Interosseous tendon inflammation in the hands of patients with clinically suspect arthralgia: analysis of MRI data from a prospective cohort study

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Interosseous tendon inflammation in the hands of patients with clinically suspect arthralgia: analysis of MRI data from a prospective cohort study

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Summary

Background Inflammation around the tendons of interosseous muscles of the hand (interosseous tendon inflammation) was recently observed with MRI for the first time in patients with rheumatoid arthritis and in at-risk individuals with detectable anti-citrullinated protein antibodies, generating the hypothesis that interosseous tendon inflammation precedes clinical arthritis. To better understand the role of interosseous tendon inflammation during the development of rheumatoid arthritis, we studied the frequency of interosseous tendon inflammation in healthy individuals and in those with arthralgia that was suspected of progressing to rheumatoid arthritis (ie, clinically suspect arthralgia) and the association of interosseous tendon inflammation with other symptoms of inflamed joint tissues and with clinical arthritis development.

Methods Adult (age ≥18 years) patients who presented with clinically suspect arthralgia and symptom-free (control) individuals underwent contrast-enhanced hand MRI. MRIs were evaluated for interosseous tendon inflammation on the radial and ulnar sides of the second to fifth metacarpophalangeal joints, and for synovitis, tenosynovitis, and osteitis using the rheumatoid arthritis MRI scoring system. Patients with clinically suspect arthralgia were followed up for clinical arthritis development. The presence of local tenosynovium was examined using immunohistochemistry for anti-CD55 and anti-CD68 on tissue from the hands of three embalmed bodies donated for scientific research. The primary outcome for the cross-sectional part of the study was the presence of interosseous tendon inflammation on MRI. The primary outcome for the longitudinal part of the study was development of clinical arthritis.

Findings Between April 3, 2012, and May 20, 2020, 667 patients with clinically suspect arthralgia (mean age 44 years [SD 13], 504 [76%] were women and 163 [24%] were men) underwent contrast-enhanced hand MRI. Between Nov 1, 2013, and Nov 30, 2014, 193 symptom-free controls were recruited (mean age 50 years [SD 16], 136 [70%] were women and 57 [30%] were men). Two (1%) of 193 symptom-free controls had interosseous tendon inflammation. Immunohistochemistry of cadaveric hand tissues showed no tenosynovium surrounding interosseous tendons. At inclusion, 67 (10%) of 667 patients with clinically suspect arthralgia had interosseous tendon inflammation (p<0·0001 *vs* symptom-free controls). Interosseous tendon inflammation occurred more frequently if synovitis (odds ratio [OR] 2·2 [95% CI 1·2–4·2]), or tenosynovitis (OR 9·7 [5·5–17·0]), was present at metacarpophalangeal joints. A three-dimensional MRI reconstruction suggested confluency of interosseous tendon inflammation with metacarpophalangeal-flexor-tenosynovitis. 91 (16%) of 558 patients with clinically suspect arthralgia developed clinical arthritis during follow-up (median total follow-up 25·3 months [95% CI 25·1–25·5]). Patients with clinically suspect arthralgia with interosseous tendon inflammation had a higher risk of developing clinical arthritis (hazard ratio [HR] 4·5 [2·8–7·2]), which was attenuated but still significant after adjusting for concomitant synovitis, tenosynovitis, or osteitis (HR 1·7 [1·02–2·8]).

Interpretation Interosseous tendon inflammation is almost absent in symptom-free individuals but occurs in people with clinically suspect arthralgia, in whom it correlates with symptoms and is associated with the development of clinical arthritis. The absence of local tenosynovium suggests that interosseous tendon inflammation arises from expanding local subclinical inflammation in the pre-arthritis phase of rheumatoid arthritis.

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Introduction

Traditionally, rheumatoid arthritis is known for targeting the intra-articular synovium. Histological and imaging studies from the past 5 years have shown that synovial tissue also occurs outside or next to the joint capsule (ie, juxta-articular)—for example, around flexor and extensor tendons of metacarpophalangeal and metatarsophalangeal joints and at intermetatarsal bursae.[1–3] In addition, imaging studies revealed that tenosynovitis and intermetatarsal bursitis are early features of

Research in context

Evidence before this study
Besides intra-articular synovitis, rheumatoid arthritis frequently involves inflammation of synovial tissue in hands or feet that is juxta-articular and surrounds tendons (tenosynovitis) or covers intermetatarsal bursae (intermetatarsal bursitis). Inflammation around the hand interosseous tendons (interosseous tendon inflammation) was also recently described using MRI. We searched PubMed from database inception to Dec 20, 2022, using the search terms "interosseous" and "inflammation" for papers published in English. We found two studies from the same centre describing interosseous tendon inflammation in small cohorts of patients with rheumatoid arthritis and in ACPA-positive individuals with musculoskeletal complaints. The latter might suggest that interosseous tendon inflammation precedes clinical rheumatoid arthritis, but longitudinal studies are absent. Furthermore, it is unclear whether interosseous tendon inflammation represents inflammation of synovial tissue, how often interosseous tendon inflammation occurs in the general population and in ACPA-negative at-risk individuals, and how it relates to other inflamed tissues.

Added value of this study
Using MRI to study cohorts of symptom-free individuals and patients with clinically suspect arthralgia, we show that interosseous tendon inflammation is almost absent in the general population but occurs in a subset of patients presenting with clinically suspect arthralgia who are at risk of developing rheumatoid arthritis. Interosseous tendon inflammation was seen in both ACPA-positive and ACPA-negative patients with clinically suspect arthralgia. If present at presentation with clinically suspect arthralgia, interosseous tendon inflammation was associated with an increased risk of developing clinical arthritis. Although interosseous tendon inflammation mostly occurred together with tenosynovitis and synovitis, immunohistochemical staining suggested absence of a tenosynovial, or synovial, lining around the interosseous tendons.

Implications of all the available evidence
Interosseous tendon inflammation is a novel feature of juxta-articular inflammation and is the first evidence of non-synovial peritendinous inflammation in rheumatoid arthritis and might reflect locally expanding subclinical joint inflammation in the pre-arthritis stage of the disease. This finding improves our understanding of local inflammation during the development of rheumatoid arthritis and suggests that future imaging and tissue-level studies on rheumatoid arthritis pathogenesis should not be limited to the synovial joint itself.

rheumatoid arthritis and contribute to symptoms, both in the pre-arthritis phase and in established rheumatoid arthritis.[1,2,4–8] As such, the emerging phenomenon of juxta-articular synovial inflammation could provide novel insights into the origins of the rheumatoid arthritis phenotype.

