Bilateral MR Imaging of the Hand and Wrist in Early and Very Early Inflammatory Arthritis: Tenosynovitis Is Associated with Progression to Rheumatoid Arthritis[1]

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Purpose: To identify bilateral hand and wrist findings of synovial inflammation associated with progression to rheumatoid arthritis (RA) in very-early–RA cohort (VERA) (duration, <3 months) and early-RA cohort (ERA) (duration, <12 but >3 months), to test tenosynovitis as a magnetic resonance (MR) imaging additional parameter for improving diagnostic accuracy of the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA classification criteria, and to evaluate the symmetry of joint and tendon involvement.

Materials and Methods: With institutional review board approval and informed consent, 32 women and three men (mean age, 45 years) with untreated recent-onset inflammatory arthritis participated in this prospective study and underwent MR imaging of both wrists and hands. After 12-month follow-up, 25 patients fulfilled the criteria for RA (10 VERA and 15 ERA patients). Ten patients did not fulfill the criteria for RA (non-RA [control] group). Possible associations between synovitis for each joint and tendon and RA diagnosis at 12 months were tested (univariate logistic regression analysis). Diagnostic performance of the ACR/EULAR RA classification criteria was evaluated (receiver operating characteristic curve analysis). Asymmetry prevalence (all joints and tendons in the analysis) was calculated.

Results: Tenosynovitis of the extensor carpi ulnaris (odds ratio, 3.21) and flexor tendons of the second finger (odds ratio, 14.61) in VERA group and synovitis of the radioulnar joint (odds ratio, 8.79) and tenosynovitis of flexor tendons of the second finger (odds ratio, 9.60) in ERA group were significantly associated with progression to RA ($P < .05$). Consideration of tenosynovitis improved areas under the receiver operating characteristic curve of ACR/EULAR criteria performance for the diagnosis of RA from 0.942 ($P < .0001$; sensitivity, 52%; specificity, 100%) to 0.972 ($P < .0001$; sensitivity, 76%; specificity, 100%), with cutoff score of 6 or greater. Asymmetry was found in 80.0% (62 of 77) (VERA patients) and 69.3% (106 of 153) (ERA patients) of joint or tendon pairs ($P < .05$).

Conclusion: Tenosynovitis is an imaging finding in early RA, and its inclusion as a scoring criterion might contribute for a better diagnostic performance of the 2010 ACR/EULAR classification; early RA is an asymmetric disease.

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There is growing consensus that optimal management of rheumatoid arthritis (RA) requires both early diagnosis and aggressive early treatment (1–3). However, therapeutic decisions are hindered by its nonspecific early clinical features (4–7); thus, the 1987 revised criteria for RA of the American College of Rheumatology (ACR), formerly the American Rheumatism Association (8), have limited value for early arthritis (9,10). The new 2010 RA classification criteria of the ACR/European League Against Rheumatism (EULAR) (11) described a new approach, emphasizing the identification of patients with relatively short duration of symptoms. However, the new criteria may still lead to substantial over- and underdiagnosis within the first 3 months after symptom onset (12). Therefore, the use of additional tests, namely more sensitive imaging techniques, would be helpful.

The synovium is targeted by the rheumatoid inflammatory process, and synovial inflammation and thickening are the histologic hallmarks and the earliest abnormalities to appear in RA (13). Magnetic resonance (MR) imaging is already known as the noninvasive imaging modality of choice for visualization of the inflamed synovium and is recognized as a useful tool for assessing established RA (14). However, the value of MR imaging in diagnosing early RA has been less studied (15–20). On the other hand, high-field-strength MR imaging at 3.0 T is known to provide precise and complete morphologic analysis of the hands and wrists (21), and the value of dynamic contrast material–enhanced 3.0-T MR imaging for quantification of disease activity in early RA patients has been previously shown (22). RA in the earlier stages is clinically characterized by a higher prevalence of asymmetry, with a tendency toward symmetry as the disease progresses (23–28). Despite this knowledge, researchers in previous MR imaging studies about early RA have focused on only the dominant, or else the clinically most affected, hand (13–20).

The tenosynovium produces proinflammatory cytokines and proteolytic enzymes in RA. Flexor tenosynovitis in the hands has already been identified as a frequent finding in early RA (29) as a risk factor for erosions (30,31) and as a potential marker of response to biologic treatment (32). Despite this fact, tenosynovitis of the wrists and hands has received far less attention in the literature than joint synovitis. In one report (33), flexor tenosynovitis diagnosed by using MR imaging of the hand was identified as a strong predictor of early RA. However, the study included patients with disease duration up to 24 months, largely exceeding the currently accepted definitions of early RA (disease duration up to 12 months) (34,35).

Therefore, we hypothesized that detection of tenosynovitis with bilateral high-field-strength MR imaging of the hands and wrists, combined with detection of joint synovitis, could have a discriminatory role in the identification of early-arthritis patients who have a high probability of developing RA.

