Early clinical and imaging features of rheumatoid arthritis: towards a more complete picture

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Chapter 9

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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ABSTRACT

Background. Inflammation around the tendons of hand interosseous muscles (interosseous tendon inflammation; ITI) was recently observed for the first time in rheumatoid arthritis (RA) patients and ACPA-positive at-risk individuals with MRI, generating the hypothesis that ITI precedes clinical arthritis. To better understand the role of ITI during RA development, we studied the frequency of ITI in healthy persons and in clinically suspect arthralgia (CSA) and its relation with other inflamed joint tissues, symptoms and clinical arthritis development. Additionally we explored the presence of local tenosynovium in the tissue using immunohistochemistry.

Methods. 193 symptom-free controls and 667 consecutively presenting CSA patients underwent contrast-enhanced hand MRI. MRIs were evaluated for ITI ulnar and radial to MCP 2–5, and for synovitis, tenosynovitis and osteitis using the RA MRI scoring system (RAMRIS). CSA patients were followed on clinical arthritis development (median follow-up 25.3 months (95%CI 25.1–25.5)). Immunohistochemistry with anti-CD55 and anti-CD68 was performed on tissue from three embalmed hands.

Findings. 1% (2/193) of symptom-free controls had ITI. Immunohistochemistry showed no tenosynovium surrounding interosseous tendons. At inclusion, 10% (67/667) of CSA patients had ITI ($p<0.0001$ vs. symptom-free controls). ITI-presence occurred more frequently if synovitis (OR 2.2 (95%CI 1.2–4.2)) and/or tenosynovitis (OR 9.7 (5.5–17.0)) was present at MCP joints. A 3D MRI reconstruction suggested confluency of ITI with MCP flexor tenosynovitis. CSA patients with ITI more often had local MCP tenderness (OR 1.6 (1.03–2.4)), difficulties making a fist (OR 1.6 (0.98–2.7)) and reduced hand functioning (β 0.20 (0.05–0.36)). Moreover they had a higher risk of developing clinical arthritis (HR 4.5 (2.8–7.2)), also independent of concomitant synovitis, tenosynovitis and/or osteitis (HR 1.7 (1.02–2.8)).

Interpretation. ITI is almost absent in the healthy situation and occurs in CSA where it correlates with symptoms and predicts clinical arthritis development. The absence of local tenosynovium suggests that ITI arises from expanding local subclinical inflammation in the pre-arthritis phase of RA.

RESEARCH IN CONTEXT

Evidence before this study

Besides intra-articular synovitis, RA frequently involves inflammation of synovial tissue in hands or feet that has a juxta-articular location and surrounds tendons (tenosynovitis) or covers intermetatarsal bursae (intermetatarsal bursitis). On top of this, inflammation around the hand interosseous tendons (interosseous tendon inflammation; ITI) was recently described using MRI. By searching PubMed for studies published up to 20 December 2022, using the search terms "interosseous" and "inflammation", we found two studies from the same centre describing ITI in small sets of RA patients and ACPA-positive individuals with musculoskeletal complaints. This may suggest that ITI precedes clinical arthritis during the development of RA, but longitudinal studies are lacking. Furthermore, it is unclear whether ITI represents inflammation of synovial tissue, how often ITI occurs in the general population and in ACPA-negative patients, and how it relates to other inflamed tissues.

Added value of this study

Using MRI in two large cohorts of symptom-free controls and patients with clinically suspect arthralgia (CSA), we show that ITI is almost absent in the general population but indeed occurs already in patients presenting with clinically suspect arthralgia (CSA) who are at risk of developing RA. This concerns both ACPA-positive and ACPA-negative CSA patients. If present at presentation with CSA, ITI confers an increased risk of developing clinical arthritis. Although ITI mostly occurred together with tenosynovitis and synovitis, immunohistochemical staining suggested absence of a (teno)synovial lining around the interosseous tendons.

Implications of all the available evidence

ITI is a novel feature of juxta-articular inflammation and is the first evidence of non-synovial (peri)tendinous inflammation in RA and may reflect locally expanding subclinical joint inflammation in the pre-arthritis stage of the disease. This improves our understanding of local inflammation during the development of RA and suggests that future imaging and tissue-level studies on RA pathogenesis should not be limited to the synovial joint itself.

INTRODUCTION

Traditionally, rheumatoid arthritis (RA) is known for targeting the intra-articular synovium. Recently, histological studies have uncovered that synovial tissue also occurs outside or next to the joint capsule (juxta-articular), e.g. around flexor and extensor

tendons of MCP and MTP joints and at intermetatarsal bursae.[1-3] In addition, imaging studies revealed that tenosynovitis and intermetatarsal bursitis (IMB) are early features of RA and contribute to symptoms, both in the pre-arthritis phase and in established RA.[1,2,4-8] As such, the emerging phenomenon of juxta-articular synovial inflammation provides novel insights into how the RA-phenotype originates.

