Tenosynovitis in rheumatoid arthritis patients on biologic treatment: involvement and sensitivity to change compared to joint inflammation

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Abstract

Objective

Extensor carpi ulnaris (ECU) and tibialis posterior (TP) tendons are often involved in RA and the present aim was to examine by ultrasound (US) their frequency of inflammation and sensitivity to change in comparison to joint involvement as well as clinical examinations.

Methods

US, clinical and laboratory assessments were performed when starting biologic DMARD (bDMARD) and after 1, 2, 3, 6 and 12 months including bilateral grey-scale (GS) and power Doppler (PD) semi-quantitatively (0–3) scoring of ECU and TP tendons and 18 joints. Changes from baseline to follow-up were explored by Wilcoxon signed rank test, associations by Spearman's rank correlations and responses to treatment by Standardised Response Means (SRMs).

Results

157 patients (mean age/disease duration 52.4/10.2 years) were included. ECU/TP tenosynovitis was frequent (baseline GS/PD pathology in 76/50% of patients) and more prevalent than synovitis of large joints. Tenosynovitis sum scores decreased throughout follow-up ($p<0.001$) and was correlated with US of joints (0.51–0.62), clinical assessments (swollen joint count (0.29-0.41) and assessor's global (0.35–0.46)) ($p<0.001$). US tenosynovitis sum scores had SRMs comparable to joint, clinical and laboratory assessments.

Conclusion

Tenosynovitis in ECU/TP tendons were frequent, sensitive to change during bDMARD treatment and were associated to joint and clinical assessments. This supports the argument for tenosynovitis to be included in US scores of RA patients, while further studies should explore which tendons.

Key words

rheumatoid arthritis, ultrasound, tendons, synovitis, bDMARDs

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Introduction

Ultrasound (US) is a sensitive tool for detection of tenosynovitis (1) and joint synovitis (2) and allows assessment of both morphological and inflammatory changes including evaluation of multiple tendons and joints during the same examination. US can discriminate between tendon and joint involvement which may be clinically challenging (3, 4). The importance of diagnosing and treating tenosynovitis is underlined by the risk of producing tendon adhesion and tendon rupture leading to severe joint deformities and loss of functional capacity (5).

Joint US is increasingly used for assessing inflammatory activity in RA patients and several joint scores have been proposed. However, it is debated whether tenosynovitis should be included in the US monitoring of RA (6). Tenosynovitis in hands and feet are common in rheumatoid arthritis (RA) both in early and late state disease (7-9), and may be predictive of developing RA (10). In early RA patients the presence of tenosynovitis has been shown to predict erosive progression at 1-year follow-up (11) supporting the importance of diagnosing tendon involvement. Previous US studies of tendons in wrists and ankles of patients with established RA showed the extensor carpi ulnaris (ECU) and tibialis posterior (TP) tendons to be the most frequently involved tendons (12, 13).

It is well established that joint inflammation as seen by US decreases during biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) treatment, but only scarce data exist on the sensitivity to change in tenosynovitis and hence the possible impact of including tendons in US evaluation and monitoring of RA patients (12-14).

The objective of the present study was to examine by US the ECU and TP tendons which are the most frequently involved tendons in RA (12, 13). We focused on frequency of inflammation and sensitivity to change in comparison to joint involvement as well as clinical assessments during follow-up of patients with established RA initiating biologic medication.

Patients and methods

Patients with RA fulfilling the ACR 1987 criteria (15) were included in the study prior to initiation or changing bDMARD treatment in the period from January 2010 to June 2013 (Anzctr.org.au identifier ACTRN12610000284066). A cohort including 212 patients has previously been used for assessing a reduced joint count for US monitoring, where the ECU and TP tendons were included in the final score (16, 17). From that cohort only patients completing the 12 months follow-up were presently included.

Clinical evaluation (number of tender and swollen joints, patient's and assessor's global visual analogue scale (VAS), laboratory assessments (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) and US examinations of tendons and joints were performed at baseline and after 1, 2, 3, 6, and 12 months. Two trained study nurses with longstanding experience in evaluation of tender and swollen joints performed the clinical evaluations blinded to the US findings. Disease Activity Score based 28 joint counts and ESR (DAS28), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) scores were calculated for each visit.