The view on juxta-articular tissue involvement in rheumatoid arthritis was expanded further by the observation of inflammation around the hand interosseous tendons on MRI (interosseous tendon inflammation) at the Leeds Institute of Rheumatic and Musculoskeletal Medicine, UK.[9,10] The interosseous muscles originate from the metacarpals and converge into tendons that run adjacent to the radial and ulnar sides of second to fifth metacarpophalangeal joint. They insert on the extensor aponeurosis, proximal phalanx, or both, depending on anatomical variation. The interosseous muscles and tendons are essential for normal hand function: in addition to finger adduction and abduction, they aid finger stability by supporting flexion at metacarpophalangeal joints and extension at proximal or distal interphalangeal joints.[11]

Using MRI, the Leeds group observed interosseous tendon inflammation in some patients with rheumatoid arthritis and in anti-citrullinated protein antibody (ACPA)-positive individuals with musculoskeletal symptoms.[9,10] This finding might suggest that interosseous tendon inflammation precedes clinical rheumatoid arthritis, and this prompted us to perform an in-depth study to address unanswered questions about interosseus tendon inflammation. Thus far, longitudinal follow-up data on the development of rheumatoid arthritis in at-risk individuals is absent. In addition, it is unknown whether interosseus tendon inflammation also occurs in individuals who are ACPA-negative but clinically at-risk of developing rheumatoid arthritis or in the general population. The relationship of interosseous tendon inflammation with other types of subclinical joint inflammation, such as synovitis, tenosynovitis, and osteitis, as well as its contribution to joint symptoms that occur in arthritis or during arthritis development, also remains elusive. Finally, since tenosynovium at several locations in the hand and forefoot was identified only recently, and because interosseous tendon inflammation on imaging represents inflammation around the tendon, the presence or absence of local tenosynovium needs to be determined.[10,12,13] A 2019 study observed no tenosynovial sheath using hematoxylin-eosin staining in a healthy joint.[10] Since a synovial lining around this small tendon in the normal situation can be thin, immunohistochemistry could be valuable to verify the absence or presence of local tenosynovium, as it was recently used to provide evidence of tenosynovium around metacarpophalangeal extensor tendons.[3]

Altogether, interosseous tendon inflammation could represent an early feature of rheumatoid arthritis-related

inflammation at the joint-level that is poorly characterised. We aimed to examine the presence of interosseous tendon inflammation in symptom-free individuals from the general population and the presence of tenosynovial tissue surrounding the interosseous tendons in the normal anatomical situation. Next, we set out to elucidate the role of interosseous tendon inflammation during rheumatoid arthritis development by using MRI to assess the occurrence of interosseous tendon inflammation in people with clinically suspect arthralgia, the association of interosseous tendon inflammation with inflammation of other local tissues (synovitis, tenosynovitis, or osteitis), clinical features (local tenderness, difficulties with making a fist, and reduced hand function), and the development of clinical arthritis.

Methods

Participants

This prospective cohort study included consecutive participants in the clinically suspect arthralgia cohort of the Leiden University Medical Centre, Netherlands; the cohort has been described in detail previously.[14] Briefly, the cohort enrols patients with recent-onset (symptom duration less than 1 year) arthralgia of small joints that is suspected of progressing to rheumatoid arthritis according to the treating rheumatologist (ie, clinically suspect arthralgia) based on clinical expertise and pattern recognition.[15] Patients were included independently of results from laboratory investigations, including auto-antibodies, which are generally not tested in primary care, in line with Dutch guidelines.[16] Patients in whom clinical arthritis was already present or in whom alternative causes of arthralgia were more probable (eg, osteoarthritis or fibromyalgia) were not included in the cohort. At inclusion, physical joint examination and blood tests were done, including IgG ACPA (measured using the anti-CCP2 ELISA EliA of Phadia, Nieuwegein, the Netherlands) and IgM rheumatoid factor (measured using an in-house ELISA).[17] Patients underwent MRI if no contra-indications were present.

In addition, symptom-free individuals (control cohort) were recruited from the general population in the Leiden region of the Netherlands, using advertisements in local newspapers and on websites. Inclusion criteria were: age 18 years or older, no history of inflammatory rheumatic disease, and no joint symptoms during the past 1 month. Volunteers were screened for these criteria by telephone and subsequently underwent physical examination of the hands and feet at the outpatient clinic to exclude presence of arthritis. The recruitment of the control cohort and the occurrence of synovitis, tenosynovitis, and osteitis in these individuals was described previously.[18] For this study, MRI images were specifically evaluated to determine the occurrence of interosseous tendon inflammation. All patients and symptom-free controls provided written informed consent.

The study protocol of the clinically suspect arthralgia cohort, with an amendment for the MRI study of symptom-free controls, was approved by the medical ethical committee of the Leiden University Medical Centre (P11.210). All anatomical specimens were obtained from human bodies that were donated according to the Dutch Burial and Cremation Act to the department of Anatomy and Embryology at the Leiden University Medical Centre for use in scientific research and medical education. Since the bodies had been donated for medical research under this act, no additional local ethics approval was needed for this specific histological research. During life, all the donors have signed an informed consent form to state that their body can be used for any kind of medical research that is approved by the mayor of the city. Patient partners were involved in designing the clinically suspect arthralgia cohort.

Microscopy and immunohistochemistry

Three embalmed human hands obtained from bodies donated for research were dissected. The studied materials belonged to individuals (two 63-year-old men and a 76-year-old woman) without morphological signs or known history of rheumatoid arthritis. Blocks containing the cutis, subcutis, extensor digitorum tendon, dorsal interosseous tendon and surrounding connective tissue were removed from the radial to dorsal side of the second metacarpophalangeal joint. This metacarpophalangeal joint was chosen since it is among the most common locations for interosseous tendon inflammation in people with clinically suspect arthralgia and is relatively accessible for dissection. Routine hematoxylin-eosin and sirius red staining for collagen were done to visualise the tendons and surrounding tissues. Immunohistochemical stainings were done using anti-CD55 (PA5–78,991, ThermoFisher, Waltham, MA, USA; 0·5 μg/mL) for detection of fibrobrast-like synoviocytes and anti-CD68 (14-0688-82, ThermoFisher; 0·5 μg/mL) for detection of macrophages. Histological methods are presented in the appendix (pp 10–11).

MRI and scoring of interosseous tendon inflammation

Contrast-enhanced unilateral 1·5T MRI (ONI, GE, Milwaukee, WI, USA) was made of the second to fifth metacarpophalangeal and wrist joints on the side with the most symptoms, or the dominant side if symptoms were symmetrical, and in symptom-free controls. The scanning protocol is described in detail in the appendix (pp 12–13).