The view on juxta-articular tissue-involvement in RA was expanded further by the recent, interesting observation of inflammation around the hand interosseous tendons on MRI (interosseous tendon inflammation; ITI) at the Leeds Institute of Rheumatic and Musculoskeletal Medicine.[9,10] The interosseous muscles originate from the metacarpals and converge into tendons that run adjacent to the radial and ulnar sides of metacarpophalangeal (MCP) joints 2–5. They insert on the extensor aponeurosis and/or proximal phalanx, which is subject to anatomical variation. The interosseous muscles and tendons are essential for normal hand functioning: in addition to finger adduction and abduction, they aid finger stability by supporting flexion at MCP joints and extension at PIP and DIP joints.[11]

Using MRI, the Leeds group observed ITI in part of RA patients and ACPA-positive individuals with musculoskeletal symptoms.[9,10] This may suggest that ITI precedes clinical arthritis during the development of RA and prompted us to perform an in-depth study as several questions about ITI remained to be answered. Thus far, longitudinal follow-up data on actual RA development in at-risk individuals is lacking. In addition, it is unknown whether ITI also occurs in ACPA-negative individuals who are clinically at-risk to develop RA and in the general population. Also the relation of ITI with other subclinical inflamed joint tissues such as (teno)synovitis and osteitis, as well as the contribution to symptoms, remains elusive. Finally, since tenosynovium at several locations in the hand and forefoot were only recently identified and because ITI at imaging represents inflammation *around* the tendon, the presence/absence of local tenosynovium needs to be determined.[10,12,13] A recent study observed no tenosynovial sheath using hematoxylin-eosin (HE) staining in a healthy joint.[10] Since a synovial lining around this small tendon in the normal situation may be thin, immunohistochemistry may be valuable to verify the absence/presence of local tenosynovium, similar to how immunohistochemistry recently provided evidence of tenosynovium around MCP extensor tendons.[3]

Altogether, ITI potentially represents an early feature of RA-related inflammation at the joint level that is yet poorly characterised. We set out to fill in the aforementioned knowledge gaps by studying presence of ITI in symptom-free persons from the general population and presence of tenosynovial tissue surrounding the interossei tendons in the

normal anatomical situation. Next, to elucidate the role of ITI during RA development, we performed an MRI study in a large cohort of consecutively included clinically suspect arthralgia (CSA) patients to assess: the prevalence of ITI in CSA, the relation with other local inflamed tissues (synovitis, tenosynovitis, osteitis) and with clinical features (local tenderness, difficulties with making a fist, reduced hand functioning), and finally the association of ITI with clinical arthritis development.

METHODS

Patients and symptom-free controls

The CSA cohort of the Leiden University Medical Centre (LUMC) was described in more detail previously.[14] In short, this Dutch cohort enrols patients with recent-onset (symptom duration <1 year) arthralgia of small joints in whom their rheumatologist suspected an increased risk of developing RA based on clinical expertise and pattern recognition.[15] Patients were included independently of results from laboratory investigations, including auto-antibodies. In line with Dutch guidelines for general practitioners these are generally not tested in primary care.[16] Notably, patients in whom clinical arthritis was already present or in whom alternative causes of arthralgia were more likely (e.g. osteoarthritis, fibromyalgia), were not included in the CSA cohort. At inclusion, physical joint examination and blood tests were conducted, including IgG anti-citrullinated protein antibodies (ACPA; measured using the anti-CCP2 ELISA EliA of Phadia, Nieuwegein) and IgM rheumatoid factor (RF; measured using an in-house ELISA).[17] Patients underwent MRI if no contra-indications were present. Between 3 April 2012 and 20 May 2020, 709 consecutive CSA patients were included in the cohort, of whom 667 (94%) underwent MRI and were thus analysed in the current study (a flowchart is presented in Online Supplementary Figure SF1).

In addition, 193 symptom-free controls were recruited between 1 November 2013 and 30 November 2014 from the general population in Leiden, The Netherlands, using advertisements in local newspapers and on websites. Inclusion criteria were: age ≥18 years, no history of inflammatory rheumatic disease and no joint symptoms during the last 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 this cohort and the occurrence of synovitis, tenosynovitis and osteitis was described previously.[18] For the current study, their MRIs were specifically evaluated to determine the occurrence of ITI.

All patients and symptom-free controls provided written informed consent.

Microscopy and immunohistochemistry

Three embalmed human hands obtained from bodies donated for research were dissected. The studied materials belonged to persons (two 63 year old males and a 76 year old female) without morphological signs or known history of RA. 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 2nd MCP joint. This MCP joint was chosen since it is among the most common locations for ITI in CSA (as shown in the results section) and is relatively accessible for dissection. Routine Hematoxylin-Eosin and Sirius Red staining for collagen were performed to visualize the tendons and surrounding tissues. Immunohistochemical stainings were performed using anti-CD55 (PA5-78,991, ThermoFisher, USA, 0.5 μg/ml) for detection of fibrobrast-like synoviocytes and anti-CD68 (14-0688-82, ThermoFisher, USA, 0.5 μg/ml) for detection of macrophages. Histological methods are presented in more detail in online Supplementary Methods SM1.

MRI scanning and scoring

MRI protocol

Contrast-enhanced unilateral 1.5T MRI (ONI, GE, Wisconsin, USA) was made of the MCP (2–5) 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 more detail in online Supplementary Methods SM1.

ITI scoring

MRIs were evaluated for ITI in line with the approach described by Mankia et al.[10] Firstly, each individual tendon was localized by looking for oblong structures with low signal intensity arising from the intrinsic hand muscles and running radially or ulnarly from their corresponding MCP joint, corresponding to the trajectory of the interosseous tendons. Secondly, it was determined whether contrast-enhancement was present around the tendon. ITI was defined as contrast-enhancement around the full circumference of the interosseous tendon at the level of the MCP joint, present in both the axial and coronal plane and ≥2 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, as illustrated in 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 from their corresponding MCP joint, respectively.

A dichotomous score (negative/positive) was assigned per tendon by a single reader (BTvD, medical doctor trained in reading extremity MRIs). In case of doubt, the definitive score

was determined by a second reader (MR, musculoskeletal radiologist with >20 years of experience). To ascertain reliability of ITI scoring, MRIs of 20 CSA patients and 10 symptom-free controls were mixed, stripped from metadata and rescored by the first reader (BTvD), which resulted in an intra-reader intraclass correlation coefficient (ICC) of 0.98.

