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# Differences and similarities of autoantibody-positive and autoantibody-negative rheumatoid arthritis during the disease course: on our way to personalized medicine

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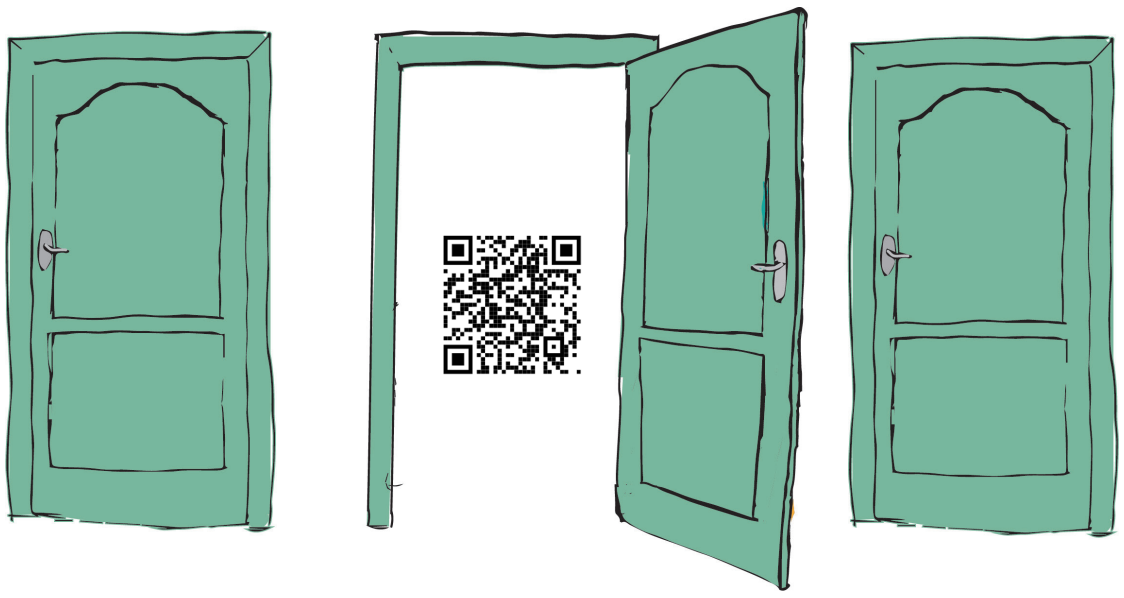
# EARLY ARTHRITIS



# CHAPTER 3

## Tenosynovitis has a high sensitivity for early ACPA-positive and ACPA-negative RA: a large cross-sectional MRI study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## ABSTRACT

**Objectives**

Clinically evident tenosynovitis can be seen in established Rheumatoid arthritis (RA). Imaging research has recently shown that tenosynovitis at small joints occurs in early RA, contributes to typical RA symptoms (including joint swelling) and is infrequent in healthy controls. Imaging-detectable tenosynovitis is often not recognizable at joint examination, hence its prevalence can therefore be underestimated. We hypothesized that if MRI-detectable tenosynovitis is a true RA-feature, the sensitivity for RA is high, in both ACPA-positive and -negative RA, and lower in other diseases that are associated with enthesitis (such as Spondyloarthritis (SpA) and Psoriatic Arthritis (PsA)). So far, no large MRI-study addressed these questions.

**Methods**

Consecutive early arthritis patients (n=1211) from one health-care region underwent contrast-enhanced 1.5T MRI of hand and foot at diagnosis. MRIs were scored for synovitis and tenosynovitis by two readers blinded for clinical data. All included patients with ACPA-positive RA (n=250), ACPA-negative RA (n=282), PsA (n=88), peripheral SpA (n=24), reactive arthritis (n=30) and self-limiting undifferentiated arthritis (UA;n=76) were studied. Sensitivity was calculated.

**Results**

The sensitivity of tenosynovitis in RA was 85%; 88% for ACPA-positive RA and 82% for and ACPA-negative RA (p=0.19). The sensitivity for RA was significantly higher than for PsA (65%;p=0.001), SpA (53%;p<0.001), reactive arthritis (36%;p<0.001) and self-limiting UA (42%;p<0.001). The observed sensitivity of MRI-synovitis was 91% in RA and ranged 83-54% in the other groups.

**Conclusions**

MRI-detected tenosynovitis has a high sensitivity for early ACPA-positive and ACPA-negative RA. This supports both juxta-articular (tenosynovitis) and intra-articular synovial involvement is characteristic for RA.




## KEY MESSAGES

**What is already known about this subject?**

- Imaging research has identified tenosynovitis at small joints in early RA and its contribution to typical RA symptoms (including joint swelling).
- So far, no large MRI-study in consecutive patients determined the sensitivity of imaging detected tenosynovitis. We hypothesized that if tenosynovitis at small joints is a true RA-feature, the sensitivity for RA is high, in both ACPA-positive and -negative RA, and lower in diseases that are associated with enthesitis (e.g. SpA, PsA).

