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Original article

Ultrasound-detected tenosynovitis independently associates with patient-reported flare in patients with rheumatoid arthritis in clinical remission: results from the observational study STARTER of the Italian Society for Rheumatology

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Abstract

Objectives. This study aimed to estimate the prevalence of US-detected tenosynovitis in RA patients in clinical remission and to explore its clinical correlates.

Methods. A total of 427 RA patients in clinical remission were consecutively enrolled from 25 Italian rheumatology centres. Tenosynovitis and synovitis were scored by US grey scale (GS) and power Doppler (PD) semi-quantitative scoring systems at wrist and hand joints. Complete clinical assessment was performed by rheumatologists blinded to the US results. A flare questionnaire was used to assess unstable remission (primary outcome), HAQ for functional disability and radiographic erosions for damage (secondary outcomes). Cross-sectional relationships between the presence of each US finding and outcome variables are presented as odds ratios (ORs) and 95% CIs, both crude and adjusted for pre-specified confounders.

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CLINICAL SCIENCE

Results. The prevalence of tenosynovitis in clinical remission was 52.5% (95% CI 0.48, 0.57) for GS and 22.7% (95% CI 0.19, 0.27) for PD, while the prevalence of synovitis was 71.6% (95% CI 0.67, 0.76) for GS and 42% (95% CI 0.37, 0.47) for PD. Among clinical correlates, PD tenosynovitis associated with lower remission duration and morning stiffness while PD synovitis did not. Only PD tenosynovitis showed a significant association with the flare questionnaire [OR 1.95 (95% CI 1.17, 3.26)]. No cross-sectional associations were found with the HAQ. The presence of radiographic erosions associated with GS and PD synovitis but not with tenosynovitis.

Conclusions. US-detected tenosynovitis is a frequent finding in RA patients in clinical remission and associates with unstable remission.

Key words: rheumatoid arthritis, remission, tenosynovitis, ultrasound, flare

Rheumatology key messages

- Ultrasound-detected tenosynovitis is a frequent finding in RA in clinical remission.
- Compared with intra-articular synovitis, active tenosynovitis is more associated with RA patients reporting unstable remission.
- The ultrasonographic assessment of tendon sheaths may help in subsetting RA patients in clinical remission.

Introduction

Remission is the current target of treatment in patients with RA [1]. Nevertheless, the definition of remission in RA is still a matter of debate. Ideally, remission may be defined as a condition characterized by the absence of clinically detectable disease activity, the arrest of radiographic progression and the normalization or maximal improvement of physical function [2]. However, the assessment of remission is frequently a challenge in clinical practice. Subclinical disease activity may be present even if a patient fits the proposed definitions of clinical remission, leading to joint damage progression [3–6] and disease flare [6, 7].

Imaging, in particular musculoskeletal ultrasonography (MSUS), is useful in overcoming the limitations of clinical measures of disease activity [3, 4, 8]. Even in the absence of clinically detectable joint swelling, imaging can reveal synovial effusion and synovial hypertrophy using grey-scale (GS) mode and synovial active inflammation using the power Doppler (PD) technique [5]. Moreover, MSUS is reliable and sensitive to change and can provide diagnostic and prognostic data in terms of risk of flare, disability and anatomical damage progression at different stages of RA [7, 9–11]. For these reasons, several MSUS studies performed in RA patients in clinical remission have focused on assessing subclinical joint synovitis to identify patients with subclinical disease activity. In several studies, the majority of patients in clinical remission showed persistent GS (50–90%) and PD synovitis (40–60%) [10, 12]. Although GS synovitis has been reported to be poorly associated with clinical and radiological outcomes [4, 13], PD occurring in RA patients in clinical remission leads to a clinically meaningful increased risk of flare over time, with odds ratios (ORs) ranging from 3 to 10, suggesting that PD may help in identifying patients with subclinical disease [9, 14]. Furthermore, the association of PD synovitis with future occurrence of disability and structural damage strengthens the plausibility of this association and the validity of such a measure [15]. However, it should be taken into account that RA inflammation may be located not only within the joints, but also at the level of the periarticular synovial structures such as tendon sheaths. Indeed, as well as synovitis, tenosynovitis is a typical manifestation of RA, which associates with pain and erosive evolution in early disease [11, 16], tendon ruptures [16, 17] and disability. In spite of this, very few data are available on both its prevalence in RA patients and its prognostic significance in the subpopulation of RA patients in clinical remission [18, 19]. This lack of information might be partially due to the difficulty in differentiating between articular and tendon swelling by clinical examination. In this context, MSUS may be the best imaging method to characterize tenosynovitis and to evaluate its frequency and prognostic significance in RA patients in clinical remission.

On this basis, the MSUS Study Group of the Italian Society for Rheumatology (SIR) prioritized its research activities on assessment of the prevalence and clinical significance of MSUS-detected tenosynovitis in RA patients in clinical remission, launching a multicentre study, the Sonographic Tenosynovitis Assessment in Rheumatoid Arthritis Patients in Remission (STARTER) study. The objective of this study was to determine the prevalence of US tenosynovitis (and synovitis) at baseline in RA patients in clinical remission and its association with unstable remission, function and damage.

Methods

Patient and study design

This is a cross-sectional analysis of the STARTER study, which is a multicentre observational study promoted by the MSUS Study Group of the SIR and includes 25 Italian rheumatology centres, recruited on voluntary basis. In this context, consecutive patients classified as RA according

to the 1987 ACR criteria or 2010 ACR/EULAR criteria and in clinical remission were recruited between October 2013 and June 2014. Patients were considered eligible if they met at least one of the following remission criteria at the screening visit: 28-joint DAS (DAS28) < 2.6 [20], Simplified Disease Activity Index (SDAI) $\leqslant 3.3$ [21], Clinical Disease Activity Index (CDAI) $\leqslant 2.8$ [22], ACR/EULAR Boolean definition [21], absence of swollen/tender joints on 28 joints [23] or remission based on clinical evaluation of an expert rheumatologist [3]. All patients underwent a complete clinical assessment and an MSUS examination.