Synovitis, tenosynovitis and osteitis scoring

MRIs were also evaluated for synovitis, tenosynovitis and osteitis in line with the RA MRI scoring system (RAMRIS) by two independent trained readers, as reported previously.[4,20,21] Inter- and intra-reader ICCs were published previously and were ≥0.90.[4,18] More details on RAMRIS scoring are described in online Supplementary Methods SM1.

Synovitis, tenosynovitis and osteitis may be seen on MRI to some extent in the general population, especially at older age and at certain locations as reported previously in the same 193 symptom-free controls presented in the current study.[18] Positivity for these features was therefore determined with measurements from the general population as a reference (also described previously).[22] In short, synovitis, tenosynovitis or osteitis was considered present if it was scored by both readers at the same location and present in <5% of age-matched symptom-free controls.

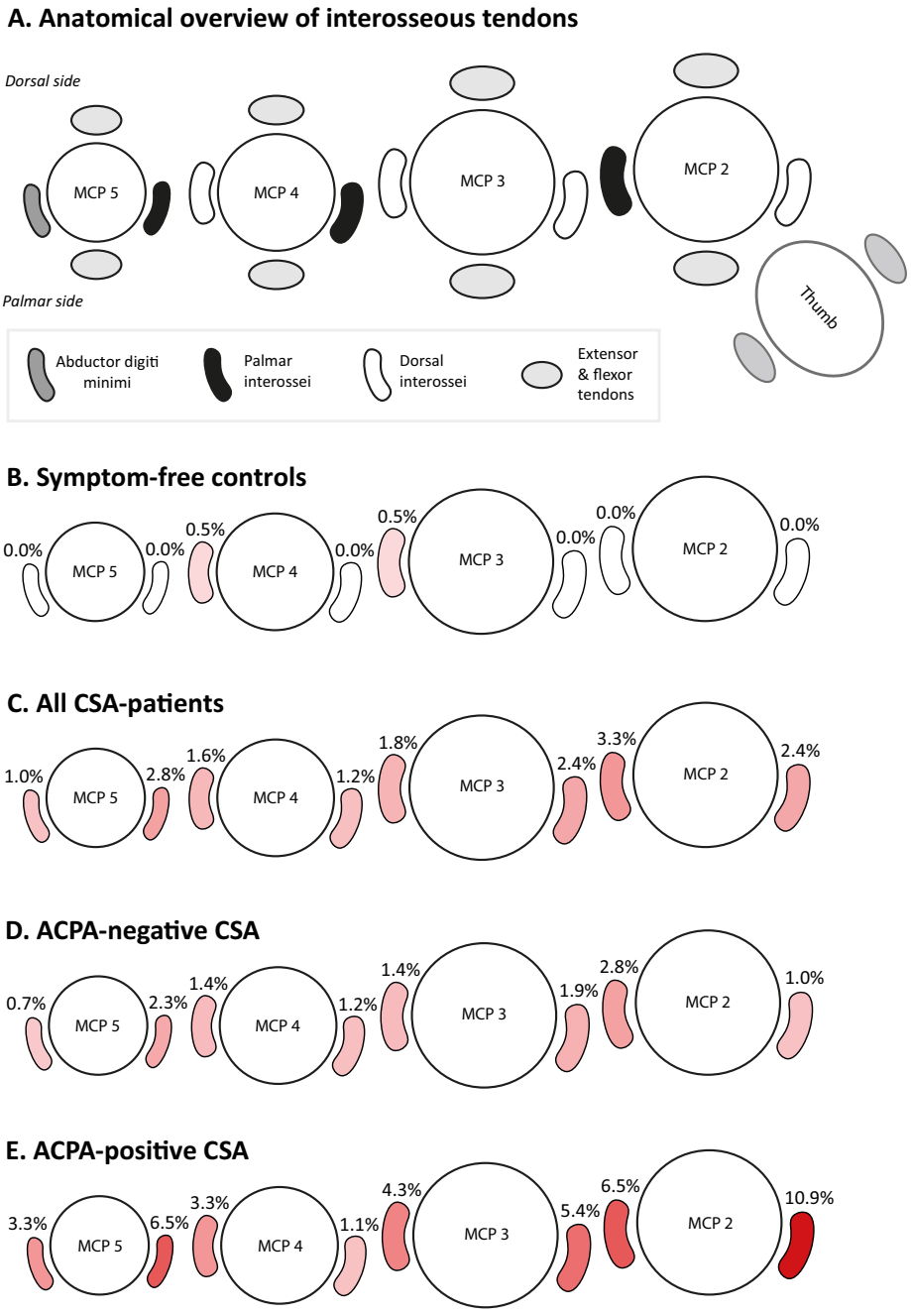
All MRIs were scored blinded for clinical data. ITI and the RAMRIS features (synovitis, tenosynovitis and osteitis) were scored at different occasions and by different readers. Assigned RAMRIS scores were unavailable during ITI scoring and vice versa.