US examinations (blinded for the results of the clinical assessments) were performed by the same experienced sonographer (HBH) throughout the study, using a Siemens Antares, Excellence version (Siemens Medical Solutions, CA, USA) equipped with a 5–13 MHz linear probe, with 11.4 MHz used for GS assessments. PD settings were optimised for inflammatory flow with PRF 391 Hz, Doppler frequency 7.3 MHz and gain just below the level of noise (18). The same US machine with the same settings were used throughout the study with no software upgrading.

At each visit, US examination was performed of 36 joints for signs of synovitis. The following joints were evaluated bilaterally: metacarpophalangeal joint (MCP) 1–5, proximal interphalangeal joint (PIP) 2–3, wrist (scoring radiocarpal, midcarpal and radioulnar joints separately), elbow, knee, talocrural and metatarsophalangeal joint (MTP) 1-5.

Each joint was scored semi-quantitatively 0-3 for GS and PD according to the US atlas by Hammer *et al*. (19). In each patient the sum score of GS as well as PD for all joints were calculated (range 0–108).

The ECU and TP tendons were examined bilaterally using the OMERACT definitions for tenosynovitis (20). The tendons were scored semi-quantitatively (0-3) for GS and PD according to severity (normal, minimal, moderate and severe) as suggested by Naredo *et al*. (21). However, since the present study was initiated before the study by Naredo *et al*. was published, intra-tendinous Doppler activity was not included into the score. Examples of the semi-quantitative GS and PD scoring system for ECU and TP tenosynovitis are shown in Figure 1. For every patient, GS and PD sum scores were calculated for the two tendons (range 0-12).

The sonographer in the present study (HBH) had previously demonstrated a high intra-observer reliability (weighted kappa 0.83 (19)) for real life joint scoring of the presently included joints. The intra-observer reliability for the tenosynovitis scoring system was assessed in a web-exercise by use of 120 US still images of tenosynovitis in RA patients (ECU and TP tendons in both longitudinal and transverse scans) with varying degrees of GS and PD pathology. The images were scored 0–3 for GS and PD separately and the images were re-read after an interval of 2 weeks.

The study was approved by the Regional Committee for Medical and Health Research Ethics South East and the patients gave written consent according to the Declaration of Helsinki (REK number 2009/1254).

Statistics

The percentage of patients with tendon and joint involvement at baseline, sum scores GS/PD for tendons and joints for each visit as well as composite scores (DAS28, CDAI and SDAI) were calculated. At each of the follow-up visits, the changes from baseline were explored by Wilcoxon signed rank test for sum US scores (tendons and joints), clinical assessments and laboratory variables. Spearman's rank correlations were used for exploring associations between cross-sectional US assessments (sum scores of tenosynovitis and joint synovitis, GS and PD), between changes from baseline of the different US scores as well as between US and clinical assessments. Correlation coefficients of <0.1 were defined as negligible, 0.1–0.3 low, 0.3–0.5 moderate, 0.5–0.7 high and >0.7 as very high correlations. The

