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Radiology

Rheumatoid Arthritis and Tenosynovitis at the Metatarsophalangeal Joints: An Anatomic and MRI Study of the Forefoot Tendon Sheaths

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Conflicts of interest are listed at the end of this article.

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Background: Although tenosynovitis in the hands is associated with rheumatoid arthritis (RA), it is unknown whether tenosynovitis of the forefoot is associated with RA.

Purpose: To determine the anatomy of tendon sheaths of the forefoot and the relationship between MRI-detected tenosynovitis at metatarsophalangeal (MTP) joints and RA.

Materials and Methods: Fourteen forefeet of donated bodies were examined at flexor tendons and extensor tendons for the presence and course of tendon sheaths. In the prospective study between June 2013 and March 2016, newly presenting patients with RA, patients with other early arthritides, and healthy control participants all underwent MRI of unilateral MTP joints 1–5. MRI studies were scored by two independent readers for tenosynovitis, synovitis, and bone marrow edema. The association between the presence of these features and RA was examined by using logistic regression.

Results: Macroscopically, all extensor and flexor tendons crossing MTP joints demonstrated sheaths surrounding tendons. Microscopically, a synovial sheath was present. MRI evaluation was performed in 634 participants: 157 newly presenting patients with RA (109 women; mean age, 59 years ± 11 [standard deviation]), 284 patients with other early arthritides (158 women; mean age, 56 years ± 17), and 193 healthy control participants (136 women; mean age, 50 years ± 16). MRI-detected tenosynovitis was associated with RA, both when compared with patients with other arthritides (odds ratio [OR], 2.5; 95% confidence interval [CI]: 1.7, 3.9; $P < .001$) and healthy control participants (OR, 46; 95% CI: 14, 151; $P < .001$). The association was OR of 2.4 (95% CI: 1.5, 3.8; $P < .001$) for flexor tendons and OR of 3.1 (95% CI: 1.9, 5.2; $P < .001$) for extensor tendons. The sensitivity of tenosynovitis in RA was 65 of 157 (41%; 95% CI: 35%, 50%). The specificity for RA was 63 of 284 (78%; 95% CI: 72%, 82%) compared with other arthritides, and three of 193 (98%; 95% CI: 96%, 99%) compared with healthy control participants.

Conclusion: Tendons at metatarsophalangeal joints are surrounded by tenosynovium. MRI-detected tenosynovitis at metatarsophalangeal joints was specific for rheumatoid arthritis when compared with findings in patients with other arthritides and findings in healthy control participants.

Online supplemental material is available for this article.

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by inflammation of the synovial joints (1). MRI is recommended for the early detection of inflammation in RA because it is sensitive in measuring synovitis, bone marrow edema (BME), and tenosynovitis (2). Tenosynovitis is defined as inflammation of the synovial lining of the tendon sheaths. MRI studies have shown that tenosynovitis at the level of the metacarpophalangeal and wrist joints is an early phenomenon in patients at risk for RA that is predictive of development of RA (3–5) and, compared with patients with arthritis from other causes, is highly specific for RA (6). In addition, tenosynovitis is associated with functional impairment in daily life (7,8).

Tendon sheaths help prevent tendon injury and help with load bearing (9). Not all tendons possess a sheath; for example, at the metacarpophalangeal joints a sheath is present around the flexor tendons but is believed to be absent around the extensor tendons (6). Regarding the metatarsophalangeal (MTP) joints, there is no consensus in the anatomic literature regarding the presence or absence of a tendon sheath. On the extensor side of the MTP joints, some sources portray extensor tendons without sheaths (10–12) and other sources do not provide information about this region (13). Regarding the flexor side of the MTP joints, there is controversy between sources. In one example a fibrous and synovial sheath is portrayed around the distal flexor tendons (10), in another case it is described

Abbreviations

BME = bone marrow edema, CI = confidence interval, EAC = early arthritis cohort, MTP = metatarsophalangeal, OMERACT = Outcome Measures in Rheumatology Clinical Trials, OR = odds ratio, RA = rheumatoid arthritis, RAMRIS = Rheumatoid Arthritis MRI Score

Summary

Flexor and extensor tendons at metatarsophalangeal joints are surrounded by tenosynovium, and MRI-detected tenosynovitis of flexor and extensor tendons at metatarsophalangeal joints was specific for rheumatoid arthritis.

Key Results

- Tendons crossing metatarsophalangeal (MTP) joints had a synovial sheath (microscopically and macroscopically) at the flexor and extensor sides.
- At the MTP joints, MRI-detected tenosynovitis was associated with rheumatoid arthritis (RA) when compared with findings in both patients with other arthritides (odds ratio [OR], 2.5; $P <$ .001) and healthy control participants (OR, 46; $P <$ .001).
- MRI-detected tenosynovitis of the MTP joints was associated with RA for flexor tendons (OR, 2.4; $P <$ .001) and extensor tendons (OR, 3.1; $P <$ .001).
- The sensitivity of tenosynovitis of the MTP joints in RA was 41%, while specificity was 78% compared with other arthritides and 98% compared with findings in healthy control participants.

as solely fibrous (14), and other sources do not provide any information on this matter (11,12).

In addition to the lack of consistent information on the normal human anatomy, the prevalence of inflammation at the level of the tendons of the MTP joints and its association with RA are unknown. Reports from a few MRI studies have discussed the presence of tenosynovitis, but these studies were small (30 or fewer patients with RA), did not include information at the joint level, and/or did not compare findings in patients with RA with reference populations (15–18). The sensitivity and specificity of MRI-detected inflammation of the tendon sheath at the MTP level for RA thus remain unknown.