Clinical features in CSA

At inclusion, tenderness of MCP 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, please see a previous description.[23] Hand functioning was evaluated using three domains of the Health Assessment Questionnaire Disability Index (HAQ) specifically related to manual daily living activities: 'dressing/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 functioning was calculated as the average of the maximum scores in each domain and ranged 0–3.[26]

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

Figure 1. Schematic overview of the eight interosseous tendons (A) and heatmaps of the frequency of ITI at each tendon as observed in symptom-free controls (B), all CSA patients (C) and separately in ACPA-negative and ACPA-positive CSA patients (D&E)



< (**A**) Schematic representation in axial view of the anatomy at the level of the MCP 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 3rd digit has two dorsal but no palmar interosseous tendons.[29]

(**B–E**) The percentages depict the proportion of CSA patients in whom inflammation around the tendon was present on MRI. Individual patients may have ITI at more than one location. The percentage of ITI presence in each group was calculated by dividing the number of patients with ITI at ≥1 tendon by the total number of patients in that group:

(B) Symptom-free controls: 2 / 193 = 1%

(C) All CSA patients: 67 / 667 = 10%

(D) ACPA-negative CSA patients: 42 / 575 = 7%

(E) ACPA-positive CSA patients: 25 / 92 = 27%

Abbreviations: ITI = interosseous tendon inflammation; CSA = clinically suspect arthralgia; MR(I) = magnetic resonance (imaging); MCP = metacarpophalangeal

Follow-up in CSA

CSA patients were followed on clinical arthritis development, defined as joint swelling palpable at physical joint examination (SJC-66). 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 23 April 2021 (whichever came first). Patients and clinicians had no access to MR images and scores.

Treatment with disease-modifying antirheumatic drugs (DMARDs, including systemic and intra-articular corticosteroids) was not allowed during follow-up. However, between 1 April 2015 and 31 August, newly presenting CSA patients could participate in a randomised placebo-controlled trial (RCT) assessing the efficacy of methotrexate in preventing clinical arthritis development when they had subclinical joint inflammation.[27,28] CSA patients who participated in this RCT were excluded from analyses on clinical arthritis development (online Supplementary Figure SF1), ensuring that patients included in analyses of the current study were not exposed to methotrexate, as described previously.[4,7] Within CSA patients eligible for participation in the RCT based on presence of MRI-detected subclinical inflammation, there were no clinically relevant differences in baseline characteristics between patients who were and were not included (online Supplementary Table ST1).

3D MRI reconstruction

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

Outcomes

The following outcomes were studied cross-sectionally in relation to ITI presence at inclusion into the CSA cohort: the prevalence of other MRI-detected local inflammation at the MCP joints (synovitis, tenosynovitis and/or osteitis), MCP tenderness, presence of difficulties making a fist and the hand functioning score measured by the HAQ. The primary outcome for the longitudinal part of the study was development of clinical arthritis. RA development defined as clinical diagnosis plus fulfillment of the 2010 or 1987 RA criteria or DMARD initiation was the secondary outcome. Classification criteria for RA 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 CSA cohort employing very 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 CSA cohort and detection of clinical arthritis at physical examination by the rheumatologist.

Statistical analyses

Logistic regression was used to study associations of ITI presence with other subclinical inflammation features at MCP joints. Synovitis, tenosynovitis and osteitis presence at ≥1 MCP joint were independent variables, while ITI presence was the dependent variable.

Associations between ITI and other subclinical inflammation was also studied at joint level. For this, generalized estimating equations (GEEs) were used wherein each patient contributed 4 MCP joints. Synovitis, tenosynovitis and osteitis presence at the MCP joint were the independent variables, while ITI presence was the dependent variable. ITI was considered present at MCP joint level if at least one of the two interosseous tendons belonging to that MCP joint had surrounding inflammation on MRI.

Next, the relation of ITI (independent variable) with symptoms was assessed. The following outcomes (dependent variables) were studied, each with the appropriate regression technique: tenderness at the same MCP joint (using GEEs), difficulties

making a fist (logistic regression) and the hand functioning score measured by the HAQ (linear regression).

Kaplan Meier curves and Cox regression assessed whether ITI presence (independent variable) predisposes for clinical arthritis development (dependent variable). This analysis was repeated with stratification for ACPA status, with an interaction term of ITI presence and ACPA status, and using RA development as outcome.

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

IBM SPSS (v25) was used. Two-sided P-values <0.05 were considered statistically significant.

RESULTS

On average, symptom-free controls were aged 50 years (SD 16). 70% (136/193) were female (Table 1, also available online as Supplementary Table ST2). ITI was present on MRI in only 1% (2/193; Figure 1B shows which tendons were affected).

No tenosynovial sheath around the interosseous tendon was observed in the transverse sections from any of the specimens. Immunohistochemical staining was performed to further characterize the peritendinous connective tissue. Results of one of the specimens are reported in Figure 2; a second example is presented in online Supplementary Figure SF2. Whilst some CD-55 positive cells were detected inside the tendon, no lining of cells positive for CD55 (fibroblast-like synoviocytes) and CD68 (macrophages) was observed surrounding the interosseous tendon in any of the specimens. This suggests that, in the normal anatomical situation, tenosynovium surrounding the interosseous tendons is absent.

Baseline characteristics of CSA patients are presented in Table 1 (also available online as Supplementary Table ST2). Their mean age was 44 years (SD 13), 76% were female (504/667) and 14% (92/667) were ACPA-positive. Median symptom duration was 19 weeks (IQR 9–43) and median tender joint count (TJC-68) was 5 (IQR 2–10). At inclusion, 10% (67/667) of CSA patients had ITI ($p<0.0001$ compared to symptom-free controls). The frequency of ITI at each tendon is presented in Figure 1C. The palmar interosseous tendon next to MCP-2 was most frequently inflamed. The average number of interosseous tendons affected among patients with ITI was 1.7 (max. 8).

Frequencies of ITI are presented separately for female and male CSA patients in online Supplementary Figure SF3.

Since ACPA-positive and ACPA-negative RA are considered different disease-subsets based on differences in pathophysiology and outcomes,[30,31] prevalences per tendon were plotted for ACPA-positive and ACPA-negative CSA patients separately (Figure 1D&E). ACPA-positive CSA patients more often had ITI than ACPA-negative CSA patients (27% (25/92) vs. 7% (42/575), p<0.0001).