Thus, our aim was to identify bilateral hand and wrist MR imaging findings of synovial inflammation in the tendons and joints that are associated with progression to RA in a very-early–RA cohort (VERA) (patients who presented within 3 months of arthritis onset) and

Advances in Knowledge

- Tenosynovitis is a major imaging finding in early rheumatoid arthritis (RA); tenosynovitis of the extensor carpi ulnaris (odds ratio, 3.21) and of the flexor tendons of the second finger (odds ratio, 14.61) in the very-early–RA cohort (VERA) and synovitis of the radioulnar joint (odds ratio, 8.79) and tenosynovitis of the flexor tendons of the second finger (odds ratio, 9.60) in the early-RA cohort (ERA) were the most significantly associated with progression to RA ($P < .05$).
- Inclusion of tenosynovitis as a scoring criterion might improve the diagnostic performance of the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) RA classification criteria; consideration of tenosynovitis improved areas under the receiver operating characteristic curve of the ACR/EULAR criteria performance for the diagnosis of RA from 0.942 ($P < .0001$; sensitivity, 52%; specificity, 100%) to 0.972 ($P < .0001$; sensitivity, 76%; specificity, 100%) for the cutoff score of 6 or greater.
- MR imaging intimates that RA may start asymmetrically; asymmetry was found in 80.0% (62 of 77) and 69.3% (106 of 153) of joint or tendon pairs in VERA and ERA patients, respectively ($P < .05$).

Implication for Patient Care

- MR imaging can contribute for a better identification of RA patients with short duration of symptoms, the phase in which treatment makes the greatest difference.

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Abbreviations:
ACR = American College of Rheumatology
AUC = area under the ROC curve
EULAR = European League Against Rheumatism
ERA = early-RA cohort
FOV = field of view
MCP = metacarpophalangeal
RA = rheumatoid arthritis
ROC = receiver operating characteristic
VERA = very-early–RA cohort

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Potential conflicts of interest are listed at the end of this article.

in an early-RA cohort (ERA) (patients who presented between 3 months and 1 year after arthritis onset) (36). In addition, we aimed to test our tenosynovitis MR imaging findings as a newer additional parameter for improving the accuracy of the 2010 ACR/EULAR RA classification criteria in early RA. It was also our purpose to evaluate symmetry of joint and tendon involvement. For the purposes of this article, hereafter *early RA* refers to RA in general, and *ERA* refers to one of the cohorts in our study, as defined.

Materials and Methods

Patients

From April 2009 until June 2011, 35 consecutive patients with untreated clinically apparent synovial swelling at four or more joints of a 68-joint count (37), including involvement of at least one joint of the wrists and hands (excluding the distal interphalangeal joints and the first carpometacarpal joint), and with a disease duration of less than 12 months were included in the study. The patients were recruited from the rheumatology outpatient clinics of Hospital da Luz (Lisbon, Portugal) and Hospital de Santa Maria (Lisbon, Portugal), and the cohort included 32 women (median age, 46.5 years; range, 18–67 years) and three men (median age, 27.7 years; range, 19–32 years) with a global median age of 45 years (range, 18–67 years).

After a follow-up of 12 months, 25 patients fulfilled the criteria for RA according to the 1987 ACR criteria (8). Of those, 10 patients had had a disease duration of less than 3 months at the time of MR imaging examination and were classified as having very-early RA (VERA), while 15 patients had had a disease duration of less than 12 months but more than 3 months and were classified as having early RA (ERA) (36). Ten patients with polyarthritis did not fulfill the criteria for RA, and they were classified as having non-RA and were considered the control group.

Exclusion criteria included pregnancy ($n = 0$) or breast-feeding ($n = 0$); inability to give informed consent ($n = 0$); current use of glucocorticoids ($n = 4$), methotrexate ($n = 2$), or other disease-modifying antirheumatic drugs ($n = 0$); active malignancy ($n = 1$); cellulitis ($n = 0$); osteomyelitis ($n = 0$); occupation or sports-related overuse ($n = 1$); trauma ($n = 0$); and contraindications to undergoing MR imaging ($n = 2$). All patients provided informed consent, and the study conformed to the ethical principles for medical research involving human subjects, according to the Declaration of Helsinki of the World Medical Association. The study was approved by the local ethics committee.

Clinical Data

Demographic information, including age and sex, was collected. The type and distribution of initial joint symptoms, disease duration prior to presentation, number of tender and swollen joints of a 28-joint count (35), and patient's overall disease activity on a visual analog scale (range, 0–100 mm) were assessed (C.R., with 8 years of experience as a board-certified rheumatologist). The erythrocyte sedimentation rate, C-reactive protein level, presence of immunoglobulin M rheumatoid factor, and presence of anticitrullinated protein antibodies were recorded. Disease activity was assessed by calculating the 28-joint disease activity score for each patient (38). A diagnosis score for the time of initial presentation was calculated according to the 2010 RA classification criteria of the ACR/EULAR (11).