**What does this study add?**

- This is the first study demonstrating the sensitivity of tenosynovitis in RA, which is high (>80%), not different for ACPA-positive and ACPA-negative RA, and lower in spondyloarthropathies.
- The sensitivity of tenosynovitis in wrist, MCP and MTP joints was comparable to synovitis, a well-established RA-feature. This supports that both juxta-articular (tenosynovitis) and intra-articular synovial involvement is characteristic for RA.

**How might this impact on clinical practice or future developments?**

- This may fuel future research into the role of juxta-articular synovial inflammation in the pathogenesis of RA.

# INTRODUCTION

Clinically evident tenosynovitis can be seen in established Rheumatoid arthritis (RA), for example at the back of the hand in patients with longstanding disease.[1] Clinically evident tenosynovitis during the disease course is less frequent than joint swelling, which is generally interpreted as a sign of synovitis. However, in contrast with clinically evident tenosynovitis, imaging studies using advanced high resolution imaging (MRI, US) have recently shown the presence of tenosynovitis in small joints of hands and feet. Imaging-detected tenosynovitis has been shown to occur in early RA and pre-RA phases, additionally it is also noted to be a strong predictor for RA development in undifferentiated arthritis and arthralgia.[2] Conversely, MRI-detected tenosynovitis is infrequent in healthy controls.[2] Furthermore, imaging-detected tenosynovitis is believed to underlie typical RA-symptoms of pain, functional limitations and morning stiffness, and it can contribute to joint swelling.[3] MRI-detectable tenosynovitis is often not recognizable at joint examination [3] and accurate detection requires high resolution contrast-enhanced MRI.[4-6] Therefore its prevalence may have been thus far underestimated. Ultrasonography is used more often than MRI but has a lower sensitivity for tenosynovitis compared to high-resolution contrast-enhanced MRI.[4-7] Consequently, the sensitivity of tenosynovitis at the level of small joints for RA remains unknown.

Previous studies that reported on the prevalence of MRI-detected tenosynovitis in RA studied selected sets of patients; only one study included a representative consecutive sample, allowing to determine the sensitivity of tenosynovitis for RA (see literature overview in Supplementary 1).[8] To our knowledge, no studies have evaluated the prevalence of tenosynovitis in ACPA-positive and ACPA-negative RA, nor has it been studied in MTP joints, a preferential location for RA. Furthermore, only three small studies compared the prevalence of MRI-detected tenosynovitis to other diagnoses that are known to be associated with enthesitis, such as spondyloarthropathies.[9-11] Enthesitis and tenosynovitis are sometimes mixed up; enthesis is inflammation of the insertion of the tendon to the bone whereas tenosynovitis is inflammation of the synovial sheath that surrounds many tendons in the hands and forefeet.

The increasing amount of data on the value of tenosynovitis in RA prompted us to conduct this study. We hypothesized that if MRI-detectable tenosynovitis is a true RA-feature, the sensitivity for RA is high, and is similar for anti-citrullinated protein antibodies (ACPA)-positive and ACPA-negative RA. This hypothesis was based on the clinical presentation of ACPA-positive and ACPA-negative RA being similar, despite the differences in risk factors and outcome.[12] Furthermore, if tenosynovitis is a true RA-feature, the sensitivity of tenosynovitis for other diseases should be low. The spondyloarthropathy group (including psoriatic arthritis (PsA), peripheral spondylarthritis (SpA) and reactive arthritis) are important to compare due to the role of enthesitis and dactylitis in these diseases. Also, self-limiting undifferentiated arthritis (self-limiting UA) is interesting, as these patients ultimately do not develop chronic arthritis.

To address these questions, we took advantage of the Leiden early arthritis cohort (EAC), a large representative consecutive cohort of >1200 early arthritis patients who received a contrast-enhanced, 1.5T extremity MRI of wrist, MCP and MTP-joints at presentation to the rheumatology outpatient clinic. Patients with RA, PsA, peripheral SpA, reactive arthritis and self-limiting UA were studied for the prevalence of tenosynovitis, and also its relation to synovitis.

# METHODS

**Patients**

Since 1993, consecutive early arthritis patients (<2 years symptom duration) presenting to the rheumatology outpatient clinic, were included in the Leiden EAC. This is the only rheumatology referral center in this region. Therefore a representative sample of early arthritis patients presents itself at this outpatient clinic. Also, a short waiting list and a special early arthritis recognition clinic without a waiting list, opened in 2010, safeguards high accessibility, this is reflected in a short symptom duration at inclusion in the EAC. More information on this inception cohort is available elsewhere.[13] Briefly, patient-characteristics, disease activity and laboratory parameters were obtained at baseline, 4-months, 12-months and yearly thereafter. From August-2010 onwards MRIs were performed at baseline.