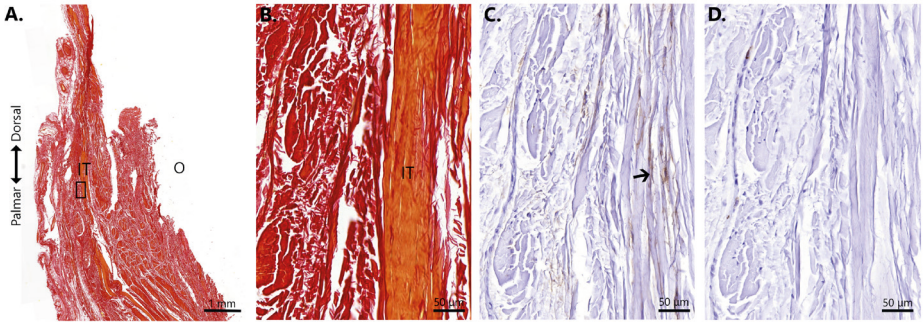
Table 1. Baseline characteristics of CSA patients (all and according to presence of ITI) and symptom-free controls that were studied

	CSA patients			Symptom-free controls
	All N = 667	No ITI N = 600	ITI N = 67	All N = 193
Age, mean ± SD	44 ± 13	43 ± 13	52 ± 13	50 ± 16
Female sex, n (%)	504 (76)	460 (77)	44 (66)	136 (70)
Male sex, n (%)	163 (24)	140 (23)	23 (34)	57 (30)
Self-reported Caucasian race/ethnicity	474 (93)	424 (93)	50 (94)	–
Symptom duration in weeks, median (IQR)	19 (9–43)	19 (9–44)	17 (9–28)	–
TJC-68, median (IQR)	5 (2–10)	5 (2–10)	4 (2–7)	–
ACPA-positive, n (%)	92 (14)	67 (11)	25 (37)	–
RF-positive, n (%)	132 (20)	101 (17)	31 (46)	–
Increased CRP (≥5.0 mg/L), n (%)	152 (23)	122 (21)	30 (45)	–
Average number of locations with ITI (range 0–8)	0.17	–	1.66	0.01

Numbers of CSA patients (percentage of total) with missing data, per variable:
Age 0 (0%); sex 0 (0%); race/ethnicity 158 (24%); symptom duration 38 (6%); TJC-68 8 (1%); ACPA-status 0 (0%); RF-status 1 (0%); CRP 32 (5%); locations with ITI 0 (0%).
Numbers of CSA patients *with no ITI* (percentage of total) with missing data, per variable:
Age 0 (0%); sex 0 (0%); race/ethnicity 144 (24%); symptom duration 35 (6%); TJC-68 8 (1%); ACPA-status 0 (0%); RF-status 1 (0%); CRP 31 (5%); locations with ITI 0 (0%).
Numbers of CSA patients *with ITI* (percentage of total) with missing data, per variable:
Age 0 (0%); sex 0 (0%); race/ethnicity 14 (21%); symptom duration 3 (5%); TJC-68 0 (0%); ACPA-status 0 (0%); RF-status 0 (0%); CRP 1 (1%); locations with ITI 0 (0%).
For symptom-free controls there was no missing data.

Abbreviations: CSA = clinically suspect arthralgia; ITI = interosseous tendon inflammation; SD = standard deviation; IQR = interquartile range; TJC = tender joint count; ACPA = anti-citrullinated protein antibodies; RF = rheumatoid factor; CRP = C-reactive protein

Figure 2. Immunohistochemical evaluation of transverse sections near MCP2 through the interosseous tendon suggesting absence of tenosynovial tissue surrounding this tendon

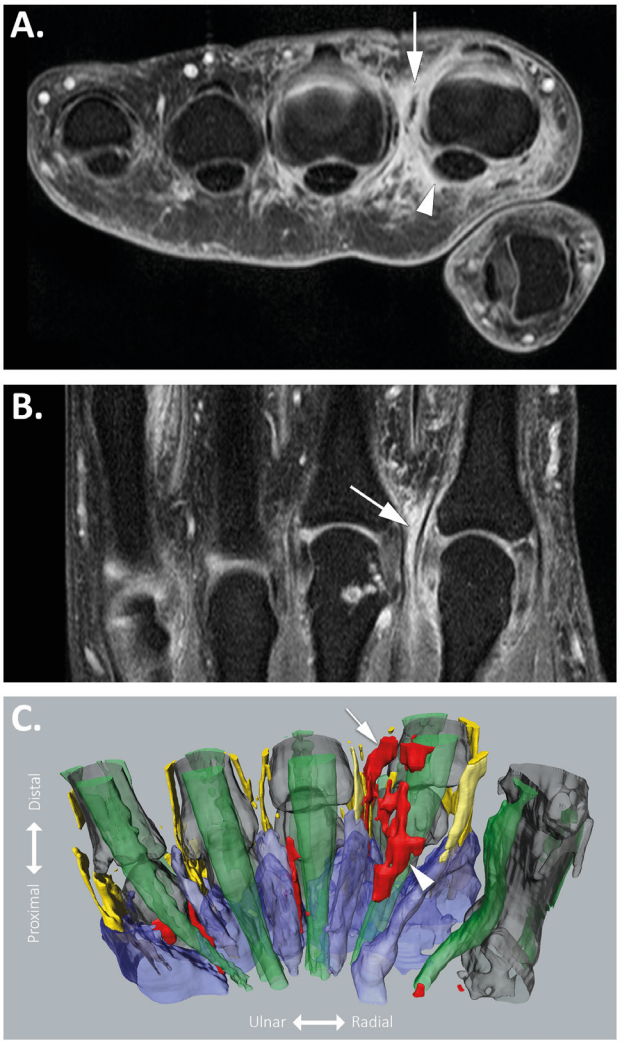


A. Sirius Red-stained transverse section of the tissue on the radial side of the 2nd MCP-joint. IT = interosseous tendon; O = location of ossa digitorum of the distal phalanx (removed from tissue block).
B. Magnification of the area marked by the rectangle in A. Red on a yellow/orange background indicates collagen fibers and is consistent with tendinous tissue. IT = interosseous tendon.
C. Adjacent transverse section with immunohistochemical staining for CD55; the brown precipitate indicates positive fibroblasts scattered throughout the tendinous tissue (arrow), but not organized as a lining around the tendon.
D. Adjacent transverse section with immunohistochemical staining for CD68. Almost no macrophages were detected within or in the surrounding of the tendon.