With this study we aimed to *(a)* elucidate the anatomic presence of a tendon sheath at the flexor and extensor sides of the MTP joints in an anatomic study to clarify whether contrast material enhancement around the tendons at the MTP level can be interpreted as tenosynovitis and *(b)* unravel whether MRI-detected tenosynovitis of the MTP joints is associated with RA, in a large cross-sectional MRI study comparing patients newly presenting with early RA with patients diagnosed with other arthritides and healthy control participants.

Materials and Methods

Anatomic Dissection

Macroscopy.—This section of the study was conducted with 11 formalin-phenol–embalmed and three fresh-frozen human feet at the Anatomy and Embryology laboratory of the Leiden University Medical Center in Leiden, the Netherlands. All specimens were obtained from bodies that had been donated according to the Dutch Burial and Cremation Act to the Department of Anatomy and Embryology at the Leiden University Medical Center for use in scientific research and medical education.

The cutis and subcutis at the flexor side of 11 embalmed feet (eight male donors, one female donor, two of unknown sex; age range, 70–95 years) and at the extensor side of three fresh-frozen feet (sex and age of donors unknown) were removed. Tissue surrounding the tendons of interests were injected with epoxy resin at the flexor side and with silicone rubber at the extensor side. Gentle massage was used to promote dissemination of the fluids. Photographs were taken of all specimens. For a more detailed description, see Appendix E1 (online).

Microscopy.—After dissection of the plantar cutis and subcutis of a noninjected foot, a block containing the flexor hallucis longus tendon and the surrounding connective tissue was removed 1–2 cm proximal to the MTP joint. In a separate noninjected foot, a block containing the extensor hallucis longus tendon and surrounding connective tissue was removed. Harvested tissues were embedded in paraffin. The paraffin blocks were transversely sliced in sections of 10 μm. The morphologic features of all tissues were examined after hematoxylin-eosin staining and evaluated by an anatomist (F.P.J., with 5 years of experience) and a pathologist (with 11 years of experience) blinded to clinical data.

Imaging Studies

Study participants.—In this prospective study, from June 2013 to March 2016, 447 consecutive patients newly presenting with clinically confirmed arthritis and symptom duration of less than 2 years who were naive to disease-modifying antirheumatic drugs were included in the Leiden Early Arthritic Clinic (early arthritis cohort [EAC]) (19). At baseline in this inception cohort, swollen joint counts were performed, serum samples were taken, and patients underwent MRI. MRI examinations of six patients were excluded because of inhomogeneous fat suppression. RA was defined as a clinical diagnosis plus fulfillment of the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria during the 1st year of follow-up (1).

Healthy control participants were recruited through advertisements in local newspapers and websites, as previously reported (20). These individuals had no history of inflammatory rheumatic disease, no joint symptoms during the previous month, and no arthritis at physical examination.

Studies using data from the EAC and from the healthy control participants have been reported in the past (20,21); however, MRI data regarding tenosynovitis at the MTP joints have thus far not been evaluated to our knowledge.

The early arthritis and the healthy control studies were both approved by the local medical ethics committee (approval numbers P10.108 and P11.210, respectively). Written informed consent was obtained from all participants.

MRI protocol.—Patients underwent unilateral MRI of MTP joints 1–5 of the more painful side, or the dominant side in the case of equally severe symptoms on both sides, 2 weeks or less

