density loss in clinically suspect arthralgia is associated with subclinical inflammation and progression to clinical arthritis. *Scand J Rheumatol* 2017; 46: 364-8.
27. KRABBEN A, STOMP W, HUIZINGA TW *et al*.: Concordance between inflammation at physical examination and on MRI in patients with early arthritis. *Ann Rheum Dis* 2015; 74: 506-12.
28. OSTENDORF B, SCHERER A, MODDER U, SCHNEIDER M: Diagnostic value of magnetic resonance imaging of the forefeet in early rheumatoid arthritis when findings on imaging of the metacarpophalangeal joints of the hands remain normal. *Arthritis Rheum* 2004; 50: 2094-102.
29. BOUTRY N, LARDE A, LAPEGUE F, SOLAU-GERVAIS E, FLIPO RM, COTTEN A: Magnetic resonance imaging appearance of the hands and feet in patients with early rheumatoid arthritis. *J Rheumatol* 2003; 30: 671-9.
30. LEE KA, MIN SH, KIM TH, LEE SH, KIM HR: Magnetic resonance imaging-assessed synovial and bone changes in hand and wrist joints of rheumatoid arthritis patients. *Korean J Intern Med* 2017.
31. NIEUWENHUIS WP, KRABBEN A, STOMP W *et al*.: Evaluation of magnetic resonance imaging-detected tenosynovitis in the hand and wrist in early arthritis. Arthritis Rheumatol 2015; 67: 869-76.
32. STOMP W, KRABBEN A, VAN DER HEIJDE D *et al*.: Are rheumatoid arthritis patients discernible from other early arthritis patients using 1.5T extremity magnetic resonance imaging? a large cross-sectional study. *J Rheumatol* 2014; 41: 1630-7.
33. MATSUMOTO T, TSURUMOTO T, SHINDO H, UETANI M: Comparative study of fat-suppressed Gd-enhanced MRI of hands in the early stage of rheumatoid arthritis (RA) and non-RA. *Mod Rheumatol* 2001; 11: 56-60.
34. JI L, LI G, XU Y, ZHOU W, ZHANG Z: Early prediction of rheumatoid arthritis by magnetic resonance imaging in the absence of anti-cyclic citrullinated peptide antibodies and radiographic erosions in undifferentiated inflammatory arthritis patients: a prospective study. *Int J Rheum Dis* 2015; 18: 859-65.
35. LI R, LIU X, YE H *et al*.: Magnetic resonance imaging in early rheumatoid arthritis: a multicenter, prospective study. *Clin Rheumatol* 2016; 35: 303-8.
36. SOLAU-GERVAIS E, LEGRAND JL, CORTET B, DUQUESNOY B, FLIPO RM: Magnetic resonance imaging of the hand for the diagnosis of rheumatoid arthritis in the absence of anti-cyclic citrullinated peptide antibodies: a prospective study. *J Rheumatol* 2006; 33: 1760-5.
37. LINDEGAARD HM, VALLO J, HORSLEV-PETERSEN K, JUNKER P, OSTERGAARD M: Low-cost, low-field dedicated extremity magnetic resonance imaging in early rheumatoid arthritis: a 1-year follow-up study. *Ann Rheum Dis* 2006; 65: 1208-12.
38. HAAVARDSHOLM EA, BOYESEN P, OSTERGAARD M, SCHILDVOLD A, KVIEN TK: Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. *Ann Rheum Dis* 2008; 67: 794-800.
39. BOYESEN P, HAAVARDSHOLM EA, OSTERGAARD M, VAN DER HEIJDE D, SESSENG S, KVIEN TK: MRI in early rheumatoid arthritis: synovitis and bone marrow oedema are independent predictors of subsequent radiographic progression. *Ann Rheum Dis* 2011; 70: 428-33.
40. ESHED I, FEIST E, ALTHOFF CE *et al*.: Early rheumatoid arthritis-do we really know what it means? Consistency and distribution of MRI findings according to different definitions for early rheumatoid arthritis. *Clin Rheumatol* 2011; 30: 551-5.
41. FORSLIND K, SVENSSON B: MRI evidence of persistent joint inflammation and progressive joint damage despite clinical remission during treatment of early rheumatoid arthritis. *Scand J Rheumatol* 2016; 45: 99-102.
42. NIEUWENHUIS WP, VAN STEENBERGEN HW, MANGNUS L *et al*.: Evaluation of the diagnostic accuracy of hand and foot MRI for early Rheumatoid Arthritis. *Rheumatology* (Oxford) 2017; 56: 1367-77.
43. ESHED I, FEIST E, ALTHOFF CE *et al*.: Tenosynovitis of the flexor tendons of the hand detected by MRI: an early indicator of rheumatoid arthritis. *Rheumatology* (Oxford) 2009; 48: 887-91.
44. BOETERS DM, NIEUWENHUIS WP, VERHEUL MK *et al*.: MRI-detected osteitis is not associated with the presence or level of ACPA alone, but with the combined presence of ACPA and RF. *Arthritis Res Ther* 2016; 18: 179.
45. NAVALHO M, RESENDE C, RODRIGUES AM *et al*.: Bilateral MR imaging of the hand and wrist in early and very early inflammatory arthritis: tenosynovitis is associated with progression to rheumatoid arthritis. *Radiology* 2012; 264: 823-33.
46. BURGERS LE, NIEUWENHUIS WP, VAN STEENBERGEN HW *et al*.: Magnetic resonance imaging-detected inflammation is associated with functional disability in early arthritis-results of a cross-sectional study. *Rheumatology* (Oxford) 2016; 55: 2167-75.