The STARTER study was approved by the local ethics committee for each of the participating sites. Written informed consent was obtained from all participants. This analysis did not require separate ethical approval.

Clinical assessment

For each patient, complete demographic (age, sex, type of occupational activity, smoking habit), anamnestic (date of RA onset and diagnosis, disease and remission duration, co-morbidities, previous and current therapy for RA) and clinimetric [weight and height, the Italian version of the HAQ [24], flare questionnaire (FQ) [25, 26], duration of morning stiffness, visual analogue scale (VAS) for joint pain, physician global assessment, patient global assessment and global health] data were collected; laboratory data such as ESR, CRP, RF and ACPA positivity and titres were recorded. In addition, a standard 28-joint count was performed. Plain radiographs of the hands, wrists and feet were also collected. The clinical assessment was performed by a clinical rheumatologist at each centre who was blinded to the US results.

Outcome measures

Unstable remission disease was set as the primary outcome of the analysis and defined according to the FQ value over its median value (3) in our study sample. Secondary outcomes included functional disability, evaluated by the Italian version of the HAQ score >0.5 [27], and bone damage, defined as the presence of typical bone erosions at baseline radiographs as reported by the investigator.

Ultrasonographic assessment

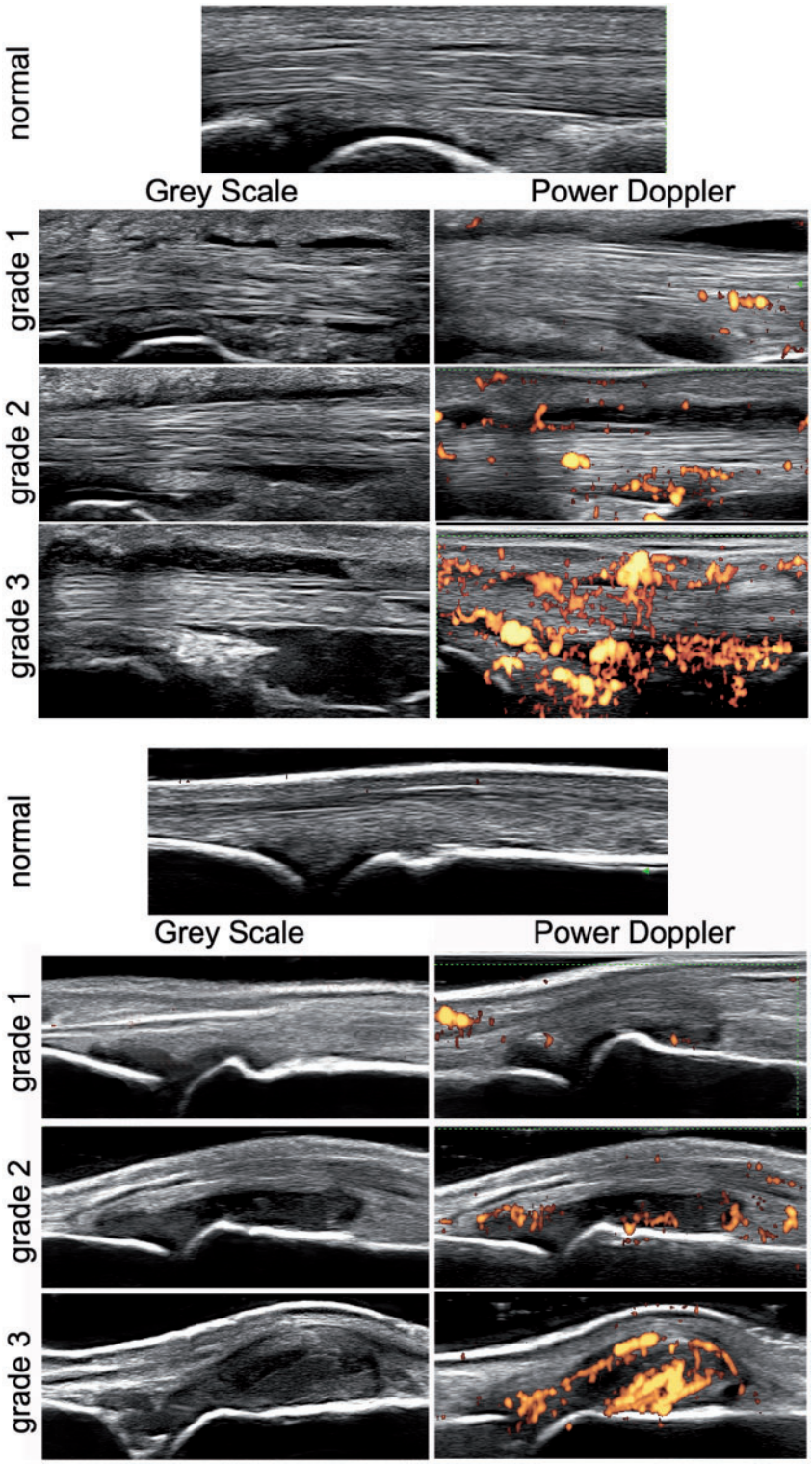
All ultrasonographers participating in the study were experts in MSUS and were selected on the basis of an inter- and intra-observer reliability exercise against a reference standard (AI) on static images using an e-learning platform. Only ultrasonographers for whom the results of the reliability assessment were from good to excellent (weighted $\kappa \geqslant 0.7$) [28] were allowed to participate in the study. In addition, the equipment level available at the different sites was assessed and only high-level US machines (MyLab 70XVG, MyLab Twice, Logiq9, LogiqE9) with high-frequency linear probes (14–18 MHz) were allowed. High-level US machines were provided by Esaote (Genoa, Italy) to those investigators who passed the reliability exercise test but who did not have an adequate US machine at their site. MSUS examination was performed according to the EULAR guidelines [29]. In each rheumatology unit, the MSUS evaluations were performed by a single rheumatologist expert in MSUS who was blinded to the clinical data.