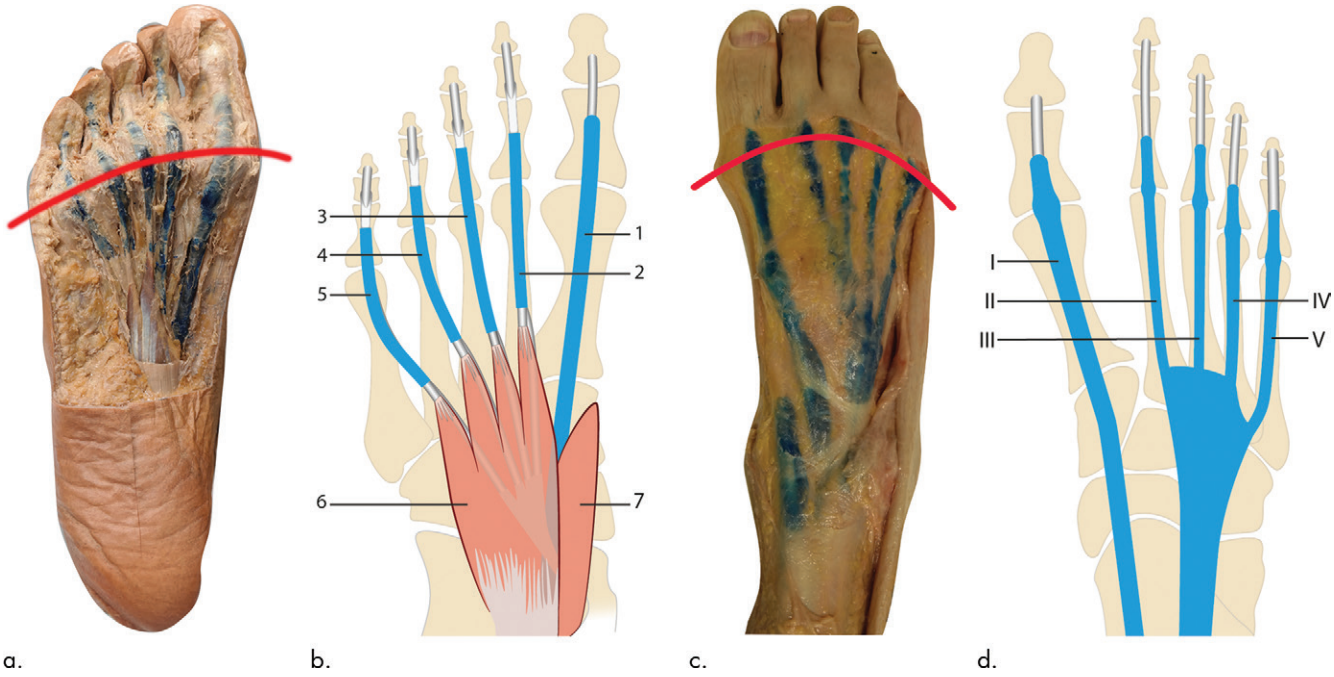

Figure 1: Macroscopic images and schematic drawings of tendon sheaths in forefeet. Red lines represent level of metatarsophalangeal (MTP) joints. Sheaths are in blue. **(a)** Plantar view of foot with resin in flexor tendon sheaths, extending proximally and distally from MTP joints. **(b)** Schematic plantar view shows tendon sheaths of musculus flexor hallucis longus tendon (FHL) (label 1) and common musculus flexor digitorum longus (FDL) and musculus flexor digitorum brevis (FDB) tendons (labels 2–5). Proximally, four tendons of FDL run deep of FDB muscle (label 6) and extend distally with common tendon sheath for FDL and FDB tendons. Tendons of FDB split to course in more dorsal position before inserting into middle phalanx; tendons of FDL continue in straight course and attach to base of distal phalanx. Tendon of FHL (label 1) proximally runs deep from musculus abductor hallucis (label 7) and FDB and inserts at base of distal phalanx. **(c)** Dorsal view of foot with silicone in extensor tendon sheaths, extending from anterior ankle to distal aspect of MTP joints. **(d)** Schematic dorsal view shows tendon sheaths of extensor hallucis longus (EHL) (I) and extensor digitorum longus (EDL) tendons (II–V), forming common sheath from proximal aspect of metatarsals to anterior ankle. EHL and EDL insert at dorsal aspect of distal phalanges. Extensor digitorum brevis tendons insert into EDL tendons II–IV at MTP joints and are not portrayed.

after the first presentation and before the initiation of disease-modifying antirheumatic drugs. In healthy control participants, imaging of the dominant side was performed. A musculoskeletal extremity 1.5-T MRI unit (Oni; GE Healthcare, Madison, Wis) was used with a 145-mm coil for the foot. After intravenous injection of gadolinium contrast agent, the following sequences were performed: T1-weighted fast spin-echo with fat suppression in the axial plane (repetition time msec/echo time msec, 700/9.5; acquisition matrix, 364 × 224; echo train length, 2) and T1-weighted fast spin-echo with fat suppression in the coronal plane (perpendicular to the axis of the MTP joints) (540/7.5; acquisition matrix, 320 × 192; echo train length, 2). Field of view was 140 mm. Coronal sequences had 20 slices with a slice thickness of 3 mm and a slice gap of 0.3 mm. Axial sequences had a slice thickness of 3 mm and a slice gap of 0.3 mm with 14 slices.

MRI evaluation.—Tenosynovitis of the MTP joints was scored according to the method of Haavardsholm et al (22). This method was developed and validated for scoring tenosynovitis in the wrist. BME and synovitis were scored according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis MRI Score (RAMRIS) system (23), with the exception that BME was assessed with a contrast-enhanced T1-weighted fat-suppressed sequence, which allows a shorter scan time and has a higher signal-to-noise ratio (24–26). The method of Haavardsholm and the OMERACT RAMRIS were designed for scoring inflammation in the hands and were found reliable when applied to the MTP joints (27,28). All tendons, joints, and bones were scored on a scale of 0–3. For tenosynovitis the score was based on the thickness of peritendinous effusion or synovial proliferation with enhancement (normal, <2 mm, 2–5 mm, >5 mm); for synovitis, on the presumed volume of enhancing tissue in the synovial compartment (none, mild, moderate, severe); and for BME, on the affected volume of the bone (no BME, <33%, 33%–66%, >66%). Tenosynovitis was scored at the flexor and extensor tendons at the MTP joints, and BME was scored at the proximal and distal part of the MTP joint. Proximal and distal BME scores were summed per joint.

Each MR image was scored independently by two trained readers who were blinded to clinical data. A total of six readers scored the images. Images from the first 215 EAC patients were scored by two readers, those from the remaining 226 EAC patients were scored by another two readers, and those from 193 healthy control participants were scored by another two readers. All six readers were physicians and doctoral candidates in the field of rheumatology and radiology with 1–2 years of experience with the scoring systems, who had scored more than 400 images from MRI by using the scoring systems during a training period of several months before evaluating the images that were part of this study. Intraclass correlation coefficients were calculated. The