MRIs were evaluated for interosseous tendon inflammation in line with the approach described by Mankia and colleagues.[10] Each individual tendon was localised by looking for oblong structures with low signal intensity arising from the intrinsic hand muscles and running radially or ulnarly from their corresponding

metacarpophalangeal joint, corresponding to the trajectory of the interosseous tendons. Next, it was determined whether contrast-enhancement was present around the tendon. Interosseous tendon inflammation was defined as contrast-enhancement around the full circumference of the interosseous tendon at the level of the metacarpophalangeal joint, present in both the axial and coronal plane and in two or more consecutive slices. In line with the literature, we also studied the abductor digiti minimi tendon since it functions as dorsal interosseus for the fifth digit.[9,10,19] Thus, we assessed

eight tendons in total (figure 1A). The interosseous tendons were discerned from the flexor and extensor tendon based on their anatomic location, since the latter are not located ulnarly or radially but palmarly and dorsally, respectively, from their corresponding metacarpophalangeal joint.

A dichotomous score (negative or positive) was assigned per tendon by a single reader (BTvD, a medical doctor trained in reading extremity MRIs). In case of doubt, the definitive score was determined by a second reader (MR, a musculoskeletal radiologist with over 20 years of experience). To ascertain reliability of interosseous tendon inflammation scoring, MRIs of 20 patients with clinically suspect arthralgia and ten symptom-free controls were mixed, stripped of metadata and rescored by the first reader (BTvD), which resulted in an intra-reader intraclass correlation coefficient (ICC) of 0·98.

MRIs were also evaluated for synovitis, tenosynovitis, and osteitis using the rheumatoid arthritis MRI scoring (RAMRIS) system by two independent trained readers (appendix pp 12–13).[4,20,21] Inter-reader and intra-reader intraclass correlation coefficient were published previously and were 0·90 or greater.[4,18]

Synovitis, tenosynovitis, or osteitis can be seen on MRI to some extent in the general population, especially in those 60 years or older and at certain locations, as reported previously in the same symptom-free controls included in this study.[18] Positivity for these features was therefore determined with measurements from the general population as a reference.[22] Briefly, synovitis, tenosynovitis, or osteitis was considered present if it was scored by both readers at the same location and was present in less than 5% of age-matched symptom-free controls.

All MRIs were scored blinded for clinical data. Interosseous tendon inflammation and the RAMRIS features (synovitis, tenosynovitis, or osteitis) were scored at different occasions and by different readers. RAMRIS data were unavailable during interosseous tendon inflammation scoring and vice versa.

Clinical features in clinically suspect arthralgia

At inclusion, tenderness of metacarpophalangeal joints and fist closure were assessed by physical examination. Patients were considered to have difficulties with making a fist if they either had incomplete fist-closure or reduced fist-strength.[23] Hand function was evaluated using three domains of the Health Assessment Questionnaire Disability Index (HAQ) specifically related to manual daily living activities: dressing or grooming, eating, and grip.[24,25] The eight questions on these domains were scored by patients on a 4-point scale representing the degree of difficulties experienced when performing the activity concerned, with 0 indicating no difficulties and 3 indicating full disability. As for the total HAQ, the HAQ score for reduced hand function was calculated as the average of the maximum scores in each domain and ranged from 0 to 3.[26]
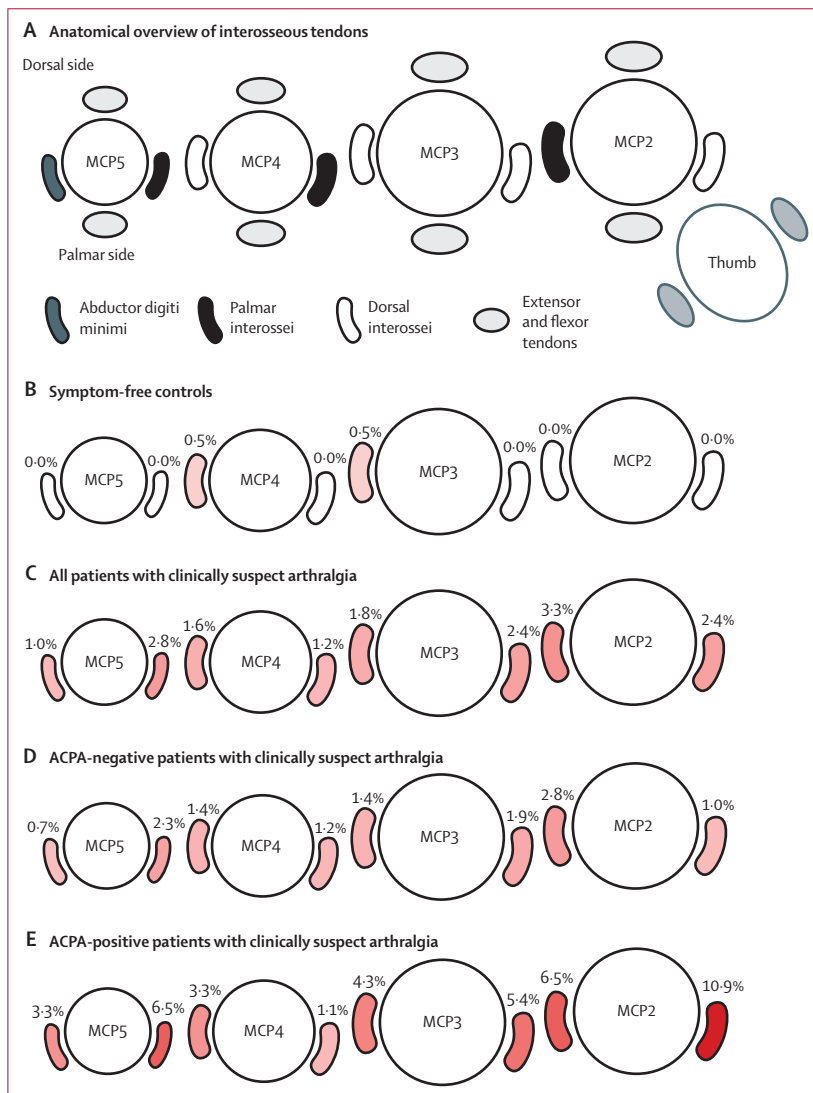
Figure 1: Schematic overview of the eight interosseous tendons and frequency of interosseous tendon inflammation at each tendon
(A) Schematic representation in axial view of the anatomy at the level of the metacarpophalangeal joints. The dorsal interosseous muscles originate from the dorso-lateral side of the metacarpals and mainly act as abductors of the fingers. The palmar interosseous tendons originate from the lateral sides of the metacarpals and mainly act as adductors of the fingers. Please note that the third digit has two dorsal but no palmar interosseous tendons.[29] (B–E) Frequency of interosseous tendon inflammation at each tendon in symptom-free controls (B), all patients with clinically suspect arthralgia (C), and separately in ACPA-negative (D) and ACPA-positive (E) patients with clinically suspect arthralgia. MCP=metacarpophalangeal joint.