As part of elucidating the role of ITI in RA development, we assessed the relation of ITI with known local inflamed tissues (synovitis, tenosynovitis and osteitis). CSA patients with ITI were more likely to also have other subclinical inflammation at MCP joints (Table 2A). Of these 67 CSA patients with ITI, 48 (72%) had other subclinical inflammation at MCPs: 25 (37%) had synovitis; 5 (7%) tenosynovitis; 18 (27%) both synovitis and tenosynovitis, while 19 (28%) did not have any MRI-detected synovitis and/or tenosynovitis at their MCP joints. Multivariable analyses adjusted for this co-occurrence showed that tenosynovitis (OR 9.7 (95%CI 5.5–17.0)) and also synovitis (2.2 (1.2–4.2)) were independently associated with ITI. Also analyses at individual MCP joint level (Table 2B) showed that tenosynovitis and synovitis were independently associated with ITI, in contrast to osteitis.

Example MR images of ITI are presented in Figure 3A&B; local tenosynovitis was present in addition to ITI. To illustrate the relation of ITI with nearby tissues, 3D MRI reconstruction was performed (online Supplementary Video and Figure 3C). This suggested that inflammation around the interosseous tendons (ITI; arrow) and around MCP flexor tendons (tenosynovitis; arrowhead) was confluent.

Figure 3. Example of MRI-detected ITI co-occurring with flexor tenosynovitis at the second MCP 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 2nd MCP joint

(**A, B & C**) Arrows: Contrast enhancement around the interosseous tendon on the ulnar side of the 2nd MCP joint, consistent with ITI

Arrowheads: Contrast enhancement around the flexor tendon of the 2nd MCP joint, consistent with tenosynovitis

(**C**) Red: Contrast-enhancement around interosseous and flexor tendons, consistent with inflammation, which appeared to be continuous between the two areas

Yellow: Interosseous tendons

Grey: Metacarpal bones and phalanges

Green: Flexor/extensor tendons of the fingers

Blue: Interosseous and lumbrical muscles

Table 2. Associations of ITI presence with presence of other subclinical inflammation features at MCP joints on patient level and joint level

		No ITI n (%)	ITI n (%)	Univariable OR (95%CI)	Multivariable# OR (95%CI)
A. Patient level					
Synovitis	–	532 (92)	44 (8)	**4.1 (2.3–7.2)**	**2.2 (1.2–4.2)**
	+	68 (75)	23 (25)		
Tenosynovitis	–	519 (96)	24 (4)	**11.5 (6.6–19.9)**	**9.7 (5.5–17.0)**
	+	81 (65)	43 (35)		
Osteitis	–	562 (91)	58 (9)	**2.3 (1.1–5.0)**	1.6 (0.6–3.8)
	+	38 (81)	9 (19)		
Any RA MRI inflammation¥	–	446 (96)	18 (4)	**7.9 (4.5–13.9)**	–
	+	154 (76)	49 (24)		
B. Joint level					
Synovitis	–	2494 (97)	69 (3)	**9.8 (5.9–16.1)**	**6.8 (3.8–12.2)**
	+	81 (77)	24 (23)		
Tenosynovitis	–	2419 (98)	56 (2)	**6.5 (3.5–12.1)**	**5.2 (2.7–10.1)**
	+	156 (81)	37 (19)		
Osteitis	–	2529 (97)	88 (3)	2.5 (0.9–7.1)	1.7 (0.5–5.0)
	+	46 (90)	5 (10)		
Any RA MRI inflammation¥	–	2318 (98)	45 (2)	**7.1 (4.2–12.0)**	–
	+	257 (84)	48 (16)		

All 667 patients were included in the analyses.

ORs depict the relative increase in odds of ITI presence when the other MRI inflammation feature of the leftmost column (synovitis, tenosynovitis or osteitis) is present, compared to the situation when the other feature is not present (reference category). For example, the first OR of 4.1 means that the odds of ITI presence is increased 4.1 times in patients with synovitis at any MCP joint, compared to patients without MRI-detected synovitis at the MCP joints. These ORs were calculated by logistic regression in patient level analyses and GEE in joint level analyses.

A. Patient level: associations between ITI presence (dependent variable) and presence of other subclinical inflammation (independent variables) at any scanned MCP joint. Goodness-of-fit of the multivariable logistic regression model: Nagelkerke $R^2 = 0.252$

B. Joint level: associations between ITI presence (dependent variable) and presence of other subclinical inflammation (independent variable) at the same MCP-joint.

Multivariable model: with synovitis, tenosynovitis and osteitis presence as separate independent variables.