The MSUS tendon scanning protocol included multiplanar longitudinal and transverse scanning of flexor and extensor tendon sheaths of the wrist and fingers bilaterally and longitudinal scanning of the dorsal aspect of the wrist (radiocarpal and mid-carpal joint) with joints in a neutral position. Specifically, extensor tendons of the wrist were examined from the Lister's tubercle to the metacarpal bones. Flexor tendons at the wrist were examined from the proximal edge of the carpal tunnel to the palm of the hand, while the flexor radialis carpi tendon was examined in its pre-insertional and insertional tract where the synovial sheath is present. Flexor digitorum tendons and flexor pollicis longus tendon were examined from the palm of the hand to the distal phalanx. The MSUS joint scanning protocol included multiplanar longitudinal scanning of the dorsal aspects of the MCP joints bilaterally and longitudinal scanning of the palmar aspects of the PIP joints bilaterally. Tenosynovitis, joint effusion and synovial hypertrophy were identified according to OMERACT definitions [30]. In particular, tenosynovitis was defined as the presence of hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit PD signal [30].

Synovial and tenosynovial PD were evaluated by selecting a region of interest that included the bony margins, joint space and a variable view of surrounding tissues, using abundant US gel to avoid pressure on the tissues. US machine settings were adjusted to the lowest permissible pulse repetition frequency (500–750 Hz) to maximize sensitivity. Doppler frequency was set high (7.5–14.3 MHz) to optimize the detection of flow at the level of small joints and superficial tissues. Colour gain was set just below the level that caused the appearance of noise artefacts. In all findings, flow was confirmed in two perpendicular planes.

GS tenosynovitis was semi-quantitatively scored from 0 to 3 (0 = normal; 1 = mild; 2 = moderate; 3 = marked); PD tenosynovitis signal was also assessed using a 0–3 semi-quantitative score (0 = absence or minimal flow; 1 = mild: single vessel signal; 2 = moderate: confluent vessels; 3 = marked: vessel signals in >50% of the tenosynovial tissue) [31]. US-detected synovitis and joint effusion were scored together according to a 0–3 semi-quantitative simplified score [32] and PD synovitis was also semi-quantitatively graded from 0 to 3, as previously reported (Fig. 1) [33]. At the end of each US exam, total scores for GS tenosynovitis, PD tenosynovitis, GS synovitis and PD synovitis were calculated by summing the scores detected at different sites. We defined GS tenosynovitis remission as a total score in GS tenosynovitis of 0, PD tenosynovitis remission as a total score in PD tenosynovitis of 0, GS synovitis remission as a total score in GS synovitis of 0 and PD synovitis remission as a total score in PD synovitis of 0. Representative scan images of each MSUS exam were recorded.

Fig. 1 US scoring system



Scoring of tenosynovitis (panel A: finger flexor at the MCP joint) and synovitis (panel B: dorsal aspect of the MCP joint). Images provided by Georgios Filippou.

Statistical analysis

The prevalence of tenosynovitis was evaluated on the basis of different remission criteria and presented with its corresponding exact 95% CI. The association between demographic, clinical, serological and treatment variables was explored by the chi-square or Wilcoxon test based on the variable type and distribution and correlation using Spearman's ρ coefficient.

The cross-sectional relationship between the presence of GS tenosynovitis/synovitis, PD tenosynovitis/synovitis and outcome variables (FQ positivity, HAQ score and erosive damage) were evaluated by logistic models and presented as ORs and 95% CIs, both crude and adjusted for pre-specified confounders, coded as follows: age (quartiles: 18–47, 48–56, 57–65, ⩾66 years), sex (categorical), disease duration (quartiles: 0–3.99, 4–7.49, 7.5–13.49, ⩾13.5 years), remission duration (0–7.9, 8–11.9, 12–23.9, ⩾24 months), musculoskeletal co-morbidities (dichotomous), RF (dichotomous), ACPA (dichotomous), concurrent DMARDs (dichotomous), biologics (dichotomous), NSAIDs (dichotomous) and systemic and locally injected glucocorticoids (dichotomous) [14, 18, 34–37].

Study data were collected and managed using Research Electronic Data Capture. Research Electronic Data Capture is a free, secure, Web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless and anonymous data downloads to common statistical packages and procedures for importing data from external sources [38]. Analyses were performed using STATA software (2009, release 11; StataCorp, College Station, TX, USA).

Results

Participants and descriptive data

A total of 427 patients were included in the analysis: complete history, clinical, clinimetric and serological characteristics of the study population are described in Table 1. Median disease duration was 7.32 years [interquartile range (IQR) 3.8–13.48] and median remission duration was 12 months (IQR 8–24). A total of 283 patients (68.52%) were in DAS28 remission, 281 patients (65.81%) were in CDAI remission, 288 patients (67.76%) were in SDAI remission and 234 patients (54.8%) fulfilled the ACR/EULAR remission criteria.

Prevalence of tenosynovitis in clinical remission

GS tenosynovitis remission was present in 203 patients [47.5% (95% CI 0.43, 0.52)] and PD tenosynovitis remission was present in 330 patients [77.3% (95% CI 0.73, 0.81)], while GS synovitis remission was present in 121 patients [28.4% (95% CI 0.24, 0.33)] and PD synovitis remission in 247 patients [57.9% (95% CI 0.53, 0.63)]. A total of 78% of patients in DAS28 remission were in PD tenosynovitis remission and 49% were in GS tenosynovitis remission (Table 2). No significant differences were found in the proportion of patients in remission according to MSUS variables within other clinical remission criteria (CDAI, SDAI and ACR/EULAR Boolean definition). The details of the distribution of MSUS variables are reported in supplementary Table S1 and Fig. S1, available at *Rheumatology* Online.

