The relationship of patient-reported joints with active synovitis detected by power Doppler ultrasonography in rheumatoid arthritis

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Abstract

Objectives

This paper aims to evaluate the relationship of patient-reported tender and swollen joints with active inflammation as detected by power Doppler (PDUS) and whether this relationship is affected by significant joint damage.

Methods

Fifty rheumatoid arthritis patients self-assessed 28 tender and swollen joints and were followed by PDUS assessment. Relationship of tender and swollen joints with active synovitis (PDUS "gold standard") was assessed at the joint level by: a) percentage agreement at each PDUS semiquantitative grade (grade 1 to 3), b) positive likelihood ratio (LR) of agreement with PDUS, and c) LR of agreement with PDUS according to radiographic damage (significant erosive disease vs. non-erosive disease). Correlation of tender and swollen joint counts with disease activity markers was analysed by Spearman's. Sensitivity analyses examined the influence of disease activity or global pain on level of agreement at the joint level.

Results

Of joints with significant active inflammation (e.g. grade 3 PDUS), patients identified 75% as tender and 63% as swollen. Swollen joints showed strong association at the joint level with active synovitis when there was no significant radiographic damage (LR 2.54, 95%CI 1.93–3.34), but with no significant radiographic damage (LR 1.32, 95% CI 0.75–2.32). Swollen joint counts were statistically correlated with PDUS-DAS28 and CRP, but not PDUS score. Sensitivity analysis showed better agreement of tender and swollen joints with active synovitis when DAS28 was ≤ 3.2 and when patient global pain was <50mm on visual analogue scale.

Conclusion

The relationship between patient-reported joints and active synovitis is stronger in the setting of low disease activity without erosive disease, affected also by degree of reported global pain. Further longitudinal studies of patient-reported joints are needed.

Key words

synovitis, rheumatoid arthritis, patient, ultrasonography, joint counts

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Introduction

Swollen and tender joints are an important part of clinical disease activity assessment, as they enable physicians to detect and quantify synovitis in rheumatoid arthritis (RA) (1). Synovitis is the main factor that drives joint destruction, which, if untreated, may lead to permanent joint damage and functional disability (2). Joint counts help steer treatment decisions in order to achieve clinical remission, which is part of the over-arching principles of "treating to target" (3).

Ultrasonography (US) has emerged as a powerful adjunctive tool for synovitis detection. It is more sensitive than clinical assessment, as it has the ability to detect synovial hypertrophy, effusion (grey-scale) (4, 5) and active inflammation through power Doppler (PDUS) (6-10). PDUS signal is due to the presence of increased vascularity within the synovium, which indicates active inflammation and may be relevant in predicting radiographic progression (11-14). Despite this advantage, access to US is still limited; therefore clinical examination remains the most feasible method of assessing synovitis in daily practice.

Formal joint counts by the rheumatologist are not always performed at clinic visits, possibly limited by constraints of time and resources (15). Due to the importance of joint counts in disease activity assessment, there is renewed interest in examining the role of patient-reported tender and swollen joint counts (16-18), which may be helpful in monitoring disease activity between clinic visits.

The relationship of patient-reported joint counts compared to trained assessors is generally good for tender joints; however, studies of swollen joints indicate lower levels of correlation (19). Compared to synovitis detected by grey-scale US, the reliability of patient assessed synovitis is poor, largely due to the insensitivity of clinical joint counts to detect (subclinical) anatomical synovitis (20). Underlying joint damage, deformities or longstanding chronic synovitis may also affect the reliability of patient-reported joint counts. Although patients cannot reliably detect anatomical synovitis, it is unclear whether there is an association with synovitis that is actively inflamed. To date, no studies have evaluated this relationship and whether significant joint damage may affect this.

The objective is to evaluate the relationship of patient-reported tender and swollen joints with active inflammation as detected by PDUS as the gold standard with comparison to the relationship of physician-reported tender and swollen joints with PDUS, and to explore if patient self-reported joints can help with differentiation of clinically active synovitis in the presence of significant joint damage.