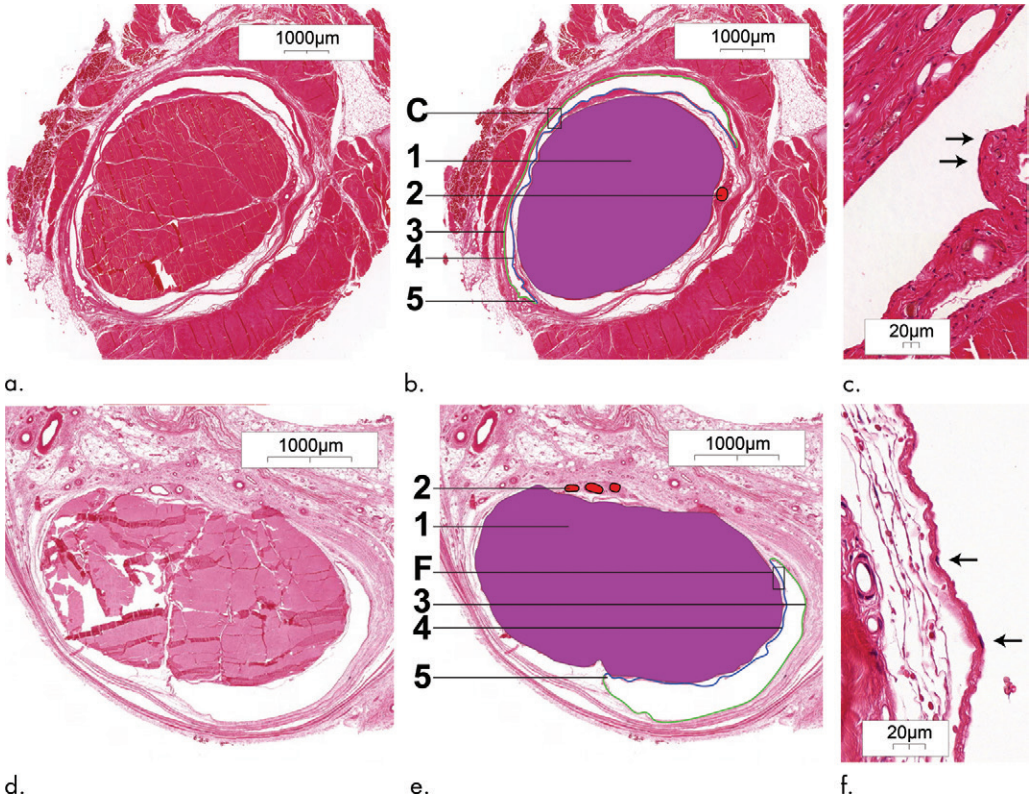

Figure 2: Histologic evaluation of hematoxylin-eosin–stained, transversely sectioned tendon sheath of **(a–c)** flexor hallucis longus (FHL) tendon and **(d–f)** extensor hallucis longus (EHL) tendon. **(a)** Overview of tendon sheath surrounding FHL tendon. **(b)** Overlay with *1*, tendon; *2*, artery in vinculum; *3*, parietal layer of tendon sheath; *4*, visceral layer of tendon sheath; *5*, cul-de-sac of tendon sheath. **(c)** Detail of **b** with visible synoviocytes (arrows). **(d)** Overview of tendon sheath surrounding EHL tendon. **(e)** Overlay with *1*, tendon; *2*, vessels in vinculum; *3*, parietal layer of tendon sheath; *4*, visceral layer of tendon sheath; *5*, cul-de-sac of tendon sheath. **(f)** Detail of **e** with visible synoviocytes (arrows).

interreader and intrareader intraclass correlation coefficients were 0.93 or greater and 0.88 or greater, respectively, in patients with arthritis (Table E1 [online]). The interreader and intrareader intraclass correlation coefficients of the two readers of images from the healthy control participants were 0.96 or greater (20).

Statistical Analysis

Nonnormally distributed MRI scores were analyzed by using the Kruskal-Wallis tests followed by a Bonferroni correction for all pairwise comparisons. Next, data of MRI scores were dichotomized per MTP joint; tenosynovitis, synovitis, and BME were considered present if a score of 1 or greater was assigned by both readers. Logistic regression analysis was used to compare MRI-detected tenosynovitis in patients with RA and in those with other arthritides and in healthy control participants. Multivariable logistic regression analyses comparing RA with other arthritides corrected for MRI-detected synovitis and BME in the same joint and subsequent analyses also were used to correct for age, swollen joint count, C-reactive protein, and anti–citrullinated peptide antibodies. Test characteristics were calculated for MRI-detected tenosynovitis.

Calculations were performed with software (SPSS Statistics, version 23.0; IBM, Armonk, NY). $P < .05$ was considered to indicate a statistically significant difference.

Results

Anatomic Studies

Macroscopy.—Hardened resin (flexor side) and silicone rubber (extensor side) were found to be confined to a sharply demarcated sheathlike structure surrounding the flexor and extensor tendons of all five digits in the foot, as is presented in Figure 1 (additional examples are presented in Fig E1 [online]). This resembled the expected image of tendon sheaths surrounding their tendons. On both the flexor and the extensor sides, the distal extensions of all tendon sheaths crossed the MTP joints. There was no exception to this pattern, but variation existed in the distal termination, which reached as far as the distal phalanx. For a more detailed description, see the supplemental material.

Microscopy.—Surrounding the flexor hallucis longus tendon, a completely delimited space was noticed (Fig 2a, 2b). Deep to the tendon, two cul-de-sacs connecting the parietal and visceral part of the sheath were visible and a vinculum between these cul-de-sacs was also visible, allowing vasculature to reach the tendon. With ×40 magnification, the delimiting cells were shown to be squamous epithelial cells representing synoviocytes (Fig 2c). At the extensor hallucis longus tendon, similar results were observed (Fig 2d–2f).

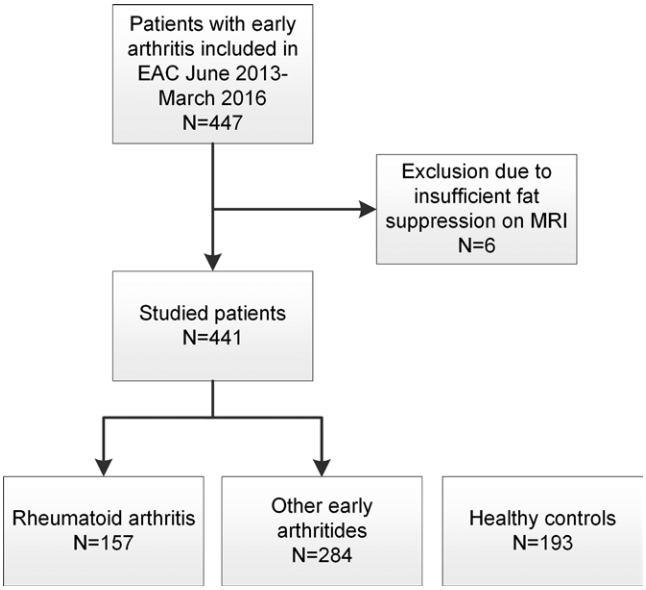

Figure 3: Flowchart shows participant selection. Rheumatoid arthritis was defined according to clinical diagnosis plus fulfillment of 2010 classification criteria. Category "other early arthritides" included diagnoses of unclassified arthritis (n = 148), psoriatic arthritis or spondyloarthritis (n = 45), inflammatory osteoarthritis (n = 23), reactive arthritis (n = 7), crystal arthropathy (n = 21), remitting seronegative symmetric synovitis with pitting edema (n = 12), and other diagnoses (n = 28). EAC = early arthritis cohort.