MR Imaging

MR imaging examination of the wrists and hands was performed at 3.0 T with an MR unit (Magnetom Verio; Siemens Healthcare, Erlangen, Germany) by using a six-channel surface phased-array body coil, including both hands simultaneously in the field of view (FOV). The patient was placed in the prone position, with the hands fixed side by side over the head with the help of several cushions. The following sequences were performed before intravenous injection: T1-weighted fast spin-echo sequence in the axial plane (repetition time msec/echo time msec, 696/31; FOV, 230 mm; section thickness, 3.5 mm; matrix, 384 × 384; turbo factor, four; and number of sections, 45) and the coronal plane (583/21; FOV, 250 mm; section thickness, 2.0 mm; matrix, 384 × 384; turbo factor, four; and number of sections, 24), proton density–weighted fast spin-echo sequence with fat saturation in the coronal plane (3040/31; FOV, 250 mm; section thickness, 2.0 mm; matrix, 384 × 384; turbo factor, 10; and number of sections, 24), and spectral adiabatic inversion-recovery T2-weighted sequence in the sagittal plane (4950/79; FOV, 250 mm; section thickness, 3.0 mm; matrix, 384 × 384; turbo factor, 14; and number of sections, 28). Intravenous injection of a gadolinium-based contrast agent (gadopentetate dimeglumine, Magnevist; Bayer Healthcare, Leverkusen, Germany) at a standard dose of 0.1 mmol/kg (0.2 mL/kg) was performed by using an automatic injector (Nemoto MRI Injector; Siemens Healthcare) with a flow rate of 2.5 mL/sec through a 20-gauge intravenous needle (Abbocath) into a cubital vein. After injection, a modified T1-weighted fast three-dimensional gradient-echo volumetric interpolated breath-hold sequence with fat saturation was performed (9.29/3.99; FOV, 250 mm; section thickness, 1.1 mm; section gap, 0.22 mm; matrix, 256 × 256; and flip angle, 10°) by using repeated acquisitions starting at 0, 28 seconds, 57 seconds, 1 minute 26 seconds, 1 minute 54 seconds, 2 minutes 23 seconds, 2 minutes 52 seconds, and 3 minutes 20 seconds after contrast agent administration (imaging time, 28 seconds for each acquisition); the acquisitions were then reconstructed in the coronal (number of sections, 43) and axial (number of sections, 48) planes at 0 minutes, corresponding to the beginning of contrast agent injection. T1-weighted fast spin-echo sequences with fat saturation in the axial (696/31; FOV, 230 mm; section thickness, 3.5 mm; matrix, 384 × 384; turbo factor, four; and number of sections, 45) and coronal (777/21; FOV, 250 mm; section thickness, 2.0 mm; matrix, 384 × 384; turbo factor, four; and number of sections, 24) planes were also performed after contrast agent injection.

MR Image Evaluation

MR image evaluation was performed by two independent readers (M.N., a fellowship-trained board-certified musculoskeletal radiologist with 4 years of experience and 9 years of cross-sectional image interpretation experience; A.G., a fellowship-trained musculoskeletal board-certified radiologist with 8 years of experience and 22 years of cross-sectional image interpretation experience) who were blinded to clinical data. Each reader separately analyzed each set of images, and the analysis included the following: quantification of synovitis in multiple joints of the hands and wrists (distal radioulnar joint; radiocarpal joint; intercarpal and carpometacarpal joints; metacarpophalangeal [MCP] joints; proximal interphalangeal joints; excluding the first intercarpal and carpometacarpal, the first MCP joint, and the first proximal interphalangeal joints). A score of 0–3 was assigned for each joint, where score 0 was normal with no synovial enhancement and score 3 was the maximum presumed volume of enhancing tissue in the synovial compartment, according to the Rheumatoid Arthritis Magnetic Resonance Imaging Score, or RAMRIS, defined by the Outcome Measures in Rheumatology Clinical Trials, or OMERACT, imaging studies (39). Assignment of tenosynovitis scores to findings on contrast-enhanced images on a scale of score 0–3 was performed, as described by Haavardsholm et al (40), but included six tendon groups on the dorsal side of the wrist (extensor pollicis brevis and abductor pollicis longus, extensor carpi radialis brevis and extensor carpi radialis longus, extensor pollicis longus, extensor digitorum and indicis longus, extensor digiti minimi, and extensor carpi ulnaris) one tendon group on the ventral side of the wrist (flexor digitorium superficialis and flexor digitorium profundus), and five tendon groups on the ventral side of the hand (first through fifth flexor tendons at the digit level). Both wrists and hands were included in the quantification. An aggregated synovitis score for each tendon or joint, obtained by adding the scores for left and right sides, was used for the statistical analysis.

Table 1

Demographic, Clinical, and Laboratory Data of Patients at Baseline

Characteristic	VERA Patients ($n = 10$)	ERA Patients ($n = 15$)	Non-RA Patients ($n = 10$)
Sex			
No. of men	0	0	3
No. of women	10	15	7
Age (y)	50.5 (20.25)	48.0 (21.0)	33.0 (15.5)
Disease duration (mo)	2.5 (1)	9.0 (3.5)	9.5 (5.0)
From 28-joint count			
Tender joint count	7.5 (4.25)*†	8.0 (8.5)*†	3.5 (3.0)*†
Swollen joint count	3.0 ± 1.75*†	4.0 (6.0)*†	2.0 (2.5)*†
Erythrocyte sedimentation rate (mm/h)	22.5 (22)*†	33.0 (33.5)*†	6.5 (5.5)*†
Overall disease activity, visual analog scale	55 (28.75)	75 (38)	57.0 (28.25)
28-Joint disease activity score	5.17 ± 0.95*†	4.85 (1.19)*†	3.5 (1.11)*†
ACR/EULAR 2010 RA score	5 ± 2*†	6.0 (2.0)*†	3.0 (1.5)*†

Note.—Except where otherwise indicated, the values are medians, and the numbers in parentheses are the difference between the 75th and 25th quartiles (interquartile range).