Clinical assessments were done without knowledge of the patient's MRI scores. MRIs were scheduled at the earliest possible occasion after presentation with clinically suspect arthralgia. Median time between inclusion into the cohort and the baseline MRI was 7 days (IQR 2–12).

Patients with clinically suspect arthralgia were followed for clinical arthritis development, defined as joint swelling palpable at physical joint examination (ie, at least one swollen joint of the 66 joints that were assessed in total). Follow-up visits including physical joint examination were scheduled at 4, 12, and 24 months after inclusion, but patients were welcomed for additional visits whenever their symptoms required, to facilitate timely detection of arthritis. Electronic hospital records were reviewed for clinical arthritis until 2·5 years after inclusion or April 23, 2021, whichever came first. Patients and clinicians had no access to MRI data.

Treatment with disease-modifying anti-rheumatic drugs (DMARDs), and systemic and intra-articular corticosteroids was not allowed during follow-up. However, between April 1, 2015, and Aug 31, 2019, newly presenting patients with clinically suspect arthralgia could participate in a randomised placebo-controlled trial assessing the efficacy of methotrexate in preventing the development of clinical arthritis when they had subclinical joint inflammation.[27,28] Patients with clinically suspect arthralgia who participated in the trial were excluded from the analyses on clinical arthritis development in this study (appendix p 1) to ensure that patients in the current study were not exposed to methotrexate.[4,7] Of those eligible for participation in the trial based on presence of MRI-detected subclinical inflammation, there were no clinically relevant differences in baseline characteristics between those who were and were not included (appendix p 6).

Three-dimensional (3D) MRI reconstruction

To provide an example of interosseous tendon inflammation and its anatomical relation to adjacent structures, a coloured 3D image was constructed from MRI in a patient with interosseous tendon inflammation using Amira software (v2021.1, ThermoFisher). The relevant structures (interosseous tendons, interosseous and lumbrical muscles, metacarpophalangeal flexor or extensor tendons, metacarpal bones, and phalanges) were identified and coloured based on the signal intensity of consecutive voxels and using the Netter Atlas of Human Anatomy as reference.[29]

Outcomes

In the cross-sectional part of the study, the frequency of interosseous tendon inflammation was assessed. Outcomes studied cross-sectionally in relation to presence of interosseous tendon inflammation at inclusion were: the prevalence of other MRI-detected local inflammation at the metacarpophalangeal joints (synovitis, tenosynovitis, or osteitis), metacarpophalangeal

tenderness, presence of difficulties making a fist and the hand function score measured by the HAQ. The primary outcome for the longitudinal part of the study was development of clinical arthritis. The secondary outcome was development of rheumatoid arthritis (defined as clinical diagnosis plus fulfilment of the 2010 or 1987 criteria for rheumatoid arthritis) or DMARD initiation. Classification criteria for rheumatoid arthritis were not part of the primary outcome since their fulfilment might be hampered by early recognition of clinical arthritis and subsequent DMARD initiation, which are facilitated by the design of the clinically suspect arthralgia cohort, which involved close monitoring of patients for the development of clinical arthritis. Time-to-event for both outcomes was calculated as the time between inclusion in the clinically suspect arthralgia cohort and detection of clinical arthritis at physical examination by the rheumatologist.

	Patients with clinically suspected arthralgia			Symptom-free controls
	All (n=667)	No interosseous tendon inflammation (n=600)	Interosseous tendon inflammation (n=67)	All (n=193)
Age, years	44 (13)	43 (13)	52 (13)	50 (16)
Sex				
Female	504 (76%)	460 (77%)	44 (66%)	136 (70%)
Male	163 (24%)	140 (23%)	23 (34%)	57 (30%)
Self-reported race or ethnicity*				
White	474 (71%)	424 (71%)	50 (75%)	..
Other	35 (5%)	32 (5%)	3 (4%)	..
Missing	158 (24%)	144 (24%)	14 (21%)	..
Symptom duration, weeks†	19 (9–43)	19 (9–44)	17 (9–28)	..
Tender joint count-68‡	5 (2–10)	5 (2–10)	4 (2–7)	..
ACPA status				
Positive	92 (14%)	67 (11%)	25 (37%)	..
Negative	575 (86%)	533 (89%)	42 (63%)	..
Rheumatoid factor status				
Positive	132 (20%)	101 (17%)	31 (46%)	..
Negative	534 (80%)	498 (83%)	36 (54%)	..
Missing	1 (<1%)	1 (<1%)	0	..
C-reactive protein				
≥5·0 mg/L	152 (23%)	122 (20%)	30 (45%)	..
<5·0 mg/L	512 (77%)	475 (79%)	37 (55%)	..
Missing	3 (<1%)	3 (1%)	0	..
Average number of locations with interosseous tendon inflammation (range 0–8)	0·17	NA	1·66	0·01

Data are mean (SD), n (%), or median (IQR). ACPA=anti-citrullinated protein antibodies. NA=not applicable. *Race and ethnicity data was not collected for controls. †Symptom duration data was missing for 38 (6%) of all patients with clinically suspect arthralgia, 35 (6%) of those with no interosseous tendon inflammation, and three (4%) of those with interosseous tendon inflammation. ‡Tender joint count-68 data was missing for eight (1%) of all patients with clinically suspect arthralgia and eight (1%) of those with no interosseous tendon inflammation.
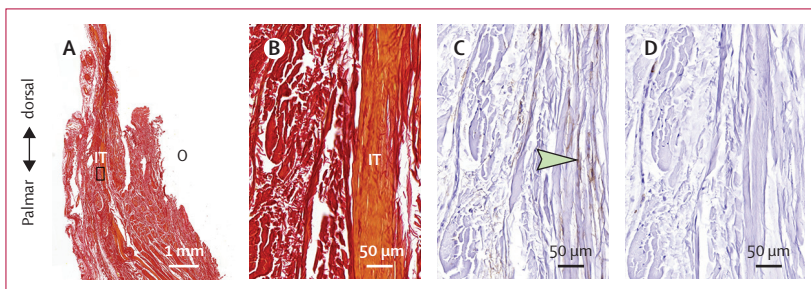
Table 1: Baseline characteristics

Statistical analyses

Logistic regression was used to study associations of the presence of interosseous tendon inflammation with other subclinical inflammation features at metacarpophalangeal joints. The presence of synovitis, tenosynovitis, or osteitis at one or more metacarpophalangeal joint were independent variables, whereas interosseous tendon inflammation was the dependent variable.