¥ Synovitis, tenosynovitis and/or osteitis

Abbreviations: ITI = interosseous tendon inflammation; MCP = metacarpophalangeal; OR = odds ratio; CI = confidence interval; + = feature present; – = feature not present; RAMRIS = rheumatoid arthritis magnetic resonance imaging scoring system

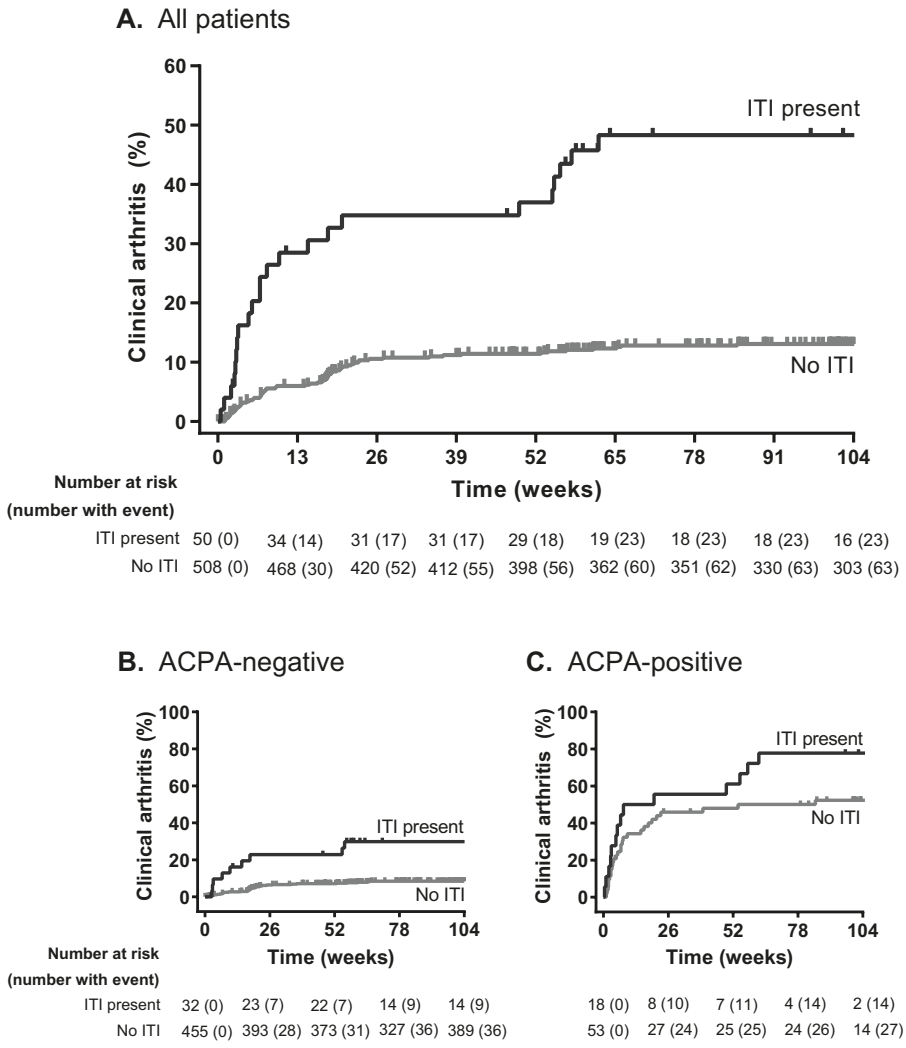
Synovitis and tenosynovitis at small joints are known to contribute to typical symptoms of CSA and early RA.[6] Analogous to this, it was explored whether ITI contributes to joint tenderness and reduced hand functioning (online Supplementary Table ST3). MCP joints with adjacent ITI were more likely to be tender on physical examination (OR 1.6 (1.03–2.4). Multivariable analysis showed that ITI was not independently associated with local MCP joint tenderness (OR 1.3 (0.8–2.1)), in contrast to tenosynovitis (OR 2.0 (1.4–2.9)). CSA patients with ITI more often had difficulties making a fist, but ITI was not independently associated (OR 1.2 (0.7–2.1)), in contrast to tenosynovitis (OR 1.6 (1.1–2.4)). Similarly, hand functioning measured by the HAQ was on average 0.20 points worse in patients with ITI (β 0.20 (0.05–0.36)), but in multivariable analyses ITI did not remain independently associated. Thus, these clinical features in CSA are primarily associated with other locally inflamed tissues rather than with ITI.

Next, we questioned whether ITI in CSA precedes and predicts clinical arthritis development. During follow-up (median 25.3 months (95%CI 25.1–25.5), 91/558 CSA patients (16.3%) developed clinical arthritis. CSA patients who had ITI at inclusion developed clinical arthritis more often than those without ITI (hazard ratio (HR) 4.5 (2.8–7.2); Figure 4A). Presence of ITI in both ACPA-negative and ACPA-positive CSA patients conferred increased risk for RA, but this risk was numerically more pronounced for ACPA-negative than ACPA-positive patients (HR 3.9 (1.9–7.9) and 1.8 (0.9–3.4) respectively; Figure 4B&C). The model with an interaction term between ITI presence and ACPA status confirmed that the association between ITI presence and clinical arthritis development was smaller in ACPA-positive CSA patients, but not statistically significantly so ($HR_{interaction}$ 0.50 (0.19–1.32), p=0.16; online Supplementary Table ST4). Development of clinical arthritis is presented separately for female and male CSA patients in online Supplementary Figure SF4.

Also in a multivariable analysis with adjustment for concomitant synovitis, tenosynovitis and osteitis, ITI presence remained independently associated with clinical arthritis development (1.7 (1.02–2.8)).

Results for ITI were similar when RA development was the outcome instead of inflammatory clinical arthritis (online Supplementary Figure SF5).