* Results of the post hoc analysis using the Mann-Whitney *U* test with $P < .05$.

† Results with the Kruskal-Wallis test with $P < .05$.

All the previously described joints or tendons were considered for symmetry evaluation. Pairs of joints or tendons were classified as asymmetric when the absolute value of the difference in synovitis scores was one or more. Pairs of joints or tendons with no evidence of synovitis were excluded from the analysis, as they would artificially increase the symmetry prevalence.

Statistical Analysis

Statistical analysis was performed by using software (SPSS, version 17.0; SPSS, Chicago, Ill). Baseline characteristics were described as proportions for categorical variables and as medians with interquartile ranges for continuous variables. All continuous variables were tested for normality with the Kolmogorov-Smirnov test. The Kruskal-Wallis test was used to identify differences between groups, and the Mann-Whitney test was used for the post hoc paired comparisons.

Possible associations between synovitis for each joint and tendon and for each group of joints and tendons and RA diagnosis at 12 months were tested by using univariate logistic regression, considering in the analysis the variables with significant differences in the post hoc paired comparisons. The goodness of fit of the model was evaluated by using the Hosmer-Lemeshow test, and the accuracy of the predictive model was tested by using the *C* statistic.

The diagnostic performance of the ACR/EULAR RA classification criteria (11) was evaluated by using receiver operating characteristic (ROC) curve analysis. The diagnostic accuracy was tested again after adding score points to patients with tenosynovitis, as identified by using MR imaging, with consideration for the tendons with significant involvement in the intergroup comparison ($P < .05$). The *Z* statistic was used for pairwise comparison of ROC curves.

The difference between the proportions of asymmetry in different groups was tested by using the χ^2 test. The interreader reliability was assessed by using the unweighted Cohen κ statistic. Values for κ less than 0.20 were considered to reflect poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81 or greater, excellent agreement.

Results

Cohort Characteristics

The demographic and clinical characteristics of the 35 patients at baseline are shown in Table 1 and are classified into groups according to their diagnoses at the 12-month follow-up. The non-RA group included one patient with systemic lupus erythematosus and nine with undifferentiated arthritis (five cases of which were self limited).

Comparison of Median Synovitis Scores for Joints and Tendons and Association between Baseline MR Findings and 12-Month RA Diagnosis

A comparison of the median values of the synovitis scores for each joint and tendon investigated between VERA or ERA patients and non-RA patients is presented in Table 2. Associations between baseline joint or tendon synovitis and RA diagnosis at 12 months were tested. Synovitis of the radiocarpal joint, flexor tendons of the second finger at the digit level, and extensor carpi ulnaris for VERA patients and of the flexor tendons of the second finger at the digit level and radioulnar and radiocarpal joints for ERA patients were significantly associated with an RA diagnosis ($P < .05$) (Table 2; Figs 1, 2).

Comparison of Median Synovitis Scores for Joint and Tendon Groups and Association between Baseline MR Findings and 12-Month RA Diagnosis

A comparison of the median values of the synovitis scores by groups of joints and tendons between VERA or ERA patients and non-RA patients is presented in Table 3.

Associations between baseline synovitis according to joint and tendon groups and RA diagnosis at 12 months were tested. Synovitis of the flexor tendons for VERA patients and of the radiocarpal and MCP joints for ERA patients was significantly associated with RA diagnosis ($P < .05$).

Symmetry Evaluation

Evaluation of MR images revealed that if pairs of joints or tendons were

Table 2

Median Synovitis Scores and Association between Baseline MR Findings and 12-Month RA Diagnosis: Univariate Logistic Regression for Individual Joint and Tendon Analysis

Joint or Tendon with Synovitis at MR	Median Score			VERA Diagnosis			ERA Diagnosis		
	VERA Patients ($n = 10$)	ERA Patients ($n = 15$)	Non-RA Patients ($n = 10$)	Odds Ratio*	Cox and Snell R^2†	*P* Value‡	Odds Ratio*	Cox and Snell R^2†	*P* Value‡
Joint									
MCP, 3rd finger	0 (1.25)	1 (3.00)§	0§	. . .	. . .	. . .	1.66	0.44	.99
Radioulnar	0 (1.25)	3 (3.00)§	0§	. . .	. . .	. . .	8.79 (1.02, 75.63)	0.47 (0.18, .98)	.04 (0.883)‖
Radiocarpal	3 (2.25)§	2 (4.00)§	0 (1.25)§	3.00 (1.19, 7.58)	0.29 (5.26, .15)	.02 (0.800)‖	2.21 (1.03, 4.78)	0.21 (3.44, .33)	.04 (0.747)‖
Intercarpal-carpometacarpal	0 (1.25)	1 (4.00)§	0§	. . .	. . .	. . .	3.59	0.27	.12
Proximal interphalangeal, 4th finger	0 (1.00)	2 (3.00)§	0 (1.25)§	. . .	. . .	. . .	2.03	0.18	.06
Extensor carpi ulnaris, 6th extensor tendon compartment	2 (4.25)§	0 (3.00)§	0§	3.21 (1.09, 9.40)	0.39 (0.43, .81)	.03 (0.825)‖	2.15	0.14	.16
Flexor tendons									
Wrist level	0 (2.50)§	0 (2.00)§	0§	11.09	0.28	.99	1.75	0.30	.99
Digit level									
2nd Finger	1.5 (3.25)§	1 (3.00)§	0§	14.61 (1.09, 194.6)	0.48 (0.05, .99)	.04 (0.875)‖	9.60 (1.17, 78.93)	0.39 (0.09, .96)	.03 (0.840)‖
3rd Finger	2 (3.00)§	1 (2.00)§	0§	4.43	0.35	.1	7.66	0.24	.06