Because a tendon sheath was present at both the flexor and the extensor sides, we assumed that MRI-detected contrast enhancement around the tendons at both sides of the MTP joints represented tenosynovitis.

Imaging Studies

Patient characteristics.—Of the 441 included EAC patients, 157 were classified as having RA (109 women; mean age, 59 years ± 11 [standard deviation]). The remaining 284 received alternative diagnoses and were grouped together as having "other arthritides" (158 women; mean age, 56 years ± 17) (Fig 3). A total of 193 healthy control participants were recruited (136 women; mean age 50 years ± 16). The baseline characteristics are presented in Table 1. Patients with RA had a median symptom duration of 10 weeks (interquartile range: 5–28), and 59% were positive for anti–citrullinated peptide antibodies. The semiquantitative MRI tenosynovitis scores were higher in patients with RA than in patients with other arthritides (mean score of 1.9 and 0.7, respectively; $P < .001$ [Table 1]). Next, the presence of tenosynovitis was dichotomized as described in the Materials and Methods section.

Association of MTP tenosynovitis at patient level for patients with RA compared with other arthritides.—Tenosynovitis was present at one or more MTP locations in 65 of 157 (41%) patients with early RA and 63 of 284 (22%) patients with other early arthritides (odds ratio [OR], 2.54; 95% confidence interval [CI]: 1.65, 3.87); $P < .001$) (Table 2).

Tenosynovitis regularly co-occurred with synovitis and BME. Therefore a multivariable analysis including the three types of MRI-detected inflammation was performed and showed that tenosynovitis was independently associated with RA (OR, 2.25; 95% CI: 1.4, 3.5; $P < .001$) after controlling for the presence of synovitis (OR, 1.6; 95% CI: 1.0, 2.5; $P = .06$) and BME (OR, 0.9; 95% CI: 0.6, 1.5; $P = .68$) (Table 2 and Table E2 [online]). In a subsequent multivariable analysis that also adjusted for age, swollen joint count, C-reactive protein, and anti–citrullinated peptide antibodies, tenosynovitis remained associated with RA (OR, 1.68; 95% CI: 1.0, 2.9; $P = .048$) (Table 2).

Next, presence of any tenosynovitis at the flexor and at the extensor side were studied separately. When compared with other arthritides, both presence of tenosynovitis at the flexor and at the extensor side were associated with RA (OR, 2.4; 95% CI: 1.5, 3.8; $P < .001$; and OR, 3.1; 95% CI: 1.9, 5.2; $P < .001$, respectively). Tenosynovitis at flexor and extensor tendons remained statistically associated with RA after local synovitis and BME were controlled for and after additional correction for clinical characteristics (Table 2).

Association of MTP tenosynovitis at joint level with RA compared with other arthritides.—Tenosynovitis was then studied at the level of individual joints. Frequencies per joint are provided in Figure 4. In univariable analyses, the following features were associated with RA: flexor tenosynovitis at all MTP joints and extensor tenosynovitis at joints MTP-1 and MTP-5 (Table 2). After correction for BME and synovitis, flexor and extensor tenosynovitis at MTP-1 was associated with RA (OR, 2.2; 95% CI: 1.0, 4.9; $P = .049$; and OR, 3.9; 95% CI: 2.0, 7.5; $P < .001$, respectively) and flexor tenosynovitis at MTP-5 was associated with RA (OR, 5.3; 95% CI: 1.1, 26; $P = .04$). After correction for clinical characteristics, similar results were obtained (Table 2). Examples of MRI-detected tenosynovitis are presented in Figure 5.

Association of MTP tenosynovitis with RA compared with healthy control participants.—To further characterize MRI-detected tenosynovitis, the occurrence of tenosynovitis in patients with RA was compared with findings in healthy control participants. In the latter group tenosynovitis at the MTP joints was rare, occurring in only three of 193 persons (1.6%, compared with 42% of patients with RA). Consequently, a strong association with RA compared with healthy control participants was observed for the presence of any tenosynovitis at one or more locations (OR, 46; 95% CI: 14, 151; $P < .001$) (Table E3 [online]). Also, flexor tenosynovitis and extensor tenosynovitis were both separately highly associated with RA when compared with findings in healthy control participants (OR, 45; 95% CI: 11, 187; $P < .001$; and OR, 78; 95% CI: 11, 570; $P < .001$, respectively).