The definite diagnosis was determined after 1 year based on routinely available data (MRI-data were not reported to clinicians). RA was defined as clinical diagnosis plus fulfillment of the 1987- or 2010-classification criteria. PsA, SpA and reactive arthritis diagnoses were made by the rheumatologist based on clinical presentation and not based on classification criteria as these are inappropriate for diagnosis of individual patients in daily practice. PsA patients had psoriasis of the skin and poly-arthritis and were treated for PsA. Peripheral SpA patients had axial spondylarthritis and arthritis of one or more peripheral joints and were treated for peripheral SpA. Self-limiting UA patients were diagnosed with UA by the rheumatologist but had resolving joint swelling and complaints within 1-year without DMARD treatment (systemic DMARDs, biological DMARDs or (intra-articular) glucocorticoids), resulting in a subsequent release from care. All patients were consecutively included and no selection was made on clinical characteristics.

Patients included in the EAC between August-2010 and March-2020 were evaluated in the present study (Flowchart in Supplementary 2). A minority of patients did not undergo an MRI evaluation (mostly due to logistical reasons such as MRI-maintenance) and some MRIs were of insufficient quality (e.g. no contrast-enhanced sequences or insufficient fat suppression), implying missingness completely at random. Baseline characteristics were similar in patients with and without MRI, substantiating this assumption (Supplementary 3). Consequently, we studied a representative consecutive sample of 1211 early arthritis patients that received an MRI at baseline.



**MRI**

MRI was performed at baseline (before DMARD-initiation). Wrist, metacarpophalangeal (MCP(2-5)), and metatarsophalangeal (MTP(1-5))-joints on the most painful side at baseline (dominant side in case of symmetric symptoms) were imaged with 1.5TMRI (GE,Wisconsin,USA). Contrast-enhanced T1-weighted FSE fatsat sequences of the wrist and MCP sequences were obtained in all patients. In June-2013, instead of axial T1 and T2-weighted FSE fatsat sequences in the axial plane, contrast-enhanced T1-weighted FSE fatsat sequences in both the coronal and axial plane of the MTPs were added to the protocol. This allowed for assessment of the influence of the MTPs on the sensitivity of tenosynovitis in 823 patients. Supplementary 4 provides a detailed scan and scoring-protocol.

MRIs were scored for synovitis and tenosynovitis in line with RAMRIS and the method of Haavardsholm by two experienced readers, blinded to any clinical data (Supplementary 4).[14-16] Intraclass correlation coefficients were excellent (≥0.93; Supplementary 5). Tenosynovitis and synovitis were considered present when both readers considered the feature present at the same location. This stringent definition was chosen to minimize false-positive results.

**Statistical analysis**

The sensitivity of tenosynovitis in early RA was calculated using all described joints in both hand and foot. This was repeated stratified for ACPA-status and compared to other diagnoses. To assess whether high tenosynovitis scores were more prevalent in RA, continuous scores for different diagnoses were plotted in a violin plot and tested with Mann-Whitney tests. For comparison, the sensitivity of MRI-detected synovitis was calculated.

To study the influence of the stringent cut-off chosen, analyses were repeated in RA patients with a less stringent cut-off: a feature was considered present when one of both readers scored the feature at that location.



In another sub analysis we evaluated the contribution of tenosynovitis at the MTP level to the sensitivity of tenosynovitis for RA, by repeating the analyses while excluding the MTPs. Although the feet are a preferential location for RA, previous studies did not scan the MTPs and omitting the MTPs increases comparability to previous studies on the prevalence of tenosynovitis. In addition it allows for inclusion of patients in which MTP tenosynovitis could not be properly scored due to MRI-protocol differences (n=388).

To investigate the distribution of synovitis and tenosynovitis, the prevalence of tenosynovitis and synovitis was assessed at the joint level in RA and other diagnoses. Moreover, simultaneous presence of those features was assessed for the individual MTPs and MCPs and the wrist. To avoid multiple testing, no statistics were performed on these joint level analyses.



Fisher's exact test was used. A narrative literature review on the prevalence of tenosynovitis in RA was performed (Supplementary 1). Results are reported according the Standards for Reporting of Diagnostic Accuracy Studies (STARD)-guidelines (Supplementary 6). No formal pre-specified study protocol was submitted prior to analyses. Patient partners were involved in design of the EAC-cohort. R4.0.0 was used. Two-sided p-values <0.05 were considered significant.

# RESULTS

1211 patients included in the EAC received MRIs: 532 had RA (n=250 ACPA-positive; n=282 ACPA-negative), 88 PsA, 24 peripheral SpA, 30 reactive arthritis and 76 self-limiting UA. Baseline characteristics are shown in Table 1 and swollen joint distribution in Supplementary 7. The diagnoses of the 461 patients that were not studied are shown in Supplementary 8.