Methods

A cross-sectional study of 50 RA patients was conducted (20). Joints were independently evaluated by patients themselves after a short 5 minute training session by a nurse (MM), then by a physician, for swelling and tenderness (presence or absence at each joint), blinded to the patients' clinical findings. The wrists, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, elbows, shoulders and knees (28 joints) were assessed. Separate blinded assessments by US were performed by one rheumatologist (ARW), assessing synovitis on grey-scale (synovial hypertrophy and effusion) (21) and active inflammation by presence of PDUS signal in the respective joints. Joints were scanned in both longitudinal and transverse planes according to the method proposed by Backhaus *et al*. (22). In particular, the hands were placed in neutral position with both dorsal and volar aspects evaluated. PDUS findings were graded semi-quantitatively according to the grading system used in a previous multi-centre RA study on US synovitis scoring systems (23), which was adapted on the grading system proposed by Szkudlarek *et al*. (24); grade 0 being no signal visualised, grade 1 having one single or several vessels visualised, grade 2 less than 50% of the region of interest having signal, grade 3 being more than 50% of the region of interest having signal. Lesions were considered as actively inflamed if PDUS grading was ≥grade 1. An Esoate MyLab60 ma-

chine (Esoate, Genoa, Italy) was used for each patient using a 10–13 MHz multifrequency transducer probe for B-mode with the identical settings optimised for power Doppler (8.3 MHz frequency, pulsed repetition frequency of 750 MHz, and medium wall filter). The intra-observer reliability of the PDUS on 9 patients within 48 hours was good with an intra-class correlation co-efficient (ICC) of 0.60 (95%CI 0.51–0.67). Finally, radiographs of the hands (*i.e.* wrists, MCP joints and PIP joints only) within the last 6 months were graded according to the method proposed by Larsen (0–5) (25). A Larsen grade of ≥3 was considered as significant erosive disease for this study.

Agreement (%) of patient-reported tender and swollen joints with PDUS synovitis

The agreement of patient-reported tender joints or swollen joints with PDUS synovitis was compared at each semi-quantitative grading of PDUS synovitis. The proportion of joints considered by patients as tender or swollen, as well as not identified as tender or swollen at each PDUS synovitis grade (*i.e.* grade 1, grade 2 and grade 3) was compared and expressed as exact percentage proportions. This was also compared to the proportion of joints considered by the physician as tender or swollen at each PDUS synovitis grade.

Patient-reported joints vs. active inflammation by PDUS as gold standard

The association of patient-reported tender or swollen joints with active synovitis on PDUS (≥grade 1) was evaluated at the joint level. Accounting for possible insensitivity of clinical joint examination to identify minimal PDUS signal (*i.e.* grade 1 PDUS signal), the association was re-evaluated with PDUS grading ≥2 as the cut-off for PDUS synovitis. Two by two tables were created, with evaluation by sensitivities, specificities and positive likelihood ratios (LR). Sensitivity referred to the number of clinically reported joints with PDUS signal divided by the total number of joints reported to be clinically involved. While on the other hand, specificity referred to the number of joints not reported as clinically involved without PDUS signal divided by the total number of joints not reported as clinically involved. LR was the probability of clinically reported joint having PDUS signal divided by the probability of joints not reported as clinically involved with PDUS signal. LR may range from 0 to infinity with a LR greater than 1 indicating an increased probability that the target disorder (*i.e.* PDUS synovitis) is present. A positive LR >2 may be considered of relevant prognostic value (26). Likewise, relationship of physician-reported tender or swollen joints with PDUS was evaluated to compare with the findings of patient-reported joints.

Patient-reported joints vs. active inflammation by PDUS according to radiographic damage

The effects of significant radiographic damage and the relationship of patient-reported joints to PDUS synovitis was evaluated by separating joints into significant erosive disease (Larsen grade of ≥3) and no significant erosive disease (Larsen grade <3). Two by two tables were constructed for tender joints and swollen joints reported by patients and compared to active PDUS signal with analyses as above. This was compared between joints with significant erosive changes and joints that had no significant erosive disease. Likewise, the relationship of physician-reported tender or swollen joints with PDUS was compared to the findings of the patient-reported joints.

Relationship between joint counts vs. PDUS score and disease activity

In order to account for potential clustering in the analysis at the joint level, the relationship between patient joint counts and PDUS scores were evaluated at the patient level using Spearman's correlation. Physician joint counts were also compared similarly with PDUS scores. The relationship of patient joint count with other disease activity markers such as C-reactive protein (CRP), DAS28, and PDUS-DAS28 was assessed, along with the level of disability (modified Health Assessment Questionnaire) (27) and radiographic damage (Larsen score). In addition, the relationship with level of global heath and global pain on visual analogue scale (VAS) (0–100mm) with patient joint counts was also evaluated. To assess the relationship in terms of composite disease activity scores, patient derived disease activity score of 28 joints (DAS28) was compared to PDUS derived DAS28 (using physician TJC), by ICC (28).