Test characteristics of MRI-detected tenosynovitis.—Finally, the test characteristics for the presence of tenosynovitis were determined. The sensitivity of MRI-detected tenosynovitis at any MTP joint was 41%. The specificity of tenosynovitis at the level of MTP joints in patients with RA was 78% compared with patients with other arthritides and 98% with healthy control participants as reference (Table E4 [online]). Analy-

Table 1: Baseline Characteristics of Patients with Rheumatoid Arthritis, Patients with Other Arthritides, and Healthy Control Participants

Parameter	Patients with Rheumatoid Arthritis (*n* = 157)	Patients with Other Arthritides (*n* = 284)*	*P* Value, Rheumatoid Arthritis vs other Arthritides	Healthy Control Participants (*n* = 193)	*P* Value, Rheumatoid Arthritis vs Healthy Control
Clinical parameters					
Age (y)†	59 ± 14	56 ± 17	.07	50 ± 16	<.001
No. of women	109 (69)	158 (56)	.005	136 (70)	.83
Body mass index (kg/m²)†	26 ± 5	27 ± 4	.52	25 ± 4	.003
Current smoker	31 (21)	44 (18)	.44	17 (9)	.001
Symptom duration (wk)‡	10 (5–28)	8 (4–26)	.13	NA	NA
Swollen joint count‡	7 (2–11)	2 (1–4)	<.001	NA	NA
C-reactive protein (mg/L)‡	9 (4–26)	6 (3–16)	<.001	NA	NA
Rheumatoid factor positive	106 (68)	51 (18)	<.001	NA	NA
Anti–citrullinated protein antibody positive	87 (59)	69 (25)	<.001	NA	NA
MRI features†					
Tenosynovitis	1.9 ± 2.5	0.7 ± 1.3	<.001	0.1 ± 0.3	<.001
Synovitis	1.9 ± 2.2	0.9 ± 1.2	<.001	0.2 ± 0.4	<.001
Bone marrow edema	1.9 ± 2.8	1.0 ± 1.9	<.001	0.3 ± 0.8	<.001

Note.—Except where indicated, data are numbers of patients, with percentages in parentheses. The 66 swollen joint count was assessed.

* This included the following diagnoses: unclassified arthritis (*n* = 148), psoriatic arthritis or spondyloarthritis (*n* = 45), inflammatory osteoarthritis (*n* = 23), reactive arthritis (*n* = 7), crystalarthropathy (*n* = 21), remitting seronegative symmetric synovitis with pitting edema (*n* = 12), and other diagnoses (*n* = 28). NA = not applicable.

† Data are means ± standard deviations.

‡ Data are medians, with interquartile ranges in parentheses.

ses for flexor and extensor tenosynovitis separately showed that tenosynovitis at the flexor side had a sensitivity of 32%, and a specificity of 84% for RA when compared with other arthritides, and 99% when compared with findings in healthy control participants. For tenosynovitis at the extensor side, these numbers were 29%, 89%, and 99%, respectively.

Discussion

The forefoot is a preferential location for inflammation in rheumatoid arthritis (RA) (29,30). Nonetheless, the feet are less often evaluated than the small joints of the hands. For instance, the 28-joint Disease Activity Score does not include the feet. Also, the majority of MRI studies performed previously did not include imaging of the feet (31). This prompted us to study tenosynovitis at the level of the forefeet in a large MRI study of patients with early arthritis. Moreover, because anatomic literature did not provide consistent information regarding the presence of a tendon sheath at the flexor and extensor sides of the metatarsophalangeal (MTP) joints, we also performed an anatomic study to determine if tenosynovial sheaths are indeed present at the MTP joints. The aim of this postmortem and MRI study was to increase the comprehension of the involvement of inflammation surrounding the tendons in RA. In all feet that were examined anatomically, we found a sheath to be present surrounding all extensor and flexor tendons at MTP joints. Histologic evaluation showed an image that was consistent with a synovial tendon sheath. Because of these anatomic findings, we assumed that MRI-detected contrast enhancement around the tendons at both sides represented tenosynovitis. This MRI-detected tenosynovitis was associated with RA ($P <$ .001) and had a high specificity for RA, when compared both with patients with other arthritides (78%) and with healthy control participants (98%). Together, these data showed that tenosynovitis at the MTP level is a characteristic of RA.

Our results are in line with those of previous studies of the hands that found MRI-detected tenosynovitis to be specific for RA (6). MRI-detected inflammation is increasingly used as an outcome measure in clinical trials in RA (2). Our data imply that tenosynovitis at the MTP level can be included in this outcome; this would require further validation according to the OMERACT Filter (31,32).

In our study, imaging was performed with MRI. US is an alternative imaging modality that is often used, and both methods are recommended in the clinical management of RA (2). Both modalities have advantages and disadvantages. Whereas US is easily available, it is operator dependent. MRI is more expensive but is generally considered to yield more reproducible results and also depicts BME that is not depicted with US. A recent study found US to be less sensitive than MRI in detecting tenosynovitis (33). This supports the choice to use MRI in our study.

The function of a tendon sheath is to provide a smooth gliding surface and thus prevent tendon injury (9). Although the presence of a tenosynovium at a high-friction location such as the MTP joints seems logical, it is surprising that the anatomic literature thus far had left undetermined whether tendons at these joints possess a synovial sheath, and some publications even portrayed this sheath to be absent. In the anatomic literature, no source studies were mentioned (10–14). For the dissection, we

Table 2: Results of Logistic Regression Analyses for Association of Metatarsophalangeal Joint Tenosynovitis with Early Rheumatoid Arthritis versus Other Early Arthritides