Note.—For median synovitis scores, numbers in parentheses are the difference between the 75th and 25th quartiles (interquartile range). Regression anlaysis was conducted only for the variables with significant differences in the post hoc paired comparisons (as identified by using $P < .05$ in the Mann-Whitney *U* test). The complete set of values of the regression model is presented for the variables with significant associations. The results are from one observer (M.N.).

* Numbers in parentheses are the 95% confidence intervals.

† The Hosmer-Lemeshow test for goodness of fit was used. The numbers in parentheses are the χ^2 statistic and the *P* value, respectively.

‡ Numbers in parentheses are the *C* statistic.

§ Results with the Mann-Whitney *U* test (used for post hoc analysis) with $P < .05$.

‖ Significant values.

classified as asymmetric when the absolute value of the difference in synovitis scores was one or more, asymmetry was found in 80.0% (62 of 77) of VERA, 69.3% (106 of 153) of ERA, and 69.6% (16 of 23) of non-RA patients. The differences between the different groups were significant ($P < .05$), with the exception of the ERA versus non-RA group comparison.

Performance of the 2010 ACR/EULAR Criteria in Identifying RA Patients

For the purpose of ROC analysis, VERA and ERA patients were considered as one group (RA group). Evaluation of the performance of the 2010 ACR/EULAR criteria for identifying RA patients revealed that the use of the criteria, as previously described (9), for identifying RA resulted in a sensitivity of 52% and specificity of 100%, with an area under the ROC curve (AUC) of 0.942. Adding one score point to each patient with at least one of the most significant tendons (as identified in Table 2) affected by synovitis resulted in a sensitivity of 76%, a specificity of 100%, and an AUC of 0.972. Adding an additional score point to each patient with at least three of those tendons affected by synovitis resulted in a sensitivity of 80%, a specificity of 100%, and an AUC of 0.976. No significant differences were identified in pairwise comparison of ROC curves (Table 4; Fig 3).

Reliability

The interreader agreement was good for both tenosynovitis and synovitis scores ($\kappa = 0.782$ and 0.798, respectively).

Figure 1

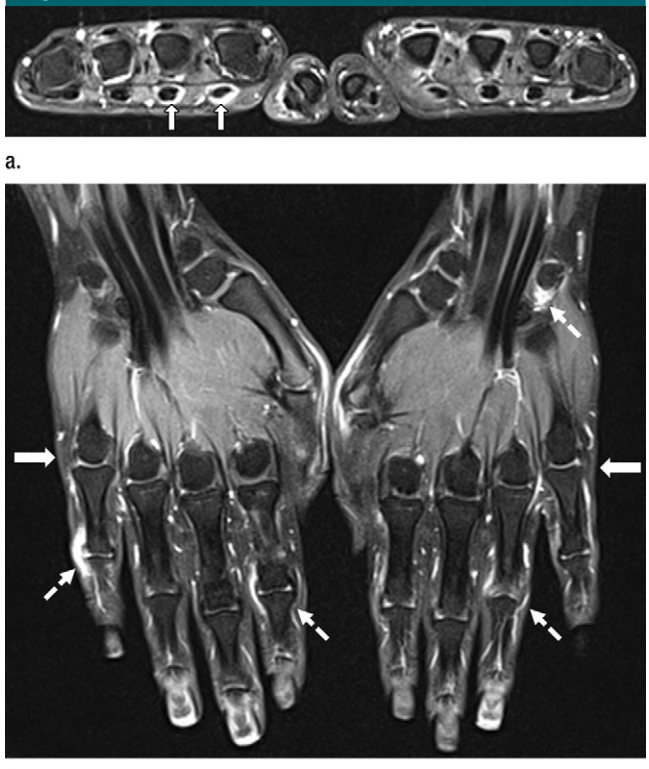

Figure 1: Bilateral MR images of the hand and wrist of a 33-year-old woman with early inflammatory arthritis with a disease duration of 3 months; she did not fulfill the criteria for a specific diagnosis at the time of MR imaging examination (with a calculated score of 5, according to the 2010 RA classification criteria of the ACR/EULAR at presentation) but did fulfill both the 1987 ACR and 2010 RA classification criteria for RA at the 12-month clinical follow-up. **(a)** Contrast-enhanced axial T1-weighted fat-saturated MR image shows grade 2 (≥2 and <5 mm synovial proliferation with enhancement) tenosynovitis of the flexor tendons of the second and third digits on the right hand (arrows). **(b)** Contrast-enhanced coronal T1-weighted fat-saturated MR image at the MCP joint level (arrows) demonstrates absence of MCP joint synovitis. Bilateral interphalangeal joint synovitis and left radiocarpal joint synovitis (pisotriquetral synovial recess) were noted (dashed arrows).