Associations between interosseous tendon inflammation and other subclinical inflammation was also studied at the joint level. For this, generalised estimating equations were used wherein each patient contributed four metacarpophalangeal joints. The presence of synovitis, tenosynovitis, or osteitis at the metacarpophalangeal joint were the independent variables, whereas the presence of interosseous tendon inflammation was the dependent variable. Interosseous tendon inflammation was considered present at the metacarpophalangeal joint level if at least one of the two interosseous tendons belonging to that metacarpophalangeal joint had surrounding inflammation on MRI.

Next, the association of interosseous tendon inflammation (independent variable) with symptoms was assessed. The following outcomes (dependent variables) were studied, each with the appropriate regression technique: tenderness at the same metacarpophalangeal joint (using generalised estimating equations), difficulties making a fist (using logistic regression) and the hand function score measured by the HAQ (using linear regression).

Kaplan-Meier curves and Cox regression models were used to assess whether the presence of interosseous tendon inflammation (independent variable) predisposes for clinical arthritis development (dependent variable). This analysis was repeated with stratification for ACPA status, with an interaction term of interosseous tendon inflammation and ACPA status, using development of rheumatoid arthritis as the outcome.

Multivariable models that included presence of synovitis, tenosynovitis, or osteitis as independent variables in addition to interosseous tendon inflammation were used to adjust for simultaneous presence of the different subclinical inflammation features on MRI.

IBM SPSS (version 25) was used. Two-sided p values <0·05 were considered statistically significant.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 3, 2012, and May 20, 2020, 709 consecutive patients with clinically suspect arthralgia were included in the cohort, of whom 667 (94%) underwent MRI and were included in this study (appendix p 1). Baseline characteristics of patients with clinically suspect arthralgia are presented in table 1. Mean age was 44 years (SD 13), 504 (76%) of 667 were women and 163 (24%) were men. 92 (14%) were ACPA-positive, median symptom duration was 19 weeks (IQR 9–43) and median tender joint count-68 was 5 (IQR 2–10). In addition, 193 symptom-free controls were recruited between Nov 1, 2013, and Nov 30, 2014, from the general population. The mean age of symptom-free controls was 50 years (SD 16), 136 (70%) of 193 were women and 57 (30%) were men (table 1).

Interosseous tendon inflammation was present on MRI in only two (1%) of 193 symptom-free controls (figure 1B). No tenosynovial sheath around the interosseous tendon was observed in the transverse sections from any of the cadaveric specimens. Immunohistochemical staining was done to further characterise the peritendinous connective tissue (figure 2; appendix p 2). Although some CD55 positive cells were detected inside the tendon, no lining of cells positive for CD55 (fibroblast-like synoviocytes) or CD68 (macrophages) was seen surrounding the interosseous tendon in any of the specimens, suggesting that in the normal anatomical situation, tenosynovium surrounding the interosseous tendons is absent.

At inclusion, 67 (10%) of 667 patients with clinically suspect arthralgia had interosseous tendon inflammation (p<0·0001 vs symptom-free controls). The frequency of interosseous tendon inflammation at each tendon is presented in figure 1C. The palmar interosseous tendon next to the second metacarpophalangeal was most frequently inflamed. The mean number of interosseous tendons affected among patients with interosseous tendon inflammation was 1·7 (maximum 8). Frequencies of interosseous tendon inflammation are presented separately for women and men with clinically suspect arthralgia in the appendix (p 3).

Since ACPA-positive and ACPA-negative rheumatoid arthritis are considered different disease-subsets based

Figure 2: Immunohistochemical evaluation of transverse sections near the second metacarpophalangeal joint through the interosseous tendon
(A) Sirius red-stained transverse section of the tissue on the radial side of the second metacarpophalangeal joint. (B) Magnification of the area marked by the rectangle in (A); red on a yellow–orange background indicates collagen fibres and is consistent with tendinous tissue. (C) Adjacent transverse section with immunohistochemical staining for CD55; the brown precipitate indicates positive fibroblasts (arrow). (D) Adjacent transverse section with immunohistochemical staining for CD68 (macrophages). IT=interosseous tendon. O=location of ossa digitorum of the distal phalanx (removed from tissue block).

on differences in pathophysiology and outcomes,[30,31] interosseous tendon inflammation was examined in ACPA-positive and ACPA-negative patients with clinically suspect arthralgia separately (figure 1D, E). ACPA-positive patients with clinically suspect arthralgia more often had interosseous tendon inflammation than did ACPA-negative patients with clinically suspect arthralgia (25 [27%] of 92 vs 42 [7%] of 575; p<0·0001).

As part of elucidating the role of interosseous tendon inflammation in rheumatoid arthritis development, we assessed the association of interosseous tendon inflammation with inflammation of other local tissues known to be involved in rheumatoid arthritis (synovitis, tenosynovitis, or osteitis). Patients with clinically suspect arthralgia with interosseous tendon inflammation were more likely to also have other subclinical inflammation at metacarpophalangeal joints (table 2). Of these 67 patients with clinically suspect arthralgia with interosseous tendon inflammation, 48 (72%) had other subclinical inflammation at metacarpophalangeals: 25 (37%) had synovitis; five (7%) tenosynovitis, and 18 (27%) both synovitis and tenosynovitis, whereas 19 (28%) did not have MRI-detected synovitis or tenosynovitis, at their metacarpophalangeal joints. Multivariable analyses adjusted for this co-occurrence showed that tenosynovitis (OR 9·7 [95% CI 5·5–17·0]) and synovitis (2·2 [1·2–4·2]) were independently associated with interosseous tendon inflammation (table 2). Analyses at individual metacarpophalangeal joint-level also showed that tenosynovitis (5·2 [2·7–10·1]) and synovitis (6·8 [3·8–12·2]) were independently associated with interosseous tendon inflammation (table 2). Osteitis was not associated with interosseous tendon inflammation at either the patient-level (1·6 [0·6–3·8] or at the joint-level (1·7 [0·5–5·0]).

Local tenosynovitis was present in addition to interosseous tendon inflammation and visible on MRI (figure 3A, B). To illustrate the proximity of interosseous tendon inflammation with nearby tissues, 3D MRI reconstruction was performed (video, figure 3C). This suggested that inflammation around the interosseous tendons (figure 3C, arrow points to interosseous tendon inflammation) and around metacarpophalangeal-flexor-tendons (figure 3C, arrowhead points to tenosynovitis) was confluent.