**Table 1:** Baseline characteristics of early arthritis patients presenting with rheumatoid arthritis, psoriatic arthritis, peripheral spondyloarthritis, reactive arthritis and self-limiting UA

| | Rheumatoid arthritis (n=532) | Psoriatic arthritis (n=88) | Peripheral spondyloarthritis (n=24) | Reactive Arthritis (n=30) | Self-limiting undifferentiated arthritis (n=76) |
|---|---|---|---|---|---|
| Women, n (%) | 343 (65) | 38 (43) | 11 (46) | 18 (60) | 41 (54) |
| Age in years, mean (SD) | 59 (14) | 49 (15) | 38 (14) | 47 (15) | 50 (15) |
| Symptom duration, weeks median (IQR) | 12 (6-29) | 16 (7-47) | 13 (5-39) | 4 (2-7) | 8 (3-16) |
| ACPA, n (%) | 250 (47) | 2 (2) | 1 (4) | 0 (0) | 0 (0) |
| 66-SJC, median (IQR) | 5 (2-10) | 2 (1-4) | 2 (1-4) | 2 (1-4) | 1 (1-2) |

**Table 1:** Continued.

| | Rheumatoid arthritis (n=532) | Psoriatic arthritis (n=88) | Peripheral spondyloarthritis (n=24) | Reactive Arthritis (n=30) | Self-limiting undifferentiated arthritis (n=76) |
|---|---|---|---|---|---|
| 68-TJC, median (IQR) | 5 (3-7) | 3 (1-5) | 2 (1-3) | 2 (1-5) | 1 (1-2) |
| ESR, median (IQR) | 28 (11-41) | 17 (6-33) | 33 (9-58) | 21 (9-33) | 11 (6-22) |
| VAS general health, median (IQR) | 70 (50-80) | 68 (50-80) | 70 (60-80) | 70 (40-80) | 60 (40-70) |
| HAQ, median (IQR) | 0.9 (0.5-1.5) | 0.5 (0.1-0.9) | 0.4 (0.2-0.8) | 0.8 (0.3-1.0) | 0.4 (0.0-0.9) |

**Legend:** n, number of patients; SD, standard deviation; IQR, inter quartile range; ACPA: anti-citrullinated protein antibodies; SJC, swollen joint count; TJC, tender joint count; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale; HAQ, health assessment questionnaire; UA, undifferentiated arthritis



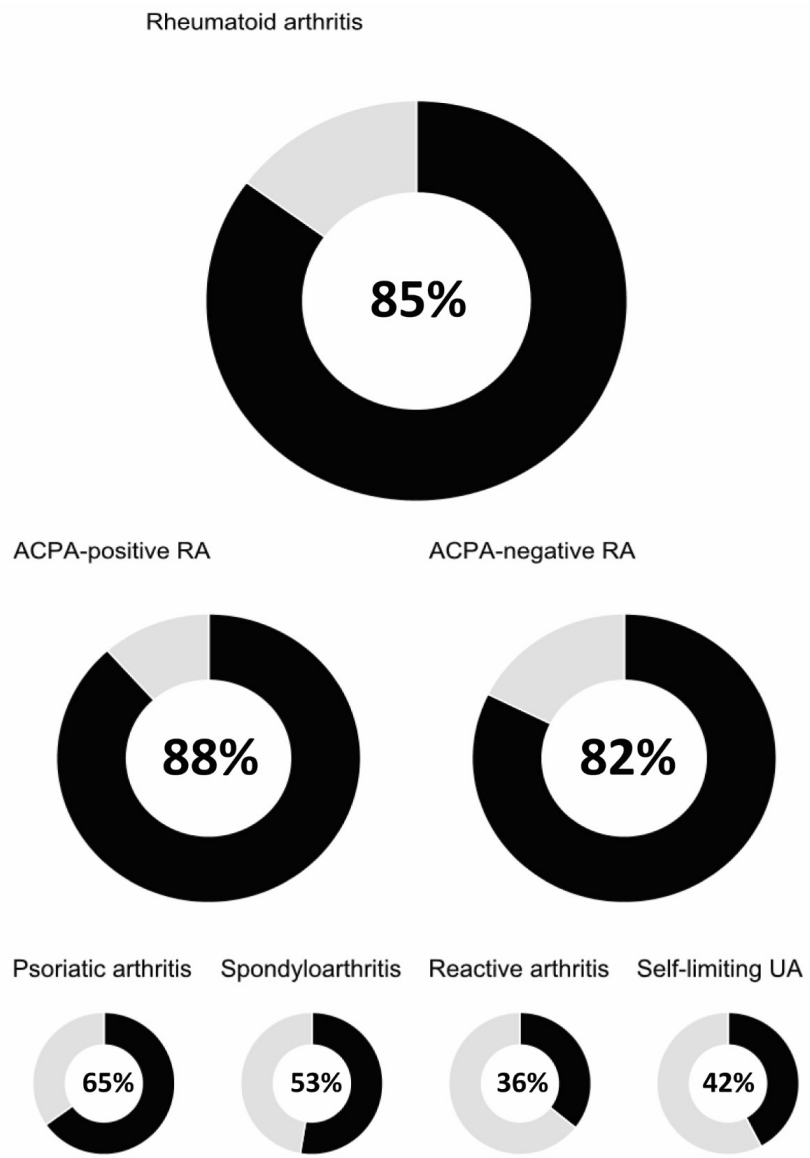
In early RA, the sensitivity of imaging-detected tenosynovitis in the hand and foot joints in early RA was 85%. Sensitivity was 88% in ACPA-positive and 82% ACPA-negative RA (p=0.19; Figure 1). This was 65% in PsA (p<0.001 vs RA), 53% in peripheral SpA (p=0.001), 36% in reactive arthritis (p<0.001) and 42% in self-limiting UA (p<0.001). Analyses of continuous scores revealed that higher tenosynovitis scores were only prevalent in RA (Figure 2; all p<0.001).