Discussion

In our study, we identified tenosynovitis as a discriminating factor of the evolution toward RA in patients with arthritis for less than 3 months in duration (VERA). Tenosynovitis of the extensor carpi ulnaris and of the flexor tendons of the second finger, in addition to radiocarpal joint synovitis, were recognized as significantly associated with progression to RA in this cohort. Even in patients with longer disease duration (3–12 months), tenosynovitis of the flexor tendons of the second finger remained one of the significant discriminating features for fulfilling RA criteria. Another result of this study was the demonstration that including MR imaging–identified tenosynovitis in the 2010 ACR/EULAR classification criteria for RA improves score performance.

In view of our results, it seems peculiar that tenosynovitis of the wrists and hands has received so little attention in previous literature. In fact, there is no Outcome Measures in Rheumatology Clinical Trials RA MR imaging (39) definition of the term *tenosynovitis*, and despite the proposal of an MR imaging tenosynovitis score for established disease (40), its use has been sparse. Even the report by Chand et al (41), the only available study applying 3.0-T MR imaging to the study of early-RA patients, focused only on joint synovitis by describing a method for determining the synovial membrane volume.

In the study by Eshed et al (33), they identified flexor tenosynovitis of

Figure 2

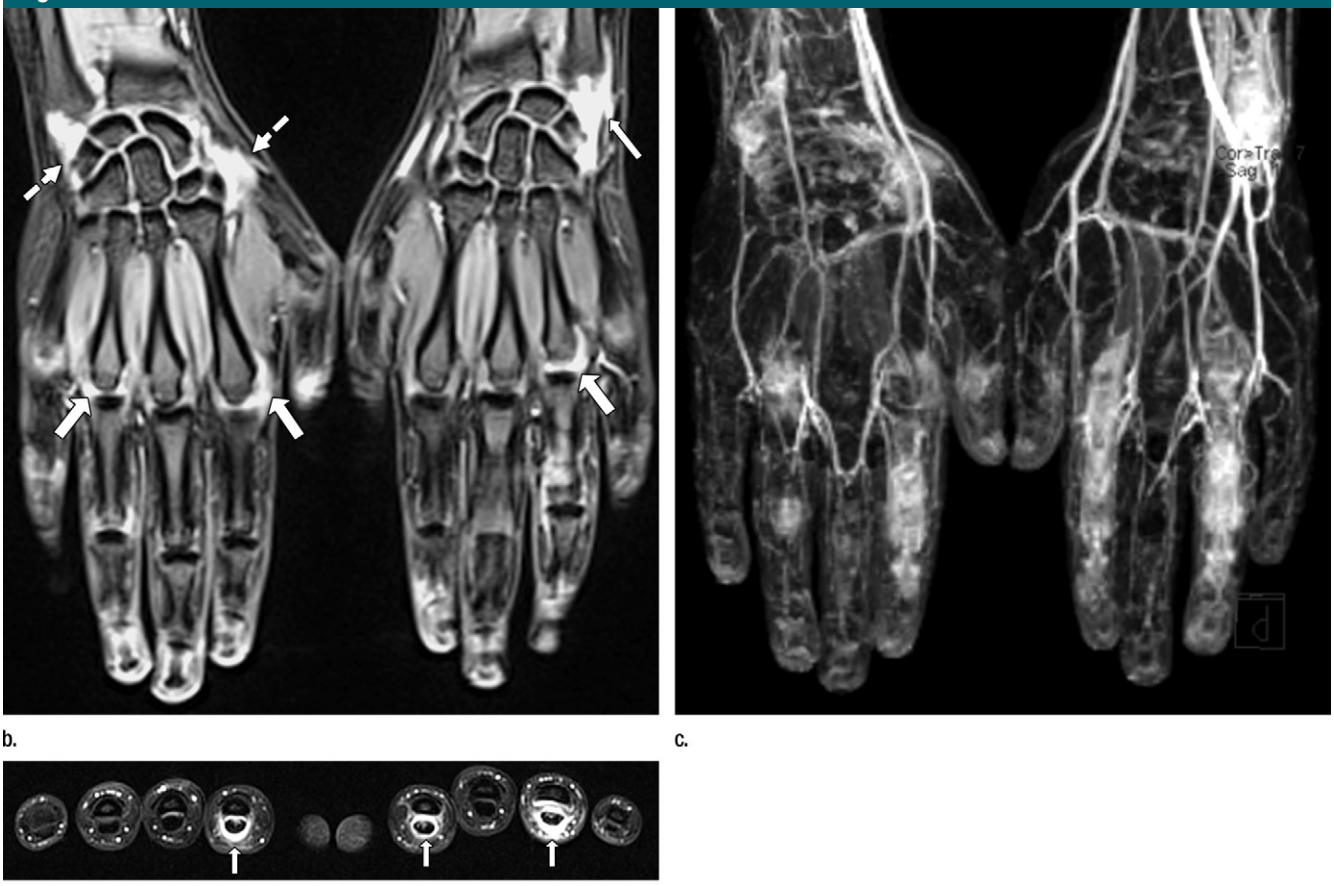

Figure 2: Bilateral MR images of the hand and wrist of an 18-year-old woman with early inflammatory arthritis with a disease duration of 8 months; she fulfilled the criteria for RA at presentation. **(a)** Contrast-enhanced axial T1-weighted fat-saturated MR image shows tenosynovitis of the flexor tendons of the second and fourth digits on the left hand and of the second digit on the right hand (arrows). **(b)** Contrast-enhanced coronal high-spatial- and high-temporal-resolution volumetric interpolated breath-hold fat-saturated MR image (section thickness, 1.1 mm), indicative of synovitis of the second and fourth MCP joints on the right hand (arrows) and of the fourth MCP joint on the left hand (arrow), as well as of the left extensor carpi ulnaris (thin arrow, left hand) and the radiocarpal and trapeziometacarpal joints (dashed arrows, right hand). **(c)** Maximum intensity projection of a three-dimensional digitally subtracted data set of the volumetric interpolated breath-hold acquisition after contrast agent administration demonstrates increased vascularity of synovitis and tenosynovitis. The tubelike appearance of digit tenosynovitis is clearly depicted.

the hand as a strong predictor of early RA. However, their work was performed with a low-field-strength (0.2 T) extremity MR imaging unit. There were other limitations in that study, such as the inclusion of patients with disease duration up to 24 months, which exceeds the currently accepted definition of early RA (34,35), and the focus on groups of tendons, masking potential findings for individual tendons. An interesting recent study of synovitis maps by Karlo et al (42) included tenosynovitis evaluation, but it addressed unspecified inflammatory disorders. The other reports on the study of tendons by using MR imaging in the context of RA are out of the scope of our current study because they have either focused on predicting tendon rupture in early RA (43) or assessed established long-standing disease (44–46).