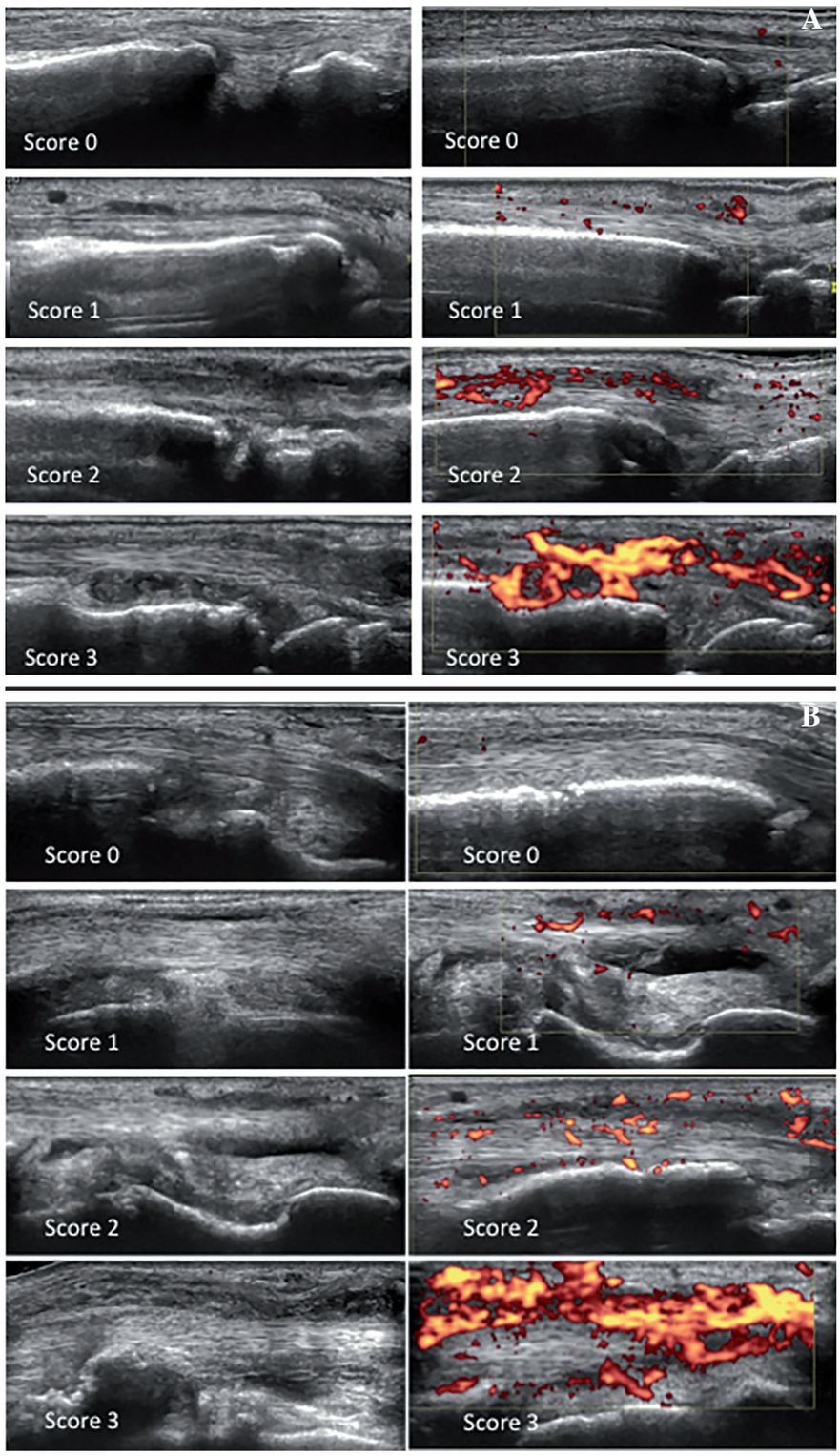

Fig. 1. A: The extensor carpi ulnaris tendon; Semi-quantitative tenosynovitis scores 0–3 of grey scale and power Doppler. **B**: The tibialis posterior tendon; Semi-quantitative tenosynovitis scores 0–3 of grey scale and power Doppler.

sensitivity to change was assessed by Standardised Response Mean (SRM) as the change of the measure divided on the standard deviation of the change. Missing data during follow-up (<5% missing values) were handled by use of last observation carried forward. Intra-observer reliability was calculated by use of linear weighted kappa. All tests for significance were two-sided, and $p<0.05$ was considered significant.

Results

Patient demographics

A total of 157 patients (82.8% women, 80.3% seropositive for anti-CCP and 74.8% for rheumatoid factor) were included, with a mean (SD) age of 52.4 (12.1) years and mean disease duration of 10.2 (8.9) years. At baseline, 56.1% used prednisolone (median (range) 7.5 (2.5–25) mg). The patients had a mean (SD) baseline DAS28 of 4.48 (1.43), including 14 patients with DAS28 <2.6 (twelve patients were on prednisolone or had been given systemic steroids before the inclusion and two patients had clinically inactive disease, but with radiographic progression and unfavorable prognostic factors). The following bDMARDs were initiated and continued during the whole study; infliximab (n=16), etanercept (n=59), adalimumab (n=8), certolizumab (n=13), golimumab (n=8), rituximab (n=37), tocilizumab (n=12) and abatacept (n=4). Eight percent of the patients were bDMARD naïve. The proportions of patients who had previously been exposed to one, two, three or four to six bDMARDs were 40%, 25%, 16% and 11%, respectively.