Regarding MSUS synovitis, 58% of patients in DAS28 remission and 62% of patients in remission as per the ACR/EULAR Boolean definition were in PD synovitis remission; 29% of patients in DAS28 remission and 32% of patients in remission as per the ACR/EULAR definition were in GS synovitis remission (Table 2). Concerning GS tenosynovitis/PD tenosynovitis, the involvement of the sixth extensor tendon compartment of the wrist bilaterally was most commonly observed, while GS synovitis/PD synovitis was mostly found at wrist and second and third MCP joints bilaterally, with a predominance of right side involvement. Other common sites of GS

Table 1 Summary of patients' characteristics (n = 427)

Sex, male, n (%)	113 (26.46)
Age, mean (S.D.), years	56.61 (13.39)
Occupation, n (%)	
No occupation	165 (38.64)
Manual work	123 (28.81)
Not manual work	139 (32.55)
BMI, mean (S.D.)	24.55 (4.09)
Smoke, n (%)	
Never	239 (56.10)
Ex-smokers	112 (26.29)
Smokers	75 (17.61)
Disease duration, years, median (IQR)	7.32 (3.8–13.48)
Remission duration, months, median (IQR)	12 (8–24)
RA extra-articular manifestation, n (%)	122 (28.57)
Musculoskeletal co-morbidities, n (%)	
FM	14 (3.28)
OA	90 (21.08)
Microcrystalline arthropathy	3 (0.70)
Ongoing DMARD therapy, n (%)[a]	322 (75.41)
Ongoing biologic therapy, n (%)[b]	183 (42.86)
Ongoing corticosteroid therapy, n (%)	187 (43.79)
Steroid infiltration in the last month, n (%)	7 (1.64)
NSAIDs, n (%)	
On-demand	237 (55.5)
Continuous	6 (1.41)
RF, n (%)	
Negative	139 (32.63)
Positive	287 (67.37)
ACPA, n (%)	
Negative	142 (33.41)
Positive	283 (66.58)
Erosive RA, n (%)	232 (54.59)
ESR, mean (S.D.)	15.66 (13.54)
Negative CRP, n (%)[c]	362 (85.18)
Flare questionnaire score, median (IQR)	3 (0–15)
HAQ, median (IQR)	0.125 (0–0.375)
Tender joints, median (IQR)	0 (0–1)
Swollen joints, median (IQR)	0 (0–0)
DAS28, mean (S.D.)	2.24 (0.85)
Morning stiffness, minutes, mean (S.D.)	7.42 (14.68)
CDAI, mean (S.D.)	2.60 (2.98)
SDAI, mean (S.D.)	2.96 (3.67)

[a]MTX, LEF, SSZ, HCQ, ciclosporin and gold salts. [b]TNF-α inhibitors, rituximab, abatacept and tocilizumab. [c]CRP under site-specific cut-off.

Table 2 Prevalence of US remission in patients in clinical remission

MSUS remission	DAS28 remission	CDAI remission	SDAI remission	ACR/EULAR remission	Clinical remission[a]
PD tenosynovitis remission	0.78 (0.73, 0.83)	0.79 (0.73, 0.83)	0.78 (0.73, 0.83)	0.79 (0.73, 0.84)	0.81 (0.76, 0.86)
GS tenosynovitis remission	0.49 (0.43, 0.55)	0.51 (0.45, 0.57)	0.5 (0.44, 0.56)	0.51 (0.44, 0.57)	0.55 (0.48, 0.61)
PD synovitis remission	0.58 (0.52, 0.63)	0.62 (0.56, 0.68)	0.61 (0.55, 0.67)	0.62 (0.55, 0.68)	0.65 (0.59, 0.71)
GS synovitis remission	0.29 (0.24, 0.35)	0.33 (0.27, 0.39)	0.32 (0.26, 0.37)	0.32 (0.26, 0.38)	0.34 (0.29, 0.41)

Values are presented as prevalence (95% CI). [a]Clinical remission: absence of swollen/tender joints on 28 joints.