Figure 4. Kaplan Meier curves of progression to clinical arthritis according to presence of ITI at inclusion, for all CSA patients (A) and separately for ACPA-negative (B) and ACPA-positive (C) patients



HR (95%CI): A. 4.5 (2.8–7.2); B. 3.9 (1.9–7.9); C. 1.8 (0.9–3.4)

Mean time to clinical arthritis development, weeks (95%CI):
A. ITI present: 77 (61–93); no ITI: 115 (112–119)
B. ITI present: 97 (79–115); no ITI: 121 (118–123)
C. ITI present: 43 (21–65); no ITI: 70 (53–86)

Presented HRs are from Cox regression analyses. Numbers of analysed patients were:
A. 558
B. 487
C. 71

Abbreviations: ITI = interosseous tendon inflammation; ACPA = anti-citrullinated protein antibody; HR = hazard ratio; CI = confidence interval

DISCUSSION

Complementing the traditional view on RA as a disease of the intra-articular synovium, two forms of juxta-articular synovial inflammation were recently identified with imaging studies in early RA and preceding RA: tenosynovitis and intermetatarsal bursitis (IMB).[1,2] This study adds that also ITI occurs in the CSA-phase, preceding the development of clinical arthritis. This identifies ITI as another juxta-articular site of local inflammation that manifests already before RA develops, in both ACPA-positive and ACPA-negative disease.

The prevalence of ITI observed in ACPA-positive CSA (27% (25/92)) was in line with the first description in ACPA-positive at-risk individuals (19% (18/93)).[10] The current study provided additional knowledge by demonstrating that ITI is almost absent in the general population, that ITI often occurs together with tenosynovitis and synovitis, and that presence of ITI in CSA associates with future development of RA. Our study was also the first to demonstrate presence of ITI in ACPA-negative CSA patients. The frequency of ITI in ACPA-negative CSA patients was lower than in ACPA-positive patients, possibly related to the intrinsically lower incidence of RA development. However, if present in ACPA-negative CSA, ITI is a strong risk factor for developing RA. In fact, the strongest relation between ITI and RA development was in ACPA-negative CSA.

To explore the possible contribution of ITI to signs and physical impairments in CSA, we studied associations with local tenderness and hand functioning limitations. Although these clinical characteristics were more severe in CSA patients with ITI than in CSA patients without ITI, this was mostly explained by concomitantly present tenosynovitis or synovitis. Hypothetically, due to the relatively small volume of ITI compared to that of e.g. tenosynovitis which can extend a few centimeters along the tendon, ITI may contribute less to these clinical characteristics.

Our study was 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 the extensor tendon of the MCP joints where similar methodology was used and presence of tenosynovium was observed.[3,32] This may support the notion that ITI does not arise from tenosynovial cells. However, in the healthy situation any synovial tissue surrounding the ITI tendon will be thin and thereby intrinsically difficult to detect. It would be highly interesting to histologically examine the inflamed tissue surrounding the interosseous tendons in CSA or RA patients. However, such materials are enormously difficult, if not impossible, to obtain.

Since a previous study in non-inflamed joints using H&E staining also observed no tenosynovium,[10] we presume that tenosynovium is absent. Since ITI most commonly occurred together with tenosynovitis and synovitis, this could imply that ITI is secondary to inflammation in nearby synovial tissue. A 3D MRI-reconstruction indeed suggested that ITI was confluent with MCP 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 ITI results from expanding inflammation of nearby inflamed tissues is somewhat contradicted by the finding that ITI could occur without concomitant tenosynovitis or synovitis. Longitudinal imaging studies would be required to determine whether in these patients tenosynovitis or synovitis occur subsequently. Nonetheless, so far ITI 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 suggests that future tissue-level studies of RA pathogenesis should not be limited to the synovial joint or (teno)synovial tissue.

Our study was subject to some limitations. We were unable to study possible influences of mechanical factors (e.g. work or hobbies involving manual labor) as such detailed information was not available. Although mechanical stress has been suggested to potentially trigger RA development and associates with local inflammatory responses at tendons,[33] to the best of our knowledge the influence on the interosseous tendons specifically is unknown. On the other hand, the near-absence of ITI in the general population, also at higher ages, may suggest a limited influence of mechanical factors or ageing.

Secondly, in longitudinal analyses for clinical arthritis development some patients were not assessed due to participation in an RCT involving 50% chance of methotrexate (online Supplementary Figure SF1). This could reduce the observed effect-size since participation in the trial required a positive MRI, which is a risk factor for clinical arthritis development.[4] Indeed, an analysis including only patients included in the CSA cohort before and after the trial inclusion period (thereby excluding any influence of the RCT) showed a higher effect-size (HR 2.7 (1.3–5.6) versus 1.7 (1.02–2.8)).

Thirdly, 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 population studied could provide more evidence on the anatomic relation between inflamed tissues, this was beyond the scope of the current study.

Finally, for ITI there is no validated MRI scoring method available, which can be considered a limitation. To aid comparability, we scored ITI in line with the approach described by Mankia et al.[10] In addition, ITI was evaluated by a single reader in our study, although a musculoskeletal radiologist with >20 years of experience was involved in training this reader and in scoring in cases of doubt. Intra-reader reliability in our study was reassuring (ICC 0.98); inter-reader reliability remains to be assessed.

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

In conclusion, ITI is present in part of ACPA-positive as well as ACPA-negative CSA patients and precedes the development of ACPA-positive and ACPA-negative disease. Histological evaluations suggest that ITI does not arise from naturally present tenosynovial tissue. ITI may therefore be considered as the first evidence of primary non-synovial peritendinous tissue involvement. Because of its frequent occurrence with subclinical tenosynovitis and synovitis, ITI may reflect locally expanding subclinical joint inflammation in the pre-arthritis stage of the disease. This study enhances the understanding of the variety of locally inflamed tissues in the at-risk phase of RA and may fuel further studies to comprehend how these different inflamed tissues interact during the development of arthritis in RA.

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