Intra-observer reliability of tenosynovitis scoring system

The intra-observer reliability for semi-quantitative scoring of 120 still images for GS or PD pathology of ECU and TP tenosynovitis had a weighted kappa of 0.88 (95% confidence interval 0.82–0.93).

US at baseline

At baseline, GS tenosynovitis score ≥1 was found in 119 patients (76%) in ECU or TP tendons and 78 of these patients (66%) had PD activity (*i.e.* 50% of all the patients). Joint synovitis (GS score ≥1) was detected in all patients, and 144 of the patients (92%) had PD activity in joints.

As shown in Table I, joint synovitis was most frequently found in the MTP, radiocarpal and MCP joints. The percentage of patients with inflammation of ECU and TP tendons was of similar magnitude as for synovitis in PIP joints, and was higher than for synovitis in large joints.

US, clinical and laboratory assessments during follow-up

The sum scores of GS and PD of ECU and TP as well as sum scores of GS and PD of all examined joints decreased significantly from baseline to each follow-up examination ($p<0.001$) as did number of swollen and tender joints, assessor's and patient's global VAS, ESR, CRP and the composite scores DAS28, CDAI and SDAI ($p<0.001$) (Table II). At 12-month follow-up, 39% of the patients had DAS28 <2.6 (remission), and 55% had DAS28 <3.2 (low disease activity). Patients with no US detected tenosynovitis at baseline (n=38) had a low occurrence of tenosynovitis during follow-up (up to 8 patients at the different time points).

Associations between US of tendons/joints and clinical assessments

The cross-sectional correlations between tenosynovitis US sum scores and joint synovitis scores were high during follow-up, with median (range) correlation coefficients for GS of 0.58 (0.55–

Table I. Percentages of joints/tendons with different baseline scores of grey scale and power Doppler. The numbers in parenthesis are the sum of right and left side joints/tendons examined (a few joints could not be examined because of prosthesis or other operations).

	Grey scale scores				Power Doppler scores			
Score	0	1	2	3	0	1	2	3
RC (n=303)	23.0	40.3	30.7	6.0	52.8	28.1	15.5	3.6
MC (n=303)	54.1	18.5	16.5	10.9	65.7	18.4	10.6	5.3
RU (n=298)	52.4	19.1	16.1	12.4	70.1	14.7	12.1	3.1
MCP 1 (n=307)	55.7	12.1	16.9	15.3	70.6	8.9	15.0	5.5
MCP 2 (n=306)	42.4	17.0	18.3	22.3	61.7	10.5	22.2	5.6
MCP 3 (n=309)	47.6	19.4	13.6	19.4	67.3	11.3	18.1	3.3
MCP 4 (n=314)	61.8	12.8	14.9	10.5	78.0	7.5	10.6	3.9
MCP 5 (n=314)	61.2	12.5	12.7	13.6	76.3	11.2	10.2	2.3
PIP 2 (n=307)	65.4	12.4	12.1	10.1	82.4	6.8	5.9	4.9
PIP 3 (n=305)	56.7	16.1	15.1	12.1	82.3	4.6	7.2	5.9
Elbow (n=309)	75.4	8.6	8.5	7.5	85.1	6.8	5.8	2.3
Knee (n=308)	71.1	20.4	6.5	2.0	95.4	3.6	1.0	0.0
Ankle (n=312)	81.7	11.3	4.4	2.6	97.4	2.0	0.6	0.0
MTP 1 (n=287)	30.2	41.2	22.6	6.0	84.0	8.6	6.7	0.7
MTP 2 (n=283)	34.2	31.2	23.0	11.6	83.7	7.1	6.7	2.5
MTP 3 (n=283)	45.3	26.3	20.0	8.4	81.8	7.8	7.9	2.5
MTP 4 (n=283)	51.1	27.6	14.2	7.1	83.6	7.8	6.8	1.8
MTP 5 (n=283)	57.5	19.1	16.3	7.1	73.8	9.9	13.8	2.5
ECU (n=314)	58.6	19.4	16.3	5.7	78.6	7.3	11.5	2.6
TP (n=314)	62.4	16.3	12.4	8.9	74.8	10.8	10.5	3.9