47. GLINATSI D, BAKER JF, HETLAND ML *et al*.: Magnetic resonance imaging assessed inflammation in the wrist is associated with patient-reported physical impairment, global assessment of disease activity and pain in early rheumatoid arthritis: longitudinal results from two randomised controlled trials. *Ann Rheum Dis* 2017; 76: 1707-15.
48. AXELSEN MB, ESHED I, HORSLEV-PETERSEN K *et al*.: A treat-to-target strategy with methotrexate and intra-articular triamcinolone with or without adalimumab effectively reduces MRI synovitis, osteitis and tenosynovitis and halts structural damage progression in early rheumatoid arthritis: results from the OPERA randomised controlled trial. *Ann Rheum Dis* 2015; 74: 867-75.
49. LISBONA M, MAYMO J, SOLANO A *et al*.: Repair of erosions in patients with rheumatoid arthritis treated with etanercept: magnetic resonance imaging findings after 1 year of follow-up. *Scand J Rheumatol* 2013; 42: 437-44.
50. LISBONA MP, MAYMO J, PERICH J, ALMIRALL M, CARBONELL J: Rapid reduction in tenosynovitis of the wrist and fingers evaluated by MRI in patients with rheumatoid arthritis after treatment with etanercept. *Ann Rheum Dis* 2010; 69: 1117-22.
51. MOLLER-BISGAARD S, EJBJERG BJ, ESHED I *et al*.: Effect of a treat-to-target strategy based on methotrexate and intra-articular betamethasone with or without additional cyclosporin on MRI-assessed synovitis, osteitis, tenosynovitis, bone erosion, and joint space narrowing in early rheumatoid arthritis: results from a 2-year randomized double-blind placebo-controlled trial (CIMESTRA). *Scand J Rheumatol* 2017; 46: 335-45.
52. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011; 70: 404-13.
53. LISBONA MP, SOLANO A, ARES J, ALMIRALL M, SALMAN-MONTE TC, MAYMO J: ACR/EULAR Definitions of Remission Are Associated with Lower Residual Inflammatory Activity Compared with DAS28 Remission on Hand MRI in Rheumatoid Arthritis. *J Rheumatol* 2016; 43: 1631-6.
54. LISBONA MP, PAMIES A, ARES J *et al*.: Association of bone edema with the progression of bone erosions quantified by hand magnetic resonance imaging in patients with rheumatoid arthritis in remission. *J Rheumatol* 2014; 41: 1623-9.
55. RANGANATH VK, MOTAMEDI K, HAAVARDSHOLM EA *et al*.: Comprehensive appraisal of magnetic resonance imaging findings in sustained rheumatoid arthritis remission: a substudy. *Arthritis Care Res* (Hoboken) 2015; 67: 929-39.
56. BACKHAUS M, BURMESTER GR, SANDROCK D *et al*.: Prospective two year follow up study comparing novel and conventional imaging procedures in patients with arthritic finger joints. *Ann Rheum Dis* 2002; 61: 895-904.
57. OSTERGAARD M, HAAVARDSHOLM EA: Imaging: MRI in healthy volunteers - important to do, and do correctly. *Nat Rev Rheumatol* 2016; 12: 563-4.
58. SAHBUDIN I, PICKUP L, NIGHTINGALE P *et al*.: The role of ultrasound-defined tenosynovitis and synovitis in the prediction of rheumatoid arthritis development. *Rheumatology* (Oxford) 2018.
59. VAN DE STADT LA, BOS WH, MEURSINGE REYNDERS M *et al*.: The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. *Arthritis Res Ther* 2010; 12: R98.

60. CERQUEIRA M, TEIXEIRA F, SOUSA NEVES J, PEIXOTO D, AFONSO MC, COSTA JA: Relationship between clinical evaluation and ultrasound assessment of rheumatoid arthritis patients using a 12 joint score. *Int J Rheum Dis* 2017; 20: 852-8.
61. HMAMOUCHI I, BAHIRI R, SRIFI N, AKTAOU S, ABOUQAL R, HAJJAJ-HASSOUNI N: A comparison of ultrasound and clinical examination in the detection of flexor tenosynovitis in early arthritis. *BMC Musculoskelet Disord* 2011; 12: 91.
62. OHRNDORF S, HALBAUER B, MARTUS P *et al*.: Detailed joint region analysis of the 7-joint ultrasound score: evaluation of an arthritis patient cohort over one year. *Int J Rheumatol* 2013; 2013: 493848.
63. AMMITZBOLL-DANIELSEN M, OSTERGAARD M, NAREDO E, TERSLEV L: Validity and sensitivity to change of the semi-quantitative OMERACT ultrasound scoring system for tenosynovitis in patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2016; 55: 2156-66.
64. JIMENEZ-BOJ E, REDLICH K, TURK B *et al*.: Interaction between synovial inflammatory tissue and bone marrow in rheumatoid arthritis. *J Immunol* 2005; 175: 2579-88.
65. SCHETT G, FIRESTEIN GS: Mr Outside and Mr Inside: classic and alternative views on the pathogenesis of rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 787-9.
66. HAYER S, REDLICH K, KORB A, HERMANN S, SMOLEN J, SCHETT G: Tenosynovitis and osteoclast formation as the initial preclinical changes in a murine model of inflammatory arthritis. *Arthritis Rheum* 2007; 56: 79-88.
67. COLEBATCH AN, EDWARDS CJ, OSTERGAARD M *et al*.: EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis* 2013; 72: 804-14.