As synovitis and tenosynovitis at small joints are known to contribute to typical symptoms of clinically

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	Patients with clinically suspect arthralgia (n=667)			
	No interosseous tendon inflammation (n=600)	Interosseous tendon inflammation (n=67)	Univariable OR (95% CI)	Multivariable* OR (95% CI)
Patient-level				
Synovitis negative (n=576)	532 (92%)	44 (8%)	1 (ref)	1 (ref)
Synovitis positive (n=91)	68 (75%)	23 (25%)	4·1 (2·3–7·2)	2·2 (1·2–4·2)
Tenosynovitis negative (n=543)	519 (96%)	24 (4%)	1 (ref)	1 (ref)
Tenosynovitis positive (n=124)	81 (65%)	43 (35%)	11·5 (6·6–19·9)	9·7 (5·5–17·0)
Osteitis negative (n=620)	562 (91%)	58 (9%)	1 (ref)	1 (ref)
Osteitis positive (n=47)	38 (81%)	9 (19%)	2·3 (1·1–5·0)	1·6 (0·6–3·8)
Any rheumatoid arthritis MRI inflammation negative† (n=464)	446 (96%)	18 (4%)	1 (ref)	NA
Any rheumatoid arthritis MRI inflammation positive† (n=203)	154 (76%)	49 (24%)	7·9 (4·5–13·9)	NA
Joint-level				
Synovitis negative (n=2563)	2494 (97%)	69 (3%)	1 (ref)	1 (ref)
Synovitis positive (n=105)	81 (77%)	24 (23%)	9·8 (5·9–16·1)	6·8 (3·8–12·2)
Tenosynovitis negative (n=2475)	2419 (98%)	56 (2%)	1 (ref)	1 (ref)
Tenosynovitis positive (n=193)	156 (81%)	37 (19%)	6·5 (3·5–12·1)	5·2 (2·7–10·1)
Osteitis negative (n=2617)	2529 (97%)	88 (3%)	1 (ref)	1 (ref)
Osteitis positive (n=51)	46 (90%)	5 (10%)	2·5 (0·9–7·1)	1·7 (0·5–5·0)
Any rheumatoid arthritis MRI inflammation negative† (n=2363)	2318 (98%)	45 (2%)	1 (ref)	NA
Any rheumatoid arthritis MRI inflammation positive† (n=305)	257 (84%)	48 (16%)	7·1 (4·2–12·0)	NA

Data are n (%) or OR (95% CI). ORs were calculated by logistic regression in patient-level analyses and generalised estimating equations in joint-level analyses. Patient-level data show associations between the presence of interosseous tendon inflammation (dependent variable) and presence of other subclinical inflammation (independent variables) at any scanned metacarpophalangeal joint with goodness-of-fit of the multivariable logistic regression model Nagelkerke R^2 of 0·252. Joint-level data show associations between the presence of interosseous tendon inflammation (dependent variable) and presence of other subclinical inflammation (independent variable) at the same metacarpophalangeal joint. NA=not applicable. OR=odds ratio. *Multivariable model: with presence of synovitis, tenosynovitis, and osteitis as separate independent variables. †Synovitis, tenosynovitis, or osteitis, or two or all three conditions.

Table 2: Associations of interosseous tendon inflammation with other subclinical inflammation features at metacarpophalangeal joints on the patient-level and the joint-level
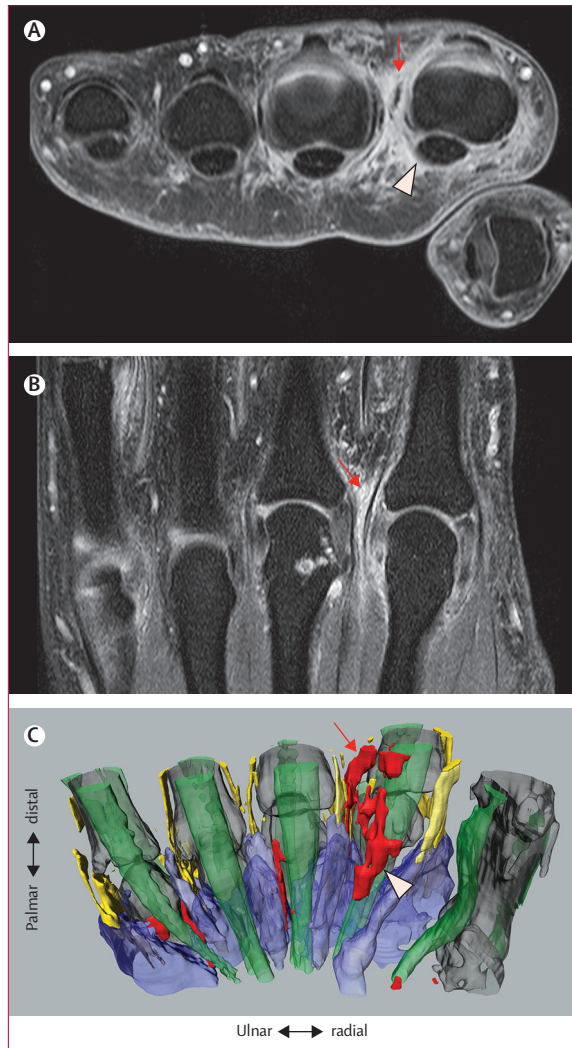
Figure 3: **MRI-detected interosseous tendon inflammation co-occurring with flexor tenosynovitis at the second metacarpophalangeal joint (A–B) and 3D MRI reconstruction (C) from the same patient**
(A–B) T1-weighted fat suppressed images after gadolinium administration at the level of the second metacarpophalangeal joint. (A–C) Arrows point to contrast enhancement around the interosseous tendon on the ulnar side of the second metacarpophalangeal joint, consistent with interosseous tendon inflammation; arrowheads point to contrast enhancement around the flexor tendon of the second metacarpophalangeal joint, consistent with tenosynovitis. (C) Contrast-enhancement (red) around interosseous and flexor tendons, consistent with inflammation, which appeared to be continuous between the two areas; interosseous tendons (yellow); metacarpal bones and phalanges (grey); flexor and extensor tendons of the fingers (green); and interosseous and lumbrical muscles (blue).

suspect arthralgia and early rheumatoid arthritis[6] we explored whether interosseous tendon inflammation is associated with joint tenderness and reduced hand function (appendix pp 7–8). In univariable analysis, metacarpophalangeal joints with adjacent interosseous tendon inflammation were more likely to be tender on physical examination (OR 1·6 [95% CI 1·03–2·4]). Multivariable analysis showed that interosseous tendon

inflammation was not independently associated with local metacarpophalangeal joint tenderness (OR 1·3 [0·8–2·1]), in contrast to tenosynovitis (OR 2·0 1·4–2·9]). Patients with clinically suspect arthralgia with interosseous tendon inflammation more often had difficulties making a fist, but interosseous tendon inflammation was not independently associated with these difficulties (OR 1·2 [0·7–2·1]), in contrast to tenosynovitis (OR 1·6 [1·1–2·4]). Similarly, hand function measured by the HAQ was on average 0·20 points worse in patients with interosseous tendon inflammation (β 0·20 [95% CI 0·05–0·36]), but in multivariable analyses interosseous tendon inflammation was not independently associated with worse hand functioning. Thus, these clinical features (joint tenderness, difficulty making a fist, and hand function) are primarily associated with other locally inflamed tissues rather than with interosseous tendon inflammation in patients with clinically suspect arthralgia.