RC: radiocarpal; MC: midcarpal; RU: radioulnar; MCP 1-5: metacarpo-phalangeal 1-5; PIP 2-3: proximal inter-phalangeal; MTP 1-5: metatarso-phalangeal; ECU: extensor carpi ulnaris; TP: tibialis posterior.

Table II. Mean (SD) of sum ultrasound scores, clinical and laboratory assessments during bDMARD treatment. Sum score tendons includes bilateral scores of extensor carpi ulnaris and tibialis posterior tendons; sum score joints includes scores from 36 joints. All variables decreased significantly from baseline ($p<0.001$).

	Baseline	1 month	2 months	3 months	6 months	12 months
Sum score GS tenosynovitis	2.7 (2.7)	2.3 (2.4)	2.1 (2.4)	1.7 (2.1)	1.8 (2.1)	1.4 (1.8)
Sum score PD tenosynovitis	1.6 (2.2)	1.3 (2.0)	1.1 (1.8)	1.0 (1.7)	0.9 (1.6)	0.5 (1.2)
Sum score GS joints	28.3 (16.8)	25.6 (15.9)	24.3 (15.6)	21.9 (14.1)	20.1 (13.7)	18.1 (12.9)
Sum score PD joints	13.3 (12.0)	10.7 (11.0)	9.7 (10.6)	8.5 (10.1)	6.8 (9.1)	5.2 (7.0)
28-swollen joint count	6.4 (5.2)	5.3 (5.0)	4.8 (4.8)	4.3 (4.8)	3.5 (4.5)	2.9 (4.1)
28-tender joint count	5.5 (6.1)	4.6 (5.4)	4.0 (5.3)	3.7 (5.6)	2.5 (4.2)	2.6 (4.4)
Patient's global VAS	46.8 (27.6)	31.7 (26.4)	26.2 (23.4)	24.5 (22.6)	22.5 (21.0)	24.6 (22.3)
Assessor's global VAS	30.2 (16.0)	23.3 (14.5)	20.9 (13.3)	17.6 (12.6)	16.5 (11.5)	15.3 (11.1)
DAS28 (ESR)	4.48 (1.43)	3.85 (1.45)	3.57 (1.44)	3.40 (1.40)	3.11 (1.25)	3.04 (1.30)
CDAI	19.6 (12.1)	15.5 (11.3)	13.5 (10.9)	12.2 (11.0)	9.9 (9.0)	9.5 (8.7)
SDAI	20.9 (12.8)	16.2 (11.9)	14.2 (11.5)	12.7 (11.2)	10.5 (9.3)	9.9 (9.0)
ESR	27.3 (20.4)	21.5 (19.0)	19.3 (15.5)	18.7 (14.9)	17.6 (14.7)	16.9 (13.4)
CRP	12.5 (20.3)	8.6 (17.8)	6.6 (14.2)	4.9 (9.4)	4.9 (9.8)	4.5 (11.1)

GS: grey scale; PD: Power Doppler; DAS28(ESR): Disease Activity Score based on 28 joints and ESR; VAS: visual analogue scale; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table III. Median (range) cross-sectional Spearman's rank correlations between sum scores GS/PD and clinical assessments during follow-up. The sum scores of tendons (bilateral extensor carpi ulnaris and tibialis posterior), joints (36 joints) and a combination of tendons and joints were calculated for all 157 RA patients at each time point during follow-up, and cross-sectional correlations were performed for baseline and the 1, 2, 3, 6 and 12 months examinations. *$p<0.05$, **$p\leq0.001$ (in bold).