Table 3 Clinical correlates of MSUS tenosynovitis

	Power Doppler			Grey scale		
Variable	Negative (n = 330)	Positive (n = 97)	P-value	Negative (n = 203)	Positive (n = 224)	P-value
Sex, male, n (%)	82 (24.85)	31 (31.96)	0.163	56 (27.59)	57 (25.45)	0.617
Age, mean (S.D.), years	56.37 (13.76)	57.4 (12.1)	0.508	54.93 (14.05)	58.13 (12.61)	0.014
BMI, mean (S.D.)	24.27 (3.99)	25.51 (4.3)	0.013	24.23 (4.17)	24.85 (4)	0.142
Smoke, n (%)						
Never	188 (56.97)	51 (53.12)	0.459	110 (54.46)	129 (57.59)	0.556
Ex-smokers	88 (26.67)	24 (25)		58 (28.71)	54 (24.11)	
Smokers	54 (16.36)	21 (21.88)		34 (16.83)	41 (18.30)	
Occupation, n (%)						
No occupation	128 (38.79)	37 (38.14)	0.967	75 (36.95)	90 (40.18)	0.258
Manual work	94 (28.48)	29 (29.90)		54 (26.60)	69 (30.80)	
Not manual work	108 (32.73)	31 (31.96)		74 (36.45)	65 (29.02)	
Disease duration, median (IQR), years	7.55 (3.91–13.2)	6.39 (3.58–13.86)	0.683	7.06 (3.79–13.2)	7.66 (3.91–13.79)	0.437
Remission duration >12 months, n (%)	168 (50.91)	30 (30.93)	0.001	107 (52.71)	91 (40.63)	0.015
Ongoing DMARDS therapy, n (%)[a]	246 (74.55)	76 (78.35)	0.444	152 (74.88)	170 (75.89)	0.808
Ongoing biologic therapy, n (%)[b]	140 (42.42)	43 (44.33)	0.739	85 (41.87)	98 (43.75)	0.695
Ongoing corticosteroid therapy, n (%)	141 (42.73)	46 (47.42)	0.413	84 (41.38)	103 (45.98)	0.338
Steroid infiltration in the last month, n (%)	5 (1.52)	2 (2.06)	0.712	5 (2.48)	2 (0.89)	0.2
NSAIDs, n (%)						
On demand	176 (53.33)	61 (62.89)	0.248	110 (54.19)	127 (56.7)	0.645
Continuous	5 (1.52)	1 (1.03)		2 (0.99)	4 (1.79)	
RF, n (%)						
Negative	125 (37.99)	14 (14.43)	<0.001	72 (35.64)	67 (29.91)	0.164
Negative, but positive in the past	38 (11.55)	7 (7.22)		16 (7.92)	29 (12.95)	
Positive	166 (50.46)	76 (78.35)		114 (56.44)	128 (57.14)	
ACPA, n (%)						
Negative	122 (37.20)	20 (20.62)	0.004	67 (33.17)	75 (33.63)	0.755
Negative, but positive in the past	31 (9.45)	7 (7.22)		16 (7.92)	22 (9.87)	
Positive	175 (53.35)	70 (72.16)		119 (58.91)	126 (56.50)	
Erosive RA, n (%)	176 (53.66)	56 (57.73)	0.479	105 (51.98)	127 (56.95)	0.304
ESR, mean (S.D.)	15.77 (14.05)	15.29 (11.79)	0.871	16.92 (15.31)	14.53 (11.65)	0.192
Negative CRP, n (%)[c]	284 (86.59)	78 (80.41)	0.133	171 (85.07)	191 (85.27)	0.955
Flare questionnaire score, median (IQR)	2 (0–14)	7 (0–17)	0.017	2 (0–19)	3 (0–13)	0.717
HAQ, median (IQR)	0.125 (0–0.375)	0.125 (0–0.5)	0.167	0.125 (0–0.375)	0.125 (0–0.375)	0.473
Tender joints, median (IQR)	0 (0–1)	0 (0–1)	0.189	0 (0–0)	0 (0–1)	0.058
Swollen joints, median (IQR)	0 (0–0)	0 (0–1)	0.017	0 (0–0)	0 (0–1)	0.003
DAS28, mean (S.D.)	2.21 (0.87)	2.33 (0.78)	0.23	2.21 (0.89)	2.27 (0.82)	0.54
CDAI, mean (S.D.)	2.49 (2.87)	3 (3.29)	0.089	2.35 (3.12)	2.83 (0.83)	0.002
SDAI, mean (S.D.)	2.89 (3.77)	3.22 (3.32)	0.163	2.63 (3.3)	3.26 (3.96)	0.003

[a]MTX, LEF, SSZ, HCQ, ciclosporin and gold salts. [b]TNF-α inhibitors, rituximab, abatacept and tocilizumab. [c]CRP under cut-off.

tenosynovitis/PD tenosynovitis detection were the fourth extensor tendon compartment of the wrist bilaterally, the flexor tendons of the second finger bilaterally and the flexor tendons of the third and fourth fingers of the right hand (supplementary Tables S2 and S3, available at *Rheumatology* Online).

Clinical correlates of US tenosynovitis and US synovitis

As shown in Table 3, shorter remission duration and higher swollen joint count were significantly and positively associated with PD and GS tenosynovitis. Higher BMI, RF

positivity, ACPA positivity and FQ score were significantly and positively associated with PD tenosynovitis, while a significant positive association was found between GS tenosynovitis and older age, higher CDAI and higher SDAI scores.

Similar results were found also for PD and GS synovitis, which were significantly and positively associated with corticosteroid therapy, RF and ACPA positivity, erosive RA, higher swollen joint count and higher CDAI and SDAI scores (Table 4). Also, GS synovitis was significantly and positively associated with male sex, older age and shorter remission duration. Analysing clinical correlates of MSUS variables as continuous variables, morning stiffness was significantly associated with PD tenosynovitis ($\rho = 0.29$, $P < 0.05$), while PD synovitis did not ($\rho = -0.01$, $P > 0.05$).

Cross-sectional associations of US tenosynovitis and US synovitis with FQ, function and damage

Exploring associations of MSUS variables with potentially relevant outcome, tenosynovitis associated with FQ score, with a 2-fold higher probability of having a higher score in patients with the presence of PD tenosynovitis, even after adjustment for pre-specified confounders. No significant associations were found for GS tenosynovitis and synovitis, both PD and GS (Table 5).

Neither tenosynovitis nor synovitis US variables showed any significant association with the presence of at least mild functional disability, as measured by the HAQ. Similar results were obtained restricting the sample to short remission duration (<12 months) and to active workers. The presence of radiographic erosions showed a significant association with synovial MSUS variables, both GS and PD synovitis, particularly GS synovitis, which showed a 2-fold increase of the probability of erosive disease, still significant even after adjusting for the full set of confounders.

Discussion

This multicentre study was designed to evaluate the prevalence of US-detected tenosynovitis in RA patients in clinical remission and to evaluate its clinical correlates and its association with the risk of flare, worsening of functional disability and damage. Although tenosynovitis is recognized as a typical extra-articular RA manifestation, few data are present in the literature on its real prevalence, and the published data on its prognostic significance in RA patients in clinical remission are even more limited [39, 40].

The diagnostic and prognostic value of US-detected articular synovitis have been demonstrated in the last few years. In particular, in the subpopulation of RA patients in clinical remission, great effort was made in defining the prognostic significance of ongoing PD-positive synovitis, leading to the conclusion that the definition of remission status should be reserved for patients who are both in a state of clinical remission defined by clinimetric indexes and show the absence of synovitis on imaging studies [8]. In this regard, the STARTER study contributes in better defining imaging remission, studying for the first time systematically US-detected tenosynovitis of the hand and wrist joints of RA patients in clinical remission.