	Patients with MRI Features		Univariable Analyses		Multivariable Analyses Adjusted for Local Synovitis and Bone Marrow Edema		Multivariable Analyses: Adjusted for Local Synovitis and Bone Marrow Edema and Age, 66 Swollen Joint Count, C-Reactive Protein, and Anti–Citrullinated Peptide Antibodies	
Finding	Rheumatoid Arthritis	Other Arthritides	Odds Ratio*	*P* Value	Odds Ratio*	*P* Value	Odds Ratio*	*P* Value
Any tenosynovitis	65 (41)	63 (22)	2.5 (1.7, 3.9)	<.001	2.3 (1.4, 3.5)	<.001	1.7 (1.0, 2.9)	.048
Any flexor tenosynovitis†	49 (31)	46 (16)	2.4 (1.5, 3.8)	<.001	2.1 (1.3, 3.4)	.002	1.9 (1.0, 3.4)	.040
Any extensor tenosynovitis†	44 (28)	32 (11)	3.1 (1.9, 5.2)	<.001	2.7 (1.6, 4.6)	<.001	2.1 (1.1, 3.9)	.017
Flexor tenosynovitis								
MTP 1	18 (12)	13 (5)	2.7 (1.3, 5.7)	0.009	2.2 (1.0, 4.9)	.049	2.7 (1.0, 6.9)	.04
MTP 2	26 (17)	27 (10)	1.9 (1.1, 3.5)	0.03	1.3 (0.7, 2.6)	.41	1.4 (0.6, 3.3)	.44
MTP 3	27 (17)	20 (7)	2.8 (1.5, 5.2)	.001	1.9 (0.9, 3.8)	.81	1.8 (0.7, 4.3)	.22
MTP 4	26 (17)	19 (7)	2.8 (1.5, 5.3)	.001	1.8 (0.8, 3.7)	.14	1.6 (0.7, 3.8)	.31
MTP 5	14 (9)	2 (1)	14.0 (3.1, 62.5)	.001	5.3 (1.1, 25.7)	.04	9.3 (1.5, 57.0)	.015
Extensor tenosynovitis								
MTP 1	31 (20)	15 (5)	4.5 (2.3, 8.6)	<.001	3.9 (2.0, 7.5)	<.001	3.1 (1.4, 6.9)	.005
MTP 2	4 (3)	4 (1)	1.8 (0.5, 7.4)	.40	1.0 (0.2, 4.4)	.98	0.5 (0.1, 2.9)	.46
MTP 3	10 (6)	14 (5)	1.3 (0.6, 3.0)	.53	0.7 (0.3, 1.9)	.51	0.9 (0.3, 2.5)	.89
MTP 4	4 (3)	8 (3)	0.9 (0.3, 3.1)	.90	0.6 (0.2, 2.0)	.37	0.3 (0.1, 1.6)	.32
MTP 5	14 (9)	4 (1)	7.0 (2.3, 21.6)	.001	2.9 (0.8, 9.8)	.09	3.5 (0.9, 13.1)	.07

Note.—Except where indicated, data are numbers of patients, with percentages in parentheses. Tenosynovitis was considered present if both readers assigned a score of ≥ 1. Other arthritides included early arthritis with a diagnosis other than rheumatoid arthritis.

* Data in parentheses are 95% confidence intervals.

† In some patients, flexor tenosynovitis and extensor tenosynovitis occurred simultaneously; therefore the percentages of patients with any flexor tenosynovitis and any extensor tenosynovitis do not add up to the percentage of patients with any tenosynovitis.

started with embalmed bodies for the flexor side; when fresh-frozen bodies became available, they were used for the extensor side. The injection of tendon sheaths was performed in a similar fashion on both sides; therefore we believe that the different methods of preserving the bodies did not negatively affect our results.

Microscopy indicated an image that was typical for a tendon sheath, with a visceral synovial layer covering the tendon surface, a parietal synovium attached to the surrounding tissues, and a vinculum for the intrinsic blood supply of the tendon (9).

Our study had several limitations. Microscopically studying these lesions in patients with RA would yield the optimal proof that MRI-detected contrast enhancement around the tendons at the MTP level reflects tenosynovitis. This, however, was infeasible, as it would have required either biopsy specimens from tenosynovial sheaths at the MTPs from living patients with RA or the use of donated bodies of patients with RA who had had MRI-detected tenosynovitis at the end of life. In addition, the MRI scoring systems used are validated for the hand but not for the foot. However, our intrareader and interreader intraclass correlation coefficients were high, indicating a high reliability of scoring. The RAMRIS system was recently updated and now includes tenosynovitis (34). For tenosynovitis we used the method described by Haavardsholm et al (22), as the updated RAMRIS system had not yet been published at the start of our study. The included patients had an established diagnosis of RA. MRI studies in other early arthritis populations are relevant to validate the diagnostic value of tenosynovitis at the MTP joints. For the predictive value, we recently observed in a longitudinal study that MTP tenosynovitis in undifferentiated arthritis was associated with the development of RA (35), which underlines the possible diagnostic value of tenosynovitis at MTP joints. It is important to note that although tenosynovitis at the MTP joints is specific for RA, the sensitivity of 41% is low. On the other hand, RA is known to be a disease in which the hands and feet are involved, and a recent study revealed a sensitivity of 75% for tenosynovitis in the hands (6). Combining the findings in hands and feet would presumably yield a higher sensitivity for tenosynovitis in RA.

In conclusion, this anatomic and imaging study showed that tendons at the metatarsophalangeal joints possess a synovial sheath (both macroscopically and microscopically, at flexor and extensor sides) and that MRI-detected tenosynovitis at the metatarsophalangeal joints is associated with, and highly specific for, rheumatoid