	Swollen joint count (n=28)	Tender joint count (n=28)	Patient's global VAS	Assessor's global VAS	DAS28	CDAI	SDAI	ESR	CRP
Sum score GS tenosynovitis	**0.38**** (0.30**-0.41**)	0.06 (-0.04-0.12)	0.06 (-0.02-0.10)	**0.38**** (0.35**-0.46**)	0.19* (0.08-0.23*)	**0.29**** (0.23*-0.35**)	**0.30**** (0.23*-0.37**)	0.11 (-0.01-0.18*)	0.22* (0.14-0.26**)
Sum score GS joints	**0.70**** (0.67**-0.77**)	0.17* (0.07-0.22*)	0.11 (0.06-0.12)	**0.65**** (0.61**-0.66**)	**0.28**** (0.24*-0.33**)	**0.50**** (0.45**-0.53**)	**0.50**** (0.46**-0.54**)	0.09 (0.04-0.25*)	**0.27**** (0.22*-0.38**)
Sum score GS tenosynovitis and joints	**0.69**** (0.67**-0.76**)	0.16* (0.06-0.22*)	0.11 (0.05-0.12)	**0.64**** (0.61**-0.67**)	**0.27**** (0.24*-0.33**)	**0.49**** (0.45**-0.53**)	**0.50**** (0.46**-0.54**)	0.09 (0.03-0.22*)	**0.28**** (0.22*-0.38**)
Sum score PD tenosynovitis	**0.39**** (0.29**-0.40**)	0.01 (-0.06-0.12)	0.04 (-0.04-0.07)	**0.41**** (0.37**-0.43**)	0.14 (0.10-0.25**)	**0.26**** (0.20*-0.32**)	**0.26**** (0.21*-0.33**)	0.15 (0.08-0.19*)	**0.26**** (0.20*-0.31**)
Sum score PD joints	**0.68**** (0.65**-0.73**)	0.22* (0.14-0.26**)	0.14 (0.06-0.20*)	**0.69**** (0.58**-0.72**)	**0.36**** (0.35**-0.38**)	**0.53**** (0.46**-0.55**)	**0.53**** (0.47**-0.56**)	0.19* (0.16*-0.30**)	**0.33**** (0.26**-0.46**)
Sum score PD tenosynovitis and joints	**0.68**** (0.63**-0.72**)	0.20* (0.11-0.25*)	0.13 (0.05-0.19*)	**0.68**** (0.61**-0.72**)	**0.35**** (0.33**-0.37**)	**0.52**** (0.45**-0.56**)	**0.52**** (0.44**-0.54**)	0.19* (0.15-0.29**)	**0.34**** (0.26**-0.45**)

GS: grey scale; PD: Power Doppler; DAS28(ESR): Disease Activity Score based on 28 joints and ESR; VAS: visual analogue scale; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

0.60) and for PD 0.54 (0.51–0.62) at the six examinations. Moderate to high correlations were also found between changes from baseline in GS/PD tenosynovitis sum scores and joint synovitis scores during the follow-up visits (median (range) correlation coefficients 0.54 (0.29–0.56) /0.52 (0.41–0.63), respectively).

The cross-sectional correlations between US sum scores (tendons, joints and tendon plus joints) and clinical assessments are shown in Table III. Sum scores GS/PD of joints had high correlations with number of swollen joints and the assessor's global VAS, moderate to high correlations with SDAI and CDAI, while GS/PD tenosynovitis sum scores showed lower correlations with these clinical variables. All the US examinations had negligible to low correlations with tender joint count and patient's global VAS. The inclusion of tenosynovitis into the comprehensive joint scores did not improve the correlations with the clinical assessments.

Standardised Response Means

Table IV shows the SRMs for US, clinical and laboratory examinations. During the first three months, the SRMs for tenosynovitis GS sum score were of similar magnitude as the SRMs for joint GS sum score and swollen joint count, and higher than for tender joint count. On the other hand, the SRMs for tenosynovitis PD sum score were of lower magnitude than for tenosynovitis GS sum score. The combination of tendons and joint sum scores (GS or PD) gave only slightly higher SRMs than for joints alone.