Next, we examined whether interosseous tendon inflammation in patients with clinically suspect arthralgia precedes and is associated with clinical arthritis development. During follow-up (median 25·3 months [95% CI 25·1–25·5]), 91 (16%) of 558 patients with clinically suspect arthralgia developed clinical arthritis. Those who had interosseous tendon inflammation at inclusion developed clinical arthritis more often than those without interosseous tendon inflammation (hazard ratio [HR] 4·5 [95% CI 2·8–7·2]; figure 4A). Presence of interosseous tendon inflammation conferred increased risk for rheumatoid arthritis in both ACPA-negative (HR 3·9 [1·9–7·9]) and ACPA-positive (1·8 [0·9–3·4]) patients with clinically suspect arthralgia (figure 4B, C). The model with an interaction term between interosseous tendon inflammation and ACPA status showed that the association between interosseous tendon inflammation and clinical arthritis development was not significantly different between ACPA-positive and ACPA-negative patients with clinically suspect arthralgia ($HR_{interaction}$ 0·50 [0·19–1·32]; p=0·16; appendix p 9). Development of clinical arthritis is presented separately for women and men in the appendix (p 4).

In a multivariable analysis with adjustment for concomitant synovitis, tenosynovitis and osteitis, presence of interosseous tendon inflammation remained independently associated with clinical arthritis development (HR 1·7 [95% CI 1·02–2·8]). Results were similar when rheumatoid arthritis development was the outcome instead of inflammatory clinical arthritis (appendix p 5).

Discussion
Complementing the traditional view of rheumatoid arthritis as a disease of the intra-articular synovium, two forms of juxta-articular synovial inflammation—tenosynovitis and intermetatarsal bursitis—were identified in 2020–21, with imaging studies in patients
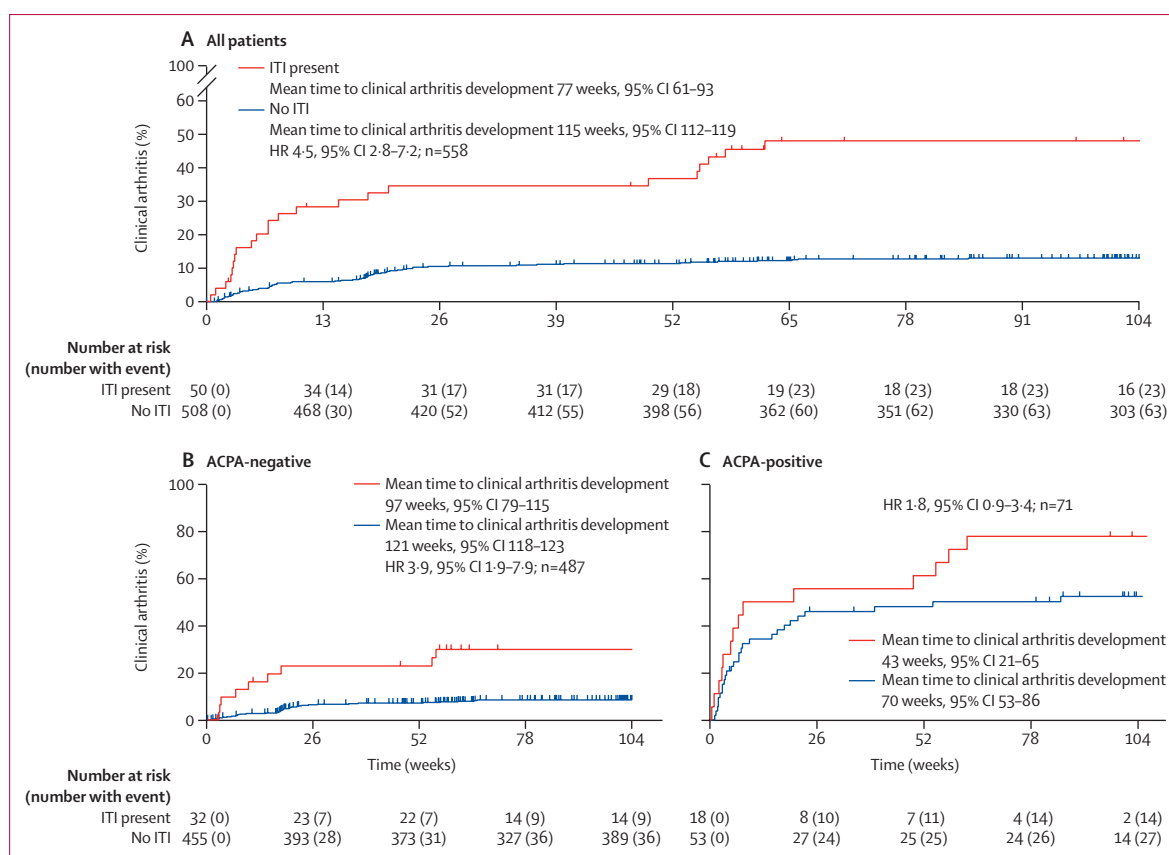
Figure 4: Kaplan Meier curves of progression to clinical arthritis according to presence of interosseous tendon inflammation at inclusion
ITI=interosseous tendon inflammation. ACPA=anti-citrullinated protein antibody. HR=hazard ratio.

with early rheumatoid arthritis and preceding rheumatoid arthritis.[1,2] This study showed that interosseous tendon inflammation also occurs in the clinically suspect arthralgia-phase, preceding the development of clinical arthritis. This finding identifies interosseous tendon inflammation as another juxta-articular site of local inflammation that manifests before rheumatoid arthritis develops, in both ACPA-positive and ACPA-negative disease.