In our bilateral study, making use of a 3.0-T MR imaging technique, joint asymmetry rates of three-quarters in VERA patients and two-thirds in ERA patients were detected. This is in line with previous clinical descriptions of early RA, depicting asymmetric joint involvement in 30%–94% of patients and symmetrization with RA progression (23–28,47). Taken together, these findings provide a morphologic confirmation that early RA may be an asymmetric disease.

Intergroup analysis revealed that, in the VERA group compared with the non-RA group, the most significant differences were found for the flexor and extensor tendons. Through regression analysis, we identified flexor tendons as the best discriminating factor between

Table 3

Median Synovitis Scores and Association between Baseline MR Findings and 12-Month RA Diagnosis: Univariate Logistic Regression for Group Joint and Tendon Analysis

Joint or Tendon with Synovitis at MR	Median Score			VERA Diagnosis			ERA Diagnosis		
	VERA Patients ($n = 10$)	ERA Patients ($n = 15$)	Non-RA Patients ($n = 10$)	Odds Ratio*	Cox and Snell R^2†	*P* Value‡	Odds Ratio*	Cox and Snell R^2†	*P* Value‡
MCP joints, 2nd–5th	1 (4.25)§‖	4 (6.00)§‖	0 (0.25)§‖	. . .	. . .	. . .	3.65 (1.15, 11.60)	0.49 (0.33; .99)	.03 (0.903)#
Carpal**	3.5 (5.25)§‖	5 (9.00)§‖	0 (0.20)§‖	1.98	0.27	.06	2.32 (1.06, 5.09)	0.43 (2.35; .79)	.04 (0.887)#
Proximal interphalangeal joints, 2nd–5th	3 (2.5)	4 (10.00)	2.5 (4.25)	. . .	. . .	. . .	. . .	. . .	. . .
Extensor††	2 (5.75)§‖	1 (6.00)§‖	0§‖	3.09	0.38	.07	2.64	0.25	.1
Flexor‡‡	5.5 (5.5)§‖	5 (8.00)§‖	0§‖	4.28 (0.98, 18.61)	0.54 (0.19, .98)	.04 (0.930)#	2.63	0.39	.08

Note.—For median synovitis scores, numbers in parentheses are the difference between the 75th and 25th quartiles (interquartile range). Regression analysis was conducted only for the variables with significant differences in the post hoc paired comparisons (as identified by using $P < .05$ in the Mann-Whitney *U* test). The complete set of values of the regression model is presented for the variables with significant associations. Results are from one observer (M.N.).

* Numbers in parentheses are the 95% confidence intervals.

† The Hosmer-Lemeshow test for goodness of fit was used. The numbers in parentheses are the χ^2 statistic and the *P* value, respectively.

‡ Numbers in parentheses are the *C* statistic.

§ Results with the Kruskal-Wallis test, with $P < .05$.

‖ Results with the Mann-Whitney *U* test (used for post hoc analysis) with $P < .05$.

Significant values.

** Carpal represents carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints.

†† Extensor represents six extensor tendon groups on the dorsal side of the wrist, as described in Materials and Methods.

‡‡ Flexor represents six tendon groups on the ventral side of the wrist and hand, as described in Materials and Methods.

VERA and non-RA patients. Involvement of the flexor tendons in the ERA group remained significantly different from that in the non-RA group, but the MCP and carpal joints also had highly significant synovitis involvement.