The results of these analyses confirm the potential role of US tenosynovial-targeted assessment in RA patients in clinical remission. To the best of our knowledge, STARTER is one of the largest cohorts of RA patients in clinical remission assessed by MSUS ever reported, including 427 patients. In our study sample we found a significant proportion of patients with the presence of GS tenosynovitis (52.5%) and PD tenosynovitis (22.7%), while the prevalence of GS synovitis (71.6%) and PD synovitis (42%) were in agreement with previous studies [10, 12].

The lower prevalence of tenosynovitis makes this US feature a possibly more specific tool to identify subclinical inflammation compared with US synovitis. Indeed, although PD synovitis is very sensitive in predicting short-term flare, it has a low positive predictive value: a large number of RA patients in clinical remission with PD synovitis do not relapse, mainly in long-standing disease [36]. The results of our study suggest that PD tenosynovitis could be more specific than PD synovitis in identifying patients with ongoing active disease and unstable clinical remission, as that was the only US variable significantly associated with FQ.

Furthermore, the combined synovial and tenosynovial US assessment could be useful to stratify patients according to the type and site of subclinical inflammation. In fact, in our population, PD tenosynovitis significantly correlated with two patient-reported outcomes (morning stiffness and FQ), while synovial US findings did not: in this context, tenosynovial involvement could explain symptoms of the subpopulation of RA patients in clinical remission characterized by mild relapses and unstable remission but not associated with severe RA in terms of disability or damage. On the other hand, our study confirms the association between erosions and the presence of subclinical US synovitis, in both the GS and PD modes.

Among the multiple and somehow predictable associations between clinical factors and US-detected tenosynovitis and synovitis, one of the most interesting refers to RF and ACPA. The association between RF positivity and clinical tenosynovitis was already evidenced in a previous study [41]. In our research we found a strong association between PD tenosynovitis/synovitis and RF and ACPA positivity, while this association was lacking for GS tenosynovitis and was even weaker for GS synovitis. Given the well-established prognostic value of RF and ACPA in RA patients, their association with imaging disease activity indexes suggests a link between these risk factors and a higher risk of subclinical active disease.

The results of the present study should be interpreted in consideration of certain limitations. In this phase the study had a cross-sectional design, making it impossible to draw any conclusions in terms of prognosis. Prospective results from this study will answer this question. Patients were consecutively—not randomly—enrolled in rheumatology clinics with expertise in US, potentially introducing a selection bias. Our cohort was apparently a

TABLE 4 Clinical correlates of MSUS synovitis

Variable	Power Doppler			Grey-scale		
	Negative (n = 247)	Positive (n = 179)	P-values	Negative (n = 121)	Positive (n = 305)	P-values
Sex, male, n (%)	59 (23.89)	54 (30.17)	0.147	23 (19.01)	90 (29.51)	0.027
Age, mean (S.D.), years	56.26 (14.16)	57.23 (12.15)	0.46	54.63 (14.01)	57.87(12.9)	0.003
BMI, mean (S.D.)	24.48 (3.99)	24.67 (4.23)	0.619	24.19 (4.09)	24.71 (4.08)	0.141
Smoke, n (%)						
Never	137 (55.69)	102 (56.98)	0.746	65 (54.17)	174 (57.05)	0.674
Ex-smokers	68 (27.64)	44 (24.58)		31 (25.83)	81 (26.56)	
Smokers	41 (16.67)	33 (18.44)		24 (20)	50 (16.39)	
Occupation, n (%)						
No occupation	101 (40.89)	64 (35.75)	0.556	42 (34.71)	123 (40.33)	0.015
Manual work	69 (27.94)	53 (29.61)		27 (22.31)	95 (31.15)	
Not manual work	77 (31.17)	62 (34.64)		52 (42.98)	87 (28.52)	
Disease duration, median (IQR), years	7.12 (3.61–12.38)	7.88 (4.21–14.99)	0.183	6.81 (3.61–11.44)	7.95 (4.10–13.87)	0.144
Remission duration >12 months, n(%)	121 (48.99)	77 (43.02)	0.238	68 (56.20)	130 (42.62)	0.013
Ongoing DMARD therapy, n (%)[a]	179 (72.47)	142 (79.33)	0.105	87 (71.90)	234 (76.72)	0.298
Ongoing biologic therapy, n (%)[b]	115 (46.56)	68 (37.99)	0.078	51 (42.15)	132 (43.28)	0.832
Ongoing corticosteroid therapy, n (%)	92 (37.25)	95 (53.07)	0.001	35 (28.93)	152 (49.84)	<0.001
Steroid infiltration in the last month, n (%)	2 (0.81)	5 (2.79)	0.113	2 (1.67)	5 (1.64)	0.984
NSAIDs, n (%)						
On demand	132 (53.44)	104 (58.10)	0.604	71 (58.68)	165 (54.10)	0.601
Continuous	4 (1.62)	2 (1.12)		1 (0.83)	5 (1.64)	
RF, n (%)						
Negative	93 (37.80)	46 (25.70)	0.002	47 (38.84)	92 (30.26)	0.037
Negative, but positive in the past	31 (12.60)	14 (7.82)		17 (14.05)	28 (9.21)	
Positive	122 (49.59)	119 (66.48)		57 (47.11)	184 (60.53)	
ACPA, n (%)						
Negative	93 (37.80)	48 (26.97)	0.019	53 (44.17)	88 (28.95)	0.006
Negative, but positive in the past	25 (10.16)	13 (7.30)		12 (10)	26 (8.55)	
Positive	128 (52.03)	117 (65.73)		55 (45.83)	190 (62.50)	
Erosive RA, n (%)	123 (50.20)	108 (60.34)	0.039	47 (39.17)	184 (60.53)	<0.001
ESR, mean (S.D.)	16.1 (13.96)	15.1 (13.02)	0.527	17.11 (14.7)	15.09 (13.05)	0.15
Negative CRP, n (%)[c]	209 (85.31)	153 (85.47)	0.961	101 (84.87)	261 (85.57)	0.855
Flare questionnaire score, median (IQR)	2 (0–15)	4 (0–15)	0.459	3 (0–12)	3 (0–16.5)	0.519
HAQ, median (IQR)	0.125 (0–0.375)	0.125 (0–0.375)	0.431	0.125 (0–0.375)	0.125 (0–0.375)	0.564
Tender joints, median (IQR)	0 (0–0)	0 (0–1)	0.078	0 (0–0)	0 (0–1)	0.286
Swollen joints, median (IQR)	0 (0–0)	0 (0–1)	<0.001	0 (0–0)	0 (0–0)	<0.001
DAS28, mean (S.D.)	2.19 (0.88)	2.3 (0.79)	0.19	2.23 (0.82)	2.24 (0.85)	0.931
CDAI, mean (S.D.)	2.18 (2.51)	3.1 (3.24)	<0.001	1.87 (2.37)	2.84 (3.01)	<0.001
SDAI, mean (S.D.)	2.65 (3.75)	3.29 (3.25)	0.002	2.12 (2.53)	3.23 (3.84)	<0.001