Discussion

Tenosynovitis was found to be frequently occurring in the ECU and TP

Table IV. Standardised Response Means of ultrasound, clinical and laboratory variables during follow-up. Sum score tendons includes bilateral score of extensor carpi ulnaris and tibialis posterior tendons; sum score joints includes scores from 36 joints.

	GS sum score tenosynovitis	GS sum score joints	GS sum score tenosynovitis and joints	PD sum score tenosynovitis	PD sum score joints	PD sum score tenosynovitis and joints	28-swollen joint count	28-tender joint count	ESR	CRP
1 month	-0.39	-0.37	-0.42	-0.24	-0.39	-0.40	-0.34	-0.25	-0.43	-0.27
2 months	-0.49	-0.46	-0.50	-0.39	-0.46	-0.48	-0.43	-0.37	-0.55	-0.42
3 months	-0.59	-0.62	-0.66	-0.41	-0.50	-0.51	-0.54	-0.38	-0.50	-0.44
6 months	-0.57	-0.77	-0.78	-0.43	-0.64	-0.65	-0.71	-0.65	-0.62	-0.44
12 months	-0.64	-0.81	-0.83	-0.55	-0.77	-0.78	-0.89	-0.59	-0.60	-0.41

GS: grey scale; PD: Power Doppler; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

tendons in patients with established RA, and the prevalence of pathology was higher in these tendons than in several joints usually included in US scores. Tenosynovitis GS and PD sum scores were found to have similar decrease during bDMARDs treatment as joint GS and PD sum scores as well as commonly used clinical and laboratory assessments. The ECU/TP tenosynovitis score had SRMs comparable to several of the commonly used markers of inflammation, but adding tenosynovitis scores into the presently comprehensive joint score of 36 joints did not increase the correlations with clinical assessments or the SRMs.

Up till now, only few US studies have focused on the response of tenosynovitis to bDMARD treatment (12-14). Our study supports the findings of tenosynovitis and joint synovitis being highly responsive to bDMARD treatment (12-14, 22, 23), and to our knowledge, this is the largest study of patients with established RA comparing the frequency and responsiveness of US tenosynovitis to US of a large number of joints.

Even if the correlations between US sum scores for tenosynovitis and joint scores were high during the study – cross-sectionally and for change scores – the levels of correlation suggest that tendon involvement is showing a complementary aspect of the inflammatory involvement in RA disease. The added information about tendon involvement could thus give an extended picture of the inflammatory condition in RA patients.

There is limited information regarding the development of tenosynovitis in RA patients. In the present study, patients with no US tenosynovitis at baseline had a low prevalence of tenosynovitis at the follow-up examinations, which may indicate that tenosynovitis rarely develops during bDMARD treatment. These findings indicate that when US tenosynovitis is present at baseline, these tendons could be assessed during bDMARD treatment which is also suggested by the recent reduced joint counts for monitoring including both joints and tendons (16, 17). However, examining tendons with normal baseline findings may be of limited value during follow-up.

The strengths of the present study are the high number of RA patients followed longitudinally when initiating effective medication in a real life clinical setting, and that the US examination was performed by a single experienced sonographer with high intra-reader reliability for both joint and tendon scores. A limitation is that only two tendons were assessed bilaterally. However, these two tendons have previously been found to be most frequently involved in RA (12, 13), and they were therefore regarded as representative tendons for exploring tendon pathology. Furthermore, only patients with established RA were included, and this group may have different occurrence of tenosynovitis than early RA, as well as possibly having permanent changes in tendons and tendon sheets that may be seen as GS pathology not improving during treatment (24). In addition, this is a clinical un-blinded, follow-up study, which may have influenced the sensitivity to change. Another limitation is that more than half of the patients were on prednisolone at baseline, and even if the majority was on low doses of prednisolone, it may potentially have reduced the degree of inflammation and thus influenced the results.

Conclusion

The results from the present study contributes to the debate regarding the importance of including tenosynovitis in US scores. Presently tenosynovitis was frequent, sensitive to change and comparable with joint synovitis regarding association with clinical assessments and development of tenosynovitis during treatment was rare.

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