The sensitivity of tenosynovitis was compared to MRI-detected synovitis in the hand and foot joints, an established feature of RA. The sensitivity of MRI-detected synovitis in wrist, MCP and MTP joints in RA was 91% (Figure 3) and 91% in ACPA-positive RA and 90% in ACPA-negative RA. This was 85% in PsA (p=0.08 vs RA), 58% in peripheral SpA (p<0.001), 47% in reactive arthritis (p=0.002) and 54% in self-limiting UA (p<0.001). Considering both features together, 94% of RA patients had synovitis or tenosynovitis in wrist, MCP or MTP joints. If a less stringent definition was considered (feature at least observed by one reader at that location), only 6 patients had no (teno-)synovitis in the joint regions that were scanned, mostly due to receiving MRIs at the least affected side, thereby diverging from protocol

Analyses were repeated excluding the MTP joints to ascertain the impact of tenosynovitis in the feet. Similar results were obtained for tenosynovitis: Sensitivity in early RA was 79% (Supplementary 9), 81% in ACPA-positive and 78% in ACPA-negative RA (p=0.34). In PsA, peripheral SpA, reactive arthritis and self-limiting UA, sensitivity was 56%, 24%, 36% and 42%, respectively (all p<0.001). For synovitis, the sensitivity in early RA decreased from 91% to 82% upon omitting the feet (Supplementary 10).



**Figure 1:** Presence of tenosynovitis (in black) in wrist, MCPs and MTPs, in rheumatoid arthritis, stratified for ACPA-status and compared to other diseases

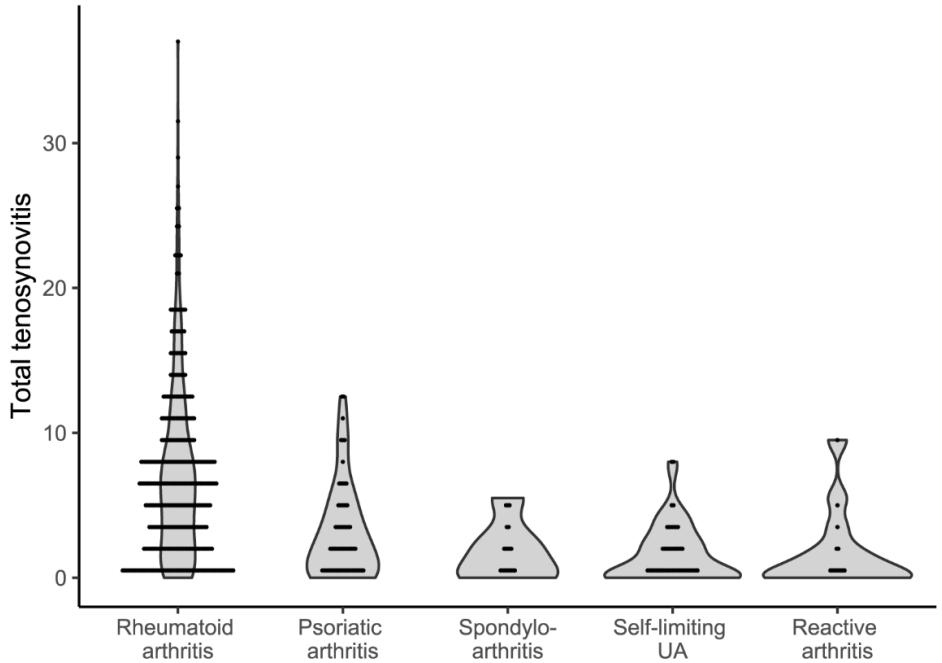



**Legend:** RA: Rheumatoid arthritis; ACPA: anti-citrullinated protein antibodies; UA: undifferentiated arthritis

Prevalence of tenosynovitis and synovitis were also assessed at the joint level. This revealed a numerically higher prevalence of tenosynovitis at the level of the individual MCP and wrist joints in RA than in other arthritides. For the MTPs, the differences observed were unclear (Figure 4-6). Information on the flexor and extensor sides of the MCP and MTP joints is provided in Supplementary 11-12; showing similar distributions. Finally, the simultaneous presence of synovitis and tenosynovitis was assessed in RA patients on joint level. As presented in Supplementary file 13 synovitis and tenosynovitis were most often simultaneously present in the same joint.