[a]MTX, LEF, SSZ, HCQ, ciclosporin and gold salts. [b]TNF-α inhibitors, rituximab, abatacept and tocilizumab. [c]CRP under cut-off.

homogeneous cohort of RA patients in clinical remission, as it included patients in remission according to different criteria and under different treatments. To handle this variability, an adequate sample size was planned. Given the multisite nature of our study, there was the risk of differences in MSUS and clinical assessment leading to highly inhomogeneous data collection. To overcome this drawback, ultrasonographers were trained and then selected by an interobserver reliability exercise that showed a high reliability rate. Also, guidelines with specific instructions on how to perform a correct clinical assessment as per the protocol were distributed to the clinical rheumatologists. The residual methodological heterogeneity might limit the precision of the results, but it is unlikely that it biases the results, supporting the generalizability of the conclusions. As well as several previous imaging studies on tenosynovitis, our scanning protocol included only hands and wrists [16–18, 42–44], excluding some potentially relevant structures in RA, such as, for example, the tibialis posterior tendon [45, 46]. This might decrease the sensitivity of our US assessment, but did not threaten the validity of our results, and clearly increased the feasibility of a large sample study and transferability into practice. Finally, the FQ instrument was used as an outcome

TABLE 5 Cross-sectional associations of US tenosynovitis and US synovitis with flare, function and damage

US finding	Flare questionnaire ⩾3		HAQ >0.5		X-ray erosions	
	OR crude	OR adjusted[a]	OR crude	OR adjusted[a]	OR crude	OR adjusted[a]
Tenosynovitis						
PD positive *vs* PD remission	**2.1 (1.31, 3.37)****	**1.95 (1.17, 3.26)***	1.05 (0.59, 1.87)	1.19 (0.62, 2.28)	1.18 (0.75, 1.86)	0.91 (0.54, 1.53)
GS positive *vs* GS remission	1.24 (0.85, 1.82)	1.13 (0.75, 1.70)	0.81 (0.5, 1.31)	0.61 (0.35, 1.05)	1.22 (0.83, 1.79)	1.13 (0.74, 1.75)
Synovitis						
PD positive *vs* PD remission	1.36 (0.92, 2)	1.14 (0.75, 1.75)	1.09 (0.67, 1.78)	1.28 (0.73, 2.26)	**1.51 (1.02, 2.23)***	1.28 (0.81, 2.02)
GS positive *vs* GS remission	1 (0.65, 1.52)	0.82 (0.51, 1.33)	1.24 (0.71, 2.16)	1.01 (0.53, 1.92)	**2.38 (1.55, 3.67)*****	**1.96 (1.18, 3.25)****

[a]Adjusted for age, sex, disease duration, remission duration, musculoskeletal co-morbidities, RF, ACPA, concurrent DMARDs, biologics and NSAIDs and systemic and locally injected glucocorticoids. Values in bold are statistically significant. *$P < 0.05$. **$P < 0.01$, ***$P < 0.001$.

measure, although this questionnaire was still not fully validated and there were no fully validated references for interpreting the FQ [26]. The FQ was developed to identify past or present RA flare, so it describes unstable remission in a setting of cross-sectional evaluation.

Despite these limitations the results of the STARTER study indicate that US-detected tenosynovitis could be a useful tool for rheumatologists to better define remission as well as a subset of RA patients in clinical remission. Tenosynovitis-targeted US evaluation should be a part of the assessment of RA patients in clinical remission.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Smolen JS, Aletaha D, Bijlsma JWJ *et al*. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631–7.

2 Felson D. Defining remission in rheumatoid arthritis. Ann Rheum Dis 2012;71(Suppl 2):i86–8.

3 Brown AK, Conaghan PG, Karim Z *et al*. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58:2958–67.

4 Brown AK, Quinn MA, Karim Z *et al*. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum 2006;54:3761–73.

5 Saleem B, Brown AK, Keen H *et al*. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Ann Rheum Dis 2011;70:792–8.

6 Sakellariou G, Scirè CA, Verstappen SMM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Ann Rheum Dis 2013;72:245–9.

7 Foltz V, Gandjbakhch F, Etchepare F *et al*. Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. Arthritis Rheum 2012;64:67–76.

8 Wakefield RJ, D'Agostino MA, Naredo E *et al*. After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? Ann Rheum Dis 2012;71:799–803.

9 Scirè CA, Montecucco C, Codullo V *et al*. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology (Oxford) 2009;48:1092–7.

10 Ten Cate DF, Luime JJ, Swen N *et al*. Role of ultrasonography in diagnosing early rheumatoid arthritis and remission of rheumatoid arthritis—a systematic review of the literature. Arthritis Res Ther 2013;15:R4.

11 Baillet A, Gaujoux-Viala C, Mouterde G *et al*. Comparison of the efficacy of sonography, magnetic resonance imaging and conventional radiography for the detection of bone erosions in rheumatoid arthritis patients: a systematic review and meta-analysis. Rheumatology (Oxford) 2011;50:1137–47.