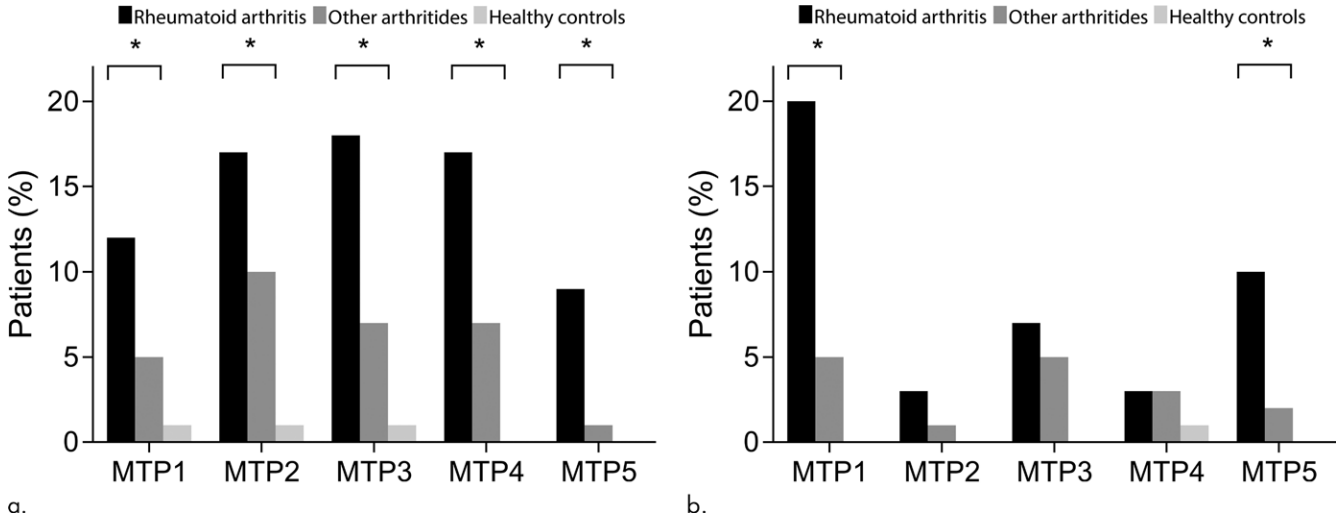

Figure 4: Frequencies of presence of **(a)** flexor and **(b)** extensor tenosynovitis per metatarsophalangeal (MTP) joint of patients with a new diagnosis of rheumatoid arthritis, patients with other early arthritides, and healthy control participants. * $P < .05$ in univariable logistic regression analyses when comparing patients with rheumatoid arthritis with other arthritides.

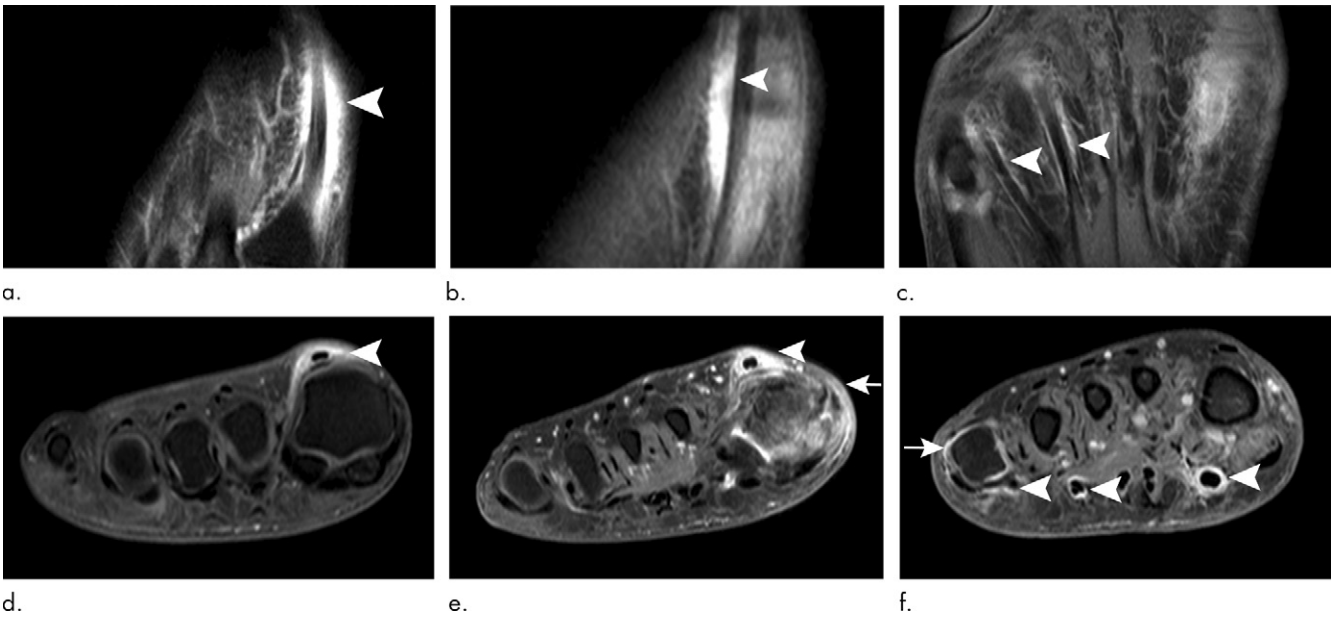

Figure 5: Images from contrast-enhanced 1.5-T MRI of forefoot in three different patients in corresponding **(a, b, c)** axial and **(d, e, f)** coronal planes. Axial sequences illustrate that tenosynovitis is sheathlike. **(a, b, e)** Images show extensor tenosynovitis at metatarsophalangeal (MTP) joint 1. **(a, d)** Circular enhancement of extensor hallucis longus (EHL) tendon is visible from level of MTP 1 to base of metatarsal 1, consistent with tenosynovitis (arrowhead). **(b, e)** Circular enhancement of the EHL tendon (arrowhead), coexisting synovitis of MTP 1 is depicted, with edema of skin and subcutis medially (arrow). **(c, f)** Circular enhancement is present at tendons of flexor hallucis and common flexor digitorum of MTP joints 1, 3, 4, and 5, consistent with flexor tenosynovitis (arrowheads). There is coexisting synovitis at MTP 5 (arrow).

arthritis. This study has increased our understanding regarding tissues that can be involved in the feet of patients with rheumatoid arthritis by showing that MRI-detected tenosynovitis at the metatarsophalangeal joints is a feature of rheumatoid arthritis.

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