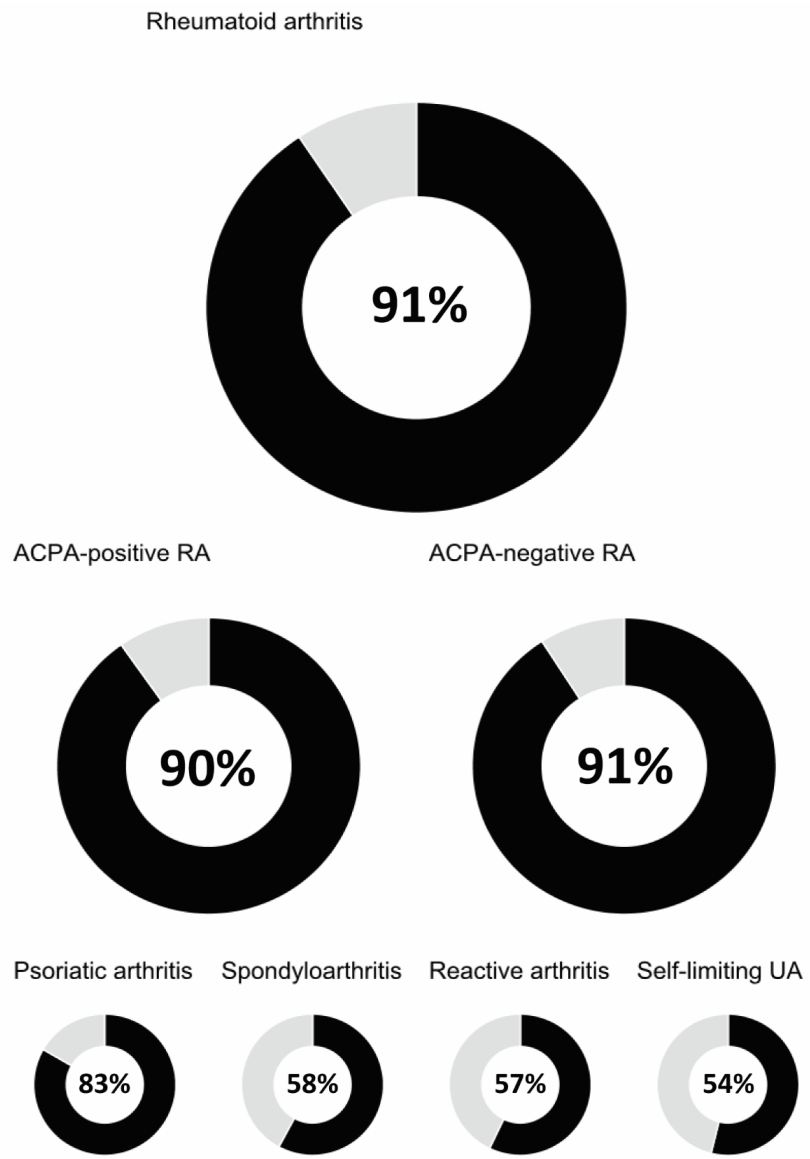
**Figure 2:** Total tenosynovitis scores in RA and similar diagnoses, showing that all high tenosynovitis scores are found in RA patients




**Legend:** Horizontal line width represents number of patients with that mean of tenosynovitis scores of two readers, rounded to a whole number. Light grey violins represent the density of patients with that mean tenosynovitis scale, scaled such that all violins have the same area, irrespective of the number of patients in that group.

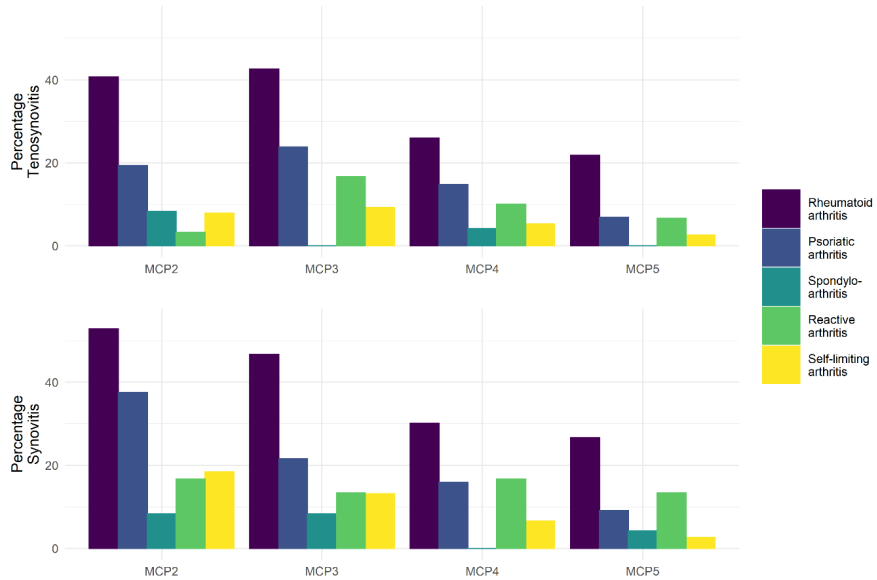


**Figure 3:** Presence of synovitis (in black) in wrist, MCPs and MTPs, in rheumatoid arthritis, stratified for ACPA-status and compared to other diseases