12 Nguyen H, Ruyssen-Witrand A, Gandjbakhch F *et al*. Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: a systematic review and meta-analysis. Rheumatology (Oxford) 2014;53:2110–8.

13 Scire CA, Montecucco C, Codullo V *et al*. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology 2009;48:1092–7.

14 Saleem B, Brown AK, Quinn M *et al*. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis 2012;71:1316–21.

15 Fukae J, Tanimura K, Atsumi T, Koike T. Sonographic synovial vascularity of synovitis in rheumatoid arthritis. Rheumatology (Oxford) 2014;53:586–91.

16 Lillegraven S, Bøyesen P, Hammer HB *et al*. Tenosynovitis of the extensor carpi ulnaris tendon predicts erosive progression in early rheumatoid arthritis. Ann Rheum Dis 2011;70:2049–50.

17 McQueen F, Beckley V, Crabbe J *et al*. Magnetic resonance imaging evidence of tendinopathy in early rheumatoid arthritis predicts tendon rupture at six years. Arthritis Rheum 2005;52:744–51.

18 Zayat AS, Conaghan PG, Sharif M *et al*. Do non-steroidal anti-inflammatory drugs have a significant effect on detection and grading of ultrasound-detected synovitis in patients with rheumatoid arthritis? Results from a randomised study. Ann Rheum Dis 2011;70:1746–51.

19 Hammer HB, Kvien TK. Ultrasonography shows significant improvement in wrist and ankle tenosynovitis in rheumatoid arthritis patients treated with adalimumab. Scand J Rheumatol 2011;40:178–82.

20 Prevoo ML, van 't Hof MA, Kuper HH *et al*. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.

21 Felson DT, Smolen JS, Wells G *et al*. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404–13.

22 Smolen JS, Breedveld FC, Schiff MH *et al*. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42:244–57.

23 Scirè CA, Lunt M, Marshall T, Symmons DPM, Verstappen SMM. Early remission is associated with improved survival in patients with inflammatory polyarthritis: results from the Norfolk Arthritis Register. Ann Rheum Dis 2014;73:1677–82.

24 Ranza R, Marchesoni A, Calori G *et al*. The Italian version of the Functional Disability Index of the Health Assessment Questionnaire. A reliable instrument for multicenter studies on rheumatoid arthritis. Clin Exp Rheumatol 1993;11:123–8.

25 Berthelot J-M, De Bandt M, Morel J *et al*. A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the 'FLARE' instrument. Ann Rheum Dis 2012;71:1110–6.

26 de Thurah A, Maribo T, Stengaard-Pedersen K. Patient self-assessment of flare in rheumatoid arthritis: criterion and concurrent validity of the Flare instrument. Clin Rheumatol 2016;35:467–71.

27 Krishnan E, Sokka T, Häkkinen A, Hubert H, Hannonen P. Normative values for the Health Assessment Questionnaire disability index: benchmarking disability in the general population. Arthritis Rheum 2004;50:953–60.

28 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.

29 Backhaus M, Burmester GR, Gerber T *et al*. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis 2001;60:641–9.

30 Wakefield RJ, Balint PV, Szkudlarek M *et al*. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 2005;32:2485–7.

31 Naredo E, D'Agostino MA, Wakefield RJ *et al*. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Ann Rheum Dis 2013;72:1328–34.

32 Scheel AK, Hermann K-GA, Kahler E *et al*. A novel ultrasonographic synovitis scoring system suitable for analyzing finger joint inflammation in rheumatoid arthritis. Arthritis Rheum 2005;52:733–43.

33 Szkudlarek M, Court-Payen M, Jacobsen S *et al*. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum 2003;48:955–62.

34 Saleem B, Brown AK, Keen H *et al*. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: a clinical and imaging comparative study. Arthritis Rheum 2009;60:1915–22.

35 van der Woude D, Young A, Jayakumar K *et al*. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. Arthritis Rheum 2009;60:2262–71.

36 Peluso G, Michelutti A, Bosello S *et al*. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis 2011;70:172–5.

37 Montecucco C, Todoerti M, Sakellariou G, Scirè CA, Caporali R. Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study. Arthritis Res Ther 2012;14:R112.

38 Harris PA, Taylor R, Thielke R *et al*. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.

39 Balsa A, de Miguel E, Castillo C, Peiteado D, Martín-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology (Oxford) 2010;49:683–90.

40 Filippucci E, Gabba A, Di Geso L *et al*. Hand tendon involvement in rheumatoid arthritis: an ultrasound study. Semin Arthritis Rheum 2012;41:752–60.

41 Suzuki T, Tohda E, Ishihara K. Power Doppler ultrasonography of symptomatic rheumatoid arthritis ankles revealed a positive association between tenosynovitis and rheumatoid factor. Mod Rheumatol 2009;19:235–44.

42 Schirmer C, Scheel AK, Althoff CE *et al*. Diagnostic quality and scoring of synovitis, tenosynovitis and erosions in low-field MRI of patients with rheumatoid arthritis: a comparison with conventional MRI. Ann Rheum Dis 2007;66:522–9.

43 Eshed I, Feist E, Althoff CE *et al*. Tenosynovitis of the flexor tendons of the hand detected by MRI: an early indicator of rheumatoid arthritis. Rheumatology (Oxford) 2009;48:887–91.

44 Freeston JE, Wakefield RJ, Conaghan PG *et al*. A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. Ann Rheum Dis 2010;69:417–9.

45 Aga A-B, Hammer HB, Olsen IC *et al*. First step in the development of an ultrasound joint inflammation score for rheumatoid arthritis using a data-driven approach. Ann Rheum Dis 2015; doi:10.1136/annrheumdis-2015-207572.

46 Barn R, Turner DE, Rafferty D, Sturrock RD, Woodburn J. Tibialis posterior tenosynovitis and associated pes plano valgus in rheumatoid arthritis: electromyography, multisegment foot kinematics, and ultrasound features. Arthritis Care Res 2013;65:495–502.