The proportion of ACPA-positive patients with clinically suspect arthralgia with interosseous tendon inflammation seen in this study (25 [27%] of 92) was in line with the first description of interosseous tendon inflammation in ACPA-positive at-risk individuals (18 [19%] of 93).[10] The current study provided additional knowledge by showing that interosseous tendon inflammation is almost absent in the general population, that it often occurs together with tenosynovitis and synovitis, and that presence of interosseous tendon inflammation in people with clinically suspect arthralgia is associated with future development of rheumatoid arthritis. Our study is also the first to show presence of interosseous tendon inflammation in ACPA-negative patients with clinically suspect arthralgia. The frequency of interosseous tendon inflammation in this population

was lower than in ACPA-positive patients, possibly related to the intrinsically lower incidence of rheumatoid arthritis development. However, if present in patients with ACPA-negative clinically suspect arthralgia, interosseous tendon inflammation is a risk factor for developing rheumatoid arthritis. In fact, the largest association between interosseous tendon inflammation and development of rheumatoid arthritis was in these individuals.

To explore the possible contribution of interosseous tendon inflammation to symptoms and physical impairments in clinically suspect arthralgia, we studied associations with local tenderness and limitations of hand function. Although these clinical characteristics were more severe in patients with clinically suspect arthralgia with interosseous tendon inflammation than in patients with clinically suspect arthralgia without interosseous tendon inflammation, this was mostly explained by concomitant tenosynovitis or synovitis. Hypothetically, due to the relatively small volume of interosseous tendon inflammation compared with that of, for example, tenosynovitis, which can extend a few centimetres along the tendon, interosseous tendon inflammation might contribute less to these clinical characteristics.

To our knowledge, our study is the first to perform immunohistochemistry on the tissue surrounding interosseous tendons. A tenosynovial lining was not observed, in contrast to previous studies from our group on, for example, the extensor tendon of the metacarpophalangeal joints, where similar methodology was used and presence of tenosynovium was observed.[3,32] This finding might support the notion that interosseous tendon inflammation does not arise from tenosynovial cells. However, in the healthy situation any synovial tissue surrounding the interosseous tendon will likely be thin and thereby intrinsically difficult to detect. It would be of interest to examine histologically the inflamed tissue surrounding the interosseous tendons in patients with clinically suspect arthralgia or rheumatoid arthritis. However, such histological samples are enormously difficult, if not impossible, to obtain. Since a previous study in non-inflamed joints using hematoxylin-eosin staining also observed no tenosynovium,[10] we presume that tenosynovium is absent. Since interosseous tendon inflammation most commonly occurred together with tenosynovitis and synovitis, this could imply that interosseous tendon inflammation is secondary to inflammation in nearby synovial tissue. A 3D MRI reconstruction suggested that interosseous tendon inflammation was confluent with metacarpophalangeal–flexor tenosynovitis. To determine this with more certainty, an MRI study with a smaller slice thickness and 3D reconstructions would be required.

The possibility that interosseous tendon inflammation results from expanding inflammation of nearby inflamed tissues is somewhat contradicted by the finding that interosseous tendon inflammation could occur without concomitant tenosynovitis or synovitis. Longitudinal imaging studies would be required to determine if tenosynovitis or synovitis occur subsequently in these patients. Nonetheless, so far interosseous tendon inflammation can be considered the first evidence of primary involvement of non-synovial peritendinous tissue in addition to involvement of tendon sheaths of small hand and foot joints. This finding suggests that future tissue-level studies of rheumatoid arthritis pathogenesis should not be limited to the synovial joint or synovial and tenosynovial tissue.

Our study has some limitations. First, we were unable to study possible influences of mechanical factors (eg, work or hobbies involving manual labour) because such such detailed information was not available. Although mechanical stress has been suggested to potentially trigger development of rheumatoid arthritis and has been associated with local inflammatory responses at tendons,[33] to the best of our knowledge the influence on the interosseous tendons specifically is unknown. However, the near absence of interosseous tendon inflammation in the general population, and in those aged 60 years or older, might suggest a limited influence of mechanical factors or ageing.

Second, in longitudinal analyses for clinical arthritis development, some patients were not assessed due to participation in a trial involving a 50% chance of being randomly assigned to methotrexate treatment. This could reduce the observed effect size since trial participation required a positive MRI for subclinical synovitis, tenosynovitis, or osteitis, which is a risk factor for clinical arthritis development.[4] Indeed, an analysis including only patients included in the cohort with clinically suspect arthralgia before and after the trial inclusion period (thereby excluding any influence of the trial) showed a higher effect size (HR 2·7 [1·3–5·6] vs 1·7 [1·02–2·8]).

Third, the quality of the 3D MRI reconstruction was limited by the resolution and slice thickness of the images. Therefore, reconstruction was performed in a single representative case for illustrative purposes. Although 3D reconstruction in the total study population could provide more evidence on the anatomic relation between inflamed tissues, this was beyond the scope of the current study.

Finally, there is no validated MRI scoring method available for interosseous tendon inflammation, which can be considered a limitation. To aid comparability, we scored interosseous tendon inflammation in line with the approach described by Mankia and colleagues.[10] In addition, interosseous tendon inflammation was evaluated by a single reader in our study, although a musculoskeletal radiologist with over 20 years of experience was involved in training this reader and in scoring interosseous tendon inflammation in cases of doubt. Intra-reader reliability in our study was high (intraclass correlation coefficient of 0·98); inter-reader reliability remains to be assessed.

Several aspects of interosseous tendon inflammation remain to be elucidated, such as if interosseous tendon inflammation independently contributes to symptoms in more advanced stages of disease, such as classified rheumatoid arthritis where local joint inflammation is generally more severe. Additionally, it would be interesting to perform a serial MRI study during progression from clinically suspect arthralgia to rheumatoid arthritis and to discover the time sequences with which the different tissues in and around the joint become inflamed. It might also be interesting to study the occurrence of interosseous tendon inflammation in consecutive patients with classifiable rheumatoid arthritis and other arthritides such as peripheral spondyloarthritis. This could provide further clues to whether interosseous tendon inflammation is primarily related to underlying rheumatoid arthritis-specific disease processes or rather is secondary to nearby joint inflammation. Lastly, the exact composition of the tissue surrounding the interosseous tendons remains unknown.

In conclusion, interosseous tendon inflammation is present in ACPA-positive as well as ACPA-negative patients with clinically suspect arthralgia and precedes the development of clinical arthritis in both populations.

Histological evaluations suggest that interosseous tendon inflammation does not arise from naturally present tenosynovial tissue. Interosseous tendon inflammation could therefore be considered as the first evidence of primary non-synovial peritendinous tissue involvement. Because of its frequent occurrence with subclinical tenosynovitis and synovitis, interosseous tendon inflammation might reflect locally expanding subclinical joint inflammation in the pre-arthritis stage of the disease. This study enhances understanding of the variety of locally inflamed tissues in the at-risk phase of rheumatoid arthritis and could stimulate further studies to comprehend how these different inflamed tissues interact during the development of clinical rheumatoid arthritis.

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