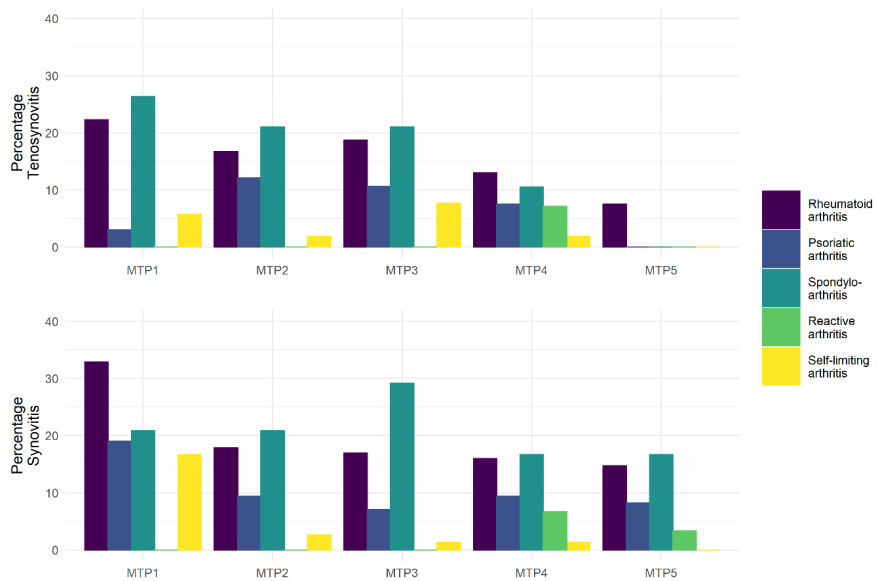

**Legend:** RA: Rheumatoid arthritis; ACPA: anti-citrullinated protein antibodies; UA: undifferentiated arthtritis

**Figure 4:** Presence of tenosynovitis and synovitis in the individual metacarpophalangeal (MCP) joints in RA and other arthritides showing a higher prevalence in RA




**Legend:** Features were considered present if both readers considered the feature present at the same location. MCP: metacarpophalangeal

**Figure 5:** Presence of tenosynovitis and synovitis in the individual metacarpophalangeal (MTP) joints in RA and other arthritides

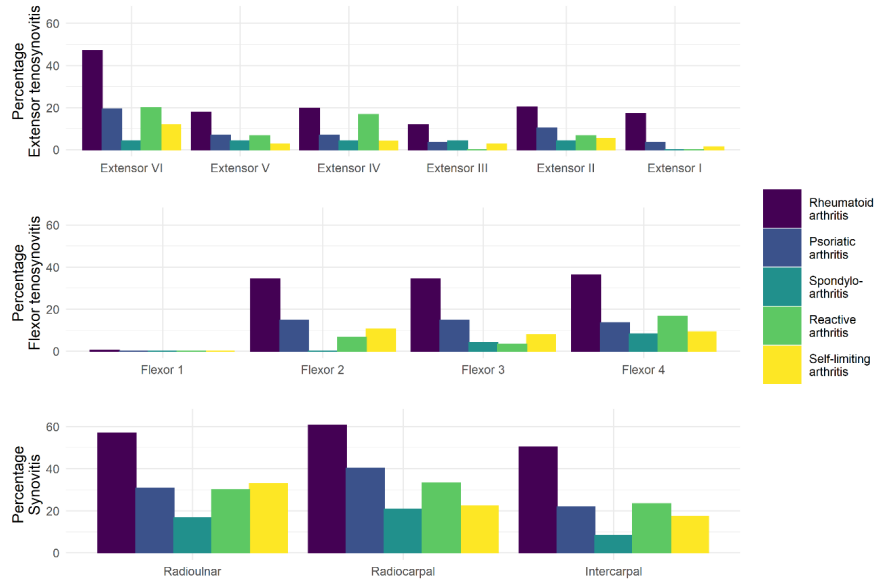



**Legend:** Features were considered present if both readers considered the feature present at the same location. MTP: metatarsophalangeal





**Figure 6:** Presence of tenosynovitis and synovitis in the individual locations within the wrist in RA and other arthritides showing a higher prevalence in RA. Because wrist tendon sheaths cannot be mapped to synovitis locations, the prevalence of synovitis and tenosynovitis cannot be compared at individual locations




**Legend:** Features were considered present if both readers considered the feature present at the same location.

# DISCUSSION

We performed a large MRI study on consecutively included early arthritis patients over 10 years, all receiving an MRI scan at baseline. Selecting RA patients from this consecutive sample enabled us to determine the sensitivity of MRI-detectable tenosynovitis in early RA. This is the first study to demonstrate the sensitivity of tenosynovitis in RA is high (>80%), does not differ between ACPA-positive and ACPA-negative disease and is lower in spondylarthritis diseases. The sensitivity of tenosynovitis was comparable to synovitis, a well-established RA-feature. This further confirms that RA is both a juxta-articular (tenosynovitis) and intra-articular (synovitis) disease.