We tried to identify a strategy by which tenosynovitis could contribute to improvement of the diagnostic performance of the 2010 ACR/EULAR RA classification criteria (11). The mean ACR/EULAR score in our VERA and ERA patients was less than six, confirming that some patients were not being identified as having RA by using the newer criteria at the time of presentation. Our results agree with those of two recent studies (12,48) with a very-early inflammatory arthritis cohort that highlighted that, despite improved performance of the 2010 criteria, over- and underdiagnosis may still remain important issues. In fact, in our cohort of RA patients, the diagnostic performance of the ACR/EULAR criteria in terms of AUC was improved by the addition of one score point to each patient with at least one of the most significant tendons in the intergroup comparison affected by synovitis. Although representing a clear tendency, the difference was not significant. We believe that small sample size was a main limitation to *Z* statistic performance; these findings need to be explored in larger numbers of patients. Adding two score points to each patient with at least three of those tendons affected by synovitis did not further improve diagnostic performance. Joint synovitis was not considered in this analysis, as joint involvement that is clinically identified and/or confirmed by using imaging studies, is already a parameter of the original 2010 ACR/EULAR criteria.

One of the limitations of our study was its small sample size, which prevented multivariate regression analysis. Small sample size was related to the strict inclusion criteria, namely disease duration, and the prospective nature of the study. However, we believe that the homogeneity of the groups in the study could mitigate this fact. Degeneration,

Figure 3

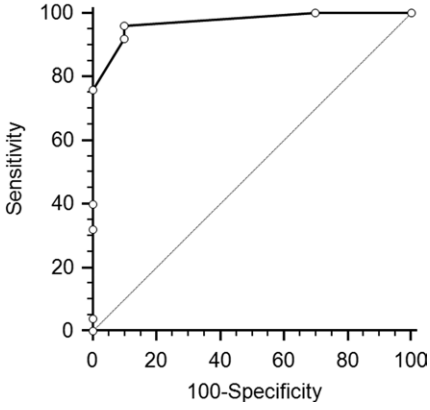

Figure 3: ROC curve for RA as an outcome by using ACR/EULAR score of 6 or greater for identifying RA patients, adding one score point to each patient with at least one of the tendons affected by synovitis with significant involvement in the intergroup comparison, as identified in Table 2 (AUC, 0.972; 95% confidence interval: 0.852, 0.999). Sensitivity, specificity, and criterion values for the nine operating points in the curve, in order of increasing sensitivity, were as follows: 1.2%, 100%, score greater than 8.70; 5.7%, 100%, score greater than 7.94; 32.9%, 100%, score greater than 6.88; 41.0%, 100%, score greater than 5.97; 78.1%, 98.7%, score greater than 4.87; 93.4%, 90.0%, score greater than 3.65; 96.0%, 90.0%, score greater than 3; 100.0%, 29.0%, score greater than 1; and 100.0%, 1.8%, score greater than 1.

Table 4

Performance of the ACR/EULAR Criteria for Identifying RA Patients and the Role of Tenosynovitis Detected with MR Imaging

Criteria	Sensitivity (%)	Specificity (%)	AUC	95% Confidence Interval	*P* Value*
ACR/EULAR ≥ 6†	52	100	0.942	0.802, 0.991	<.0001
ACR/EULAR + 1 ≥ 6‡	76	100	0.972	0.852, 0.999	<.0001
ACR/EULAR + 2 ≥ 6§	80	100	0.976	0.858, 1.000	<.0001

* Determined with ROC analysis. All values were significant ($P < .05$)

† ACR/EULAR ≥ 6 is the performance of the ACR/EULAR score of 6 or greater for identifying RA patients.

‡ ACR/EULAR + 1 ≥ 6 is the performance of the ACR/EULAR score of 6 or greater for identifying RA patients, adding one score point to each patient with at least one of the tendons affected by synovitis, with significant involvement in the intergroup comparison (as identified in Table 2).

§ ACR/EULAR + 2 ≥ 6 is the performance of ACR/EULAR score of 6 or greater for identifying RA patients, adding an additional score point to each patient with at least three of the tendons affected by synovitis, with significant involvement in the intergroup comparison (as identified in Table 2).

impingement, and overuse are known causes of tenosynovitis (49) and could also be a source of bias. Still, we believe that the recruitment from the rheumatology outpatient clinics of patients with clinical involvement of four or more joints, the exclusion of typical degenerative territories from the joint count (distal interphalangeal joints and the first carpometacarpal joint) (49), and the exclusion of patients with obvious occupation- or sports-related symptoms should lessen this problem. Although tendinosis may cause MR imaging signal intensity changes within tendons, studies (50–52) have shown the established pathologic findings to consist of tendon degeneration with a complete absence of inflammatory cells. In contrast, in RA, the synovium is directly targeted by the rheumatoid inflammatory process, and synovial thickening is the histologic hallmark and the earliest abnormality (13). In this way, evaluation of tendinosis or other intrasubstance tendon characteristics was out of the scope of this study, which focused on synovial membrane evaluation.

In conclusion, our data confirm that tenosynovitis is a common imaging finding in early RA, and its inclusion as a scoring criterion might contribute for a better diagnostic performance of the 2010 ACR/EULAR classification. In addition, our study identifies early RA as an asymmetric disease, suggesting the importance of a bilateral acquisition protocol.

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