Sensitivity of tenosynovitis was comparable to that of synovitis for RA (85% and 91% respectively). Also, 94% of RA patients had synovitis and/or tenosynovitis in wrist, MCP or MTP joints. In RA-patients tenosynovitis and synovitis predominantly presented in the same joints (Supplementary 13), implying that local inflammation manifests both juxta- and intra- articularly. Whilst synovitis frequency in RA was comparable to that of other diagnoses assessed (e.g. 83% in PsA), tenosynovitis was more frequent in RA than

other diagnoses. Therefore it can be concluded that the characteristics of tenosynovitis in RA are similar to synovitis, a well-known RA-feature, but that tenosynovitis is less frequently observed in other diagnoses.

Although ACPA-positive and ACPA-negative RA have different risk factors, outcomes and are hypothesized to have a different pathogenesis, the clinical presentation of both ACPA-subsets of RA is similar.[12] Our data shows that tenosynovitis is also highly frequent in both disease subsets. This underlines the notion that, although the pathogenesis and the severity of the disease course are different between ACPA-positive and ACPA-negative RA, the disease presentation is similar at the time of diagnosis, both with respect to the clinical presentation and high resolution imaging features.

ACPA-negative RA encompasses a heterogenous set of patients, which can raise concerns about phenotypic misclassification. Our data addressed this issue by confirming there is a difference in tenosynovitis between ACPA-negative RA and other inflammatory arthritides, such as PsA. This is in line with findings from recent studies on metabolites.[17] Together this supports the idea that ACPA-negative RA is a separate entity and not only a selection of patients that have other forms of arthritis that are misclassified.

We studied self-limiting arthritis in the form of reactive arthritis and self-limiting UA, the clinical distinction between the two being a recognized infectious illness preceding the onset of arthritis. Remarkably, both groups had a similar prevalence of both synovitis and tenosynovitis, possibly suggesting an overlapping or similar underlying disease mechanism between the two conditions.

Dactylitis is a known feature of PsA; the classic 'sausage digits' are caused by synovitis, soft tissue edema and tenosynovitis.[18,19] Importantly, this affects the digits mostly distal from the MCP- and MTP-joints. These distal areas were not imaged. Hence the current findings on tenosynovitis and its frequent occurrence in RA concern tenosynovitis at the level of wrist, MCP- and MTP-joints.

The feet are recognized as a preferential location for RA, however no previous studies have investigated the prevalence of the tenosynovitis in this location. The sensitivity of MRI-detected tenosynovitis in RA, including the feet (85%), was comparable to the sensitivity without the feet (79%). Previous studies that did not include the feet reported prevalences ranging from 43%-84% but most were ≥75% (Supplementary 1). The relatively small difference between the prevalence of tenosynovitis when the feet are included or excluded suggest that patients that have tenosynovitis at MTP level often also have tenosynovitis in the hand joints.

To our knowledge, this is the first large study on the sensitivity of MRI-detected tenosynovitis in RA to make a direct comparison to other inflammatory rheumatological diseases that are associated with enthesitis. The setup of the EAC cohort ascertains a representative sample of early arthritis patients are included. Therefore we were able calculate an estimate of the sensitivity of imaging-detected tenosynovitis in the general RA population, as opposed to describing a prevalence in a selection of RA-patients as typically done in previous research.

A limitation of this study is MTPs of some patients could not be scored for tenosynovitis due to a different MRI protocol. Reassuringly, a large number of patients (833 of which 362 were diagnosed with RA) remained, in whom the sensitivity of tenosynovitis and synovitis could be calculated while including the MTPs.

The current study aimed to increase the understanding of the frequency of tendon sheath involvement in RA. Nonetheless the MRI-protocol that we used might not be feasible in clinical practice: barriers include high cost and availability of MRI. Unfortunately, some clinical manifestations related to imaging-detectable tenosynovitis in clinical practice, such as swollen joints, incomplete fist closure, and also ultrasound-detectable tenosynovitis, have low sensitivity for imaging-detectable tenosynovitis.[3,7,20] Also, low-field MRI or MRI without contrast-enhancement is less sensitive for detection of tenosynovitis.[4-6] Therefore high field (≥1.5 Tesla) MRI is the ideal test for understanding and depicting which tissues are involved in RA.

Given the high sensitivity of tenosynovitis for RA and the lower prevalence in other inflammatory arthritides, future research could help to elucidate in which patients and phase of disease it is cost-effective to perform an MRI to detect tenosynovitis and distinguish RA from other diseases in an early disease stage. Moreover, it is relevant to study the morphologic, histologic and molecular characteristics of tenosynovitis in early RA. These are still unexplored areas that warrant further investigations.

In conclusion, this is the first large consecutive study on MRI-detected tenosynovitis in early arthritis patients and we have demonstrated that the large majority of RA patients have tenosynovitis at the level of small hand and foot joints, irrespective of ACPA-status. This further confirms that tenosynovitis, aside from synovitis, is a true RA feature and may fuel future research into the role of juxta-articular synovial inflammation in the pathogenesis of RA. Finally this study provided an example that a large MRI study can expand the knowledge on novel characteristics of RA, even 70 years after the first description of RA as a separate disease entity.[21]

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