Sensitivity analysis

A sensitivity analysis was performed to examine whether disease activity states or level of global pain may influence the agreement between tender and swollen joints with PD synovitis by: a) comparing the agreement when DAS28 ≤3.2 (minimal to low disease activity) and DAS28 >3.2 (moderate to high disease activity), and b) comparing the agreement when patient-reported global pain VAS <50mm with higher level of global pain, *i.e.* ≥=50mm.

All analysis was performed using SPSS version 18 (SPSS, Chicago, IL, USA).

Results

Patients had longstanding disease with a median disease duration of 15 years (interquartile range; 10, 21), moderate disease activity with median disease activity score (DAS28) of 3.5 (2.6, 4.5) and a median physician swollen joint count of 5 (3, 7) (Table I). Majority was on methotrexate (n=39, 78%) and 64% were on steroids with a median dose of 5 mg (5, 6). Biological disease modifying anti-rheumatic drugs were used in 35 patients (70%), highlighting a group that originally had active disease.

Agreement of patient-reported tender and swollen joints with PDUS

The level of percentage agreement of tender or swollen joints with PDUS synovitis is illustrated in Figure 1, divided according to PDUS semi-quantitative grading. Of the joints that had grade 1 PDUS synovitis, only 36% were reported to be tender and 22% as swollen by patients compared to 22% and 29% by the physician, respectively. As the grade of PDUS synovitis increased, the proportion considered as tender

Table I. Baseline characteristics of the 50 rheumatoid arthritis patients.

Characteristics	
Sex, n (%), female	38 (76)
Age, years	60 (50–69)
Disease duration, years	15 (10–21)
Physician derived TJC	2 (0–6)
Physician derived SJC	5 (3–7)
Patient derived TJC	7 (2–11)
Patient derived SJC	3 (0–8)
Patient global disease activity VAS (0–100mm)	40 (30–60)
Patient global level of pain VAS (0–100mm)	40 (20–50)
Modified HAQ	0.6 (0.1–1.1)
US-detected synovitis joint count	10 (7–14)
US-detected synovitis with PDUS signal joint count ¶	4 (2–7)
Physician DAS28	3.5 (2.6–4.5)
Larsen grade, n (%)^	
<3	924 (84)
≥3	176 (16)

*Results are median (interquartile ranges), unless stated otherwise.
PDUS: power Doppler; DAS28: disease activity score; TJC: tender joint count; SJC: swollen joint count; HAQ: Health Assessment Questionnaire; VAS: visual analogue scale.
¶PDUS signal defined as semi-quantitative grade ≥1; ^missing n=300.

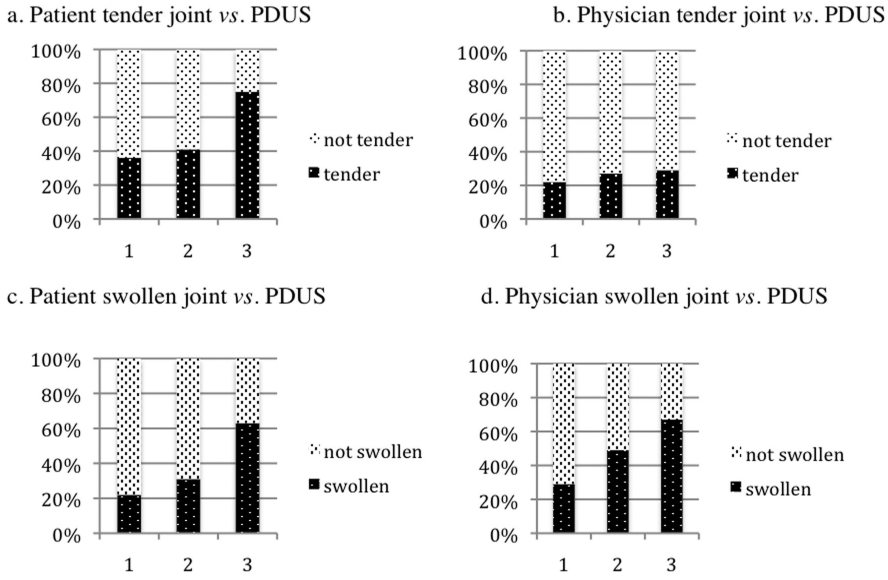

Fig. 1. Percentage agreement of tender joints and swollen joints derived by patients and physician with US detected synovitis according to PDUS grading.
x-axis: PDUS semiquantitative grade.
y-axis: percentage agreement.
PDUS: power Doppler ultrasonography.

and swollen by patients at each semi-quantitative grade increased and was greatest in joints with grade 3 PDUS synovitis (significantly inflamed). In this situation, 75% of joints were tender and 63% were considered swollen by patients. Overall, patient reported-tender joints had a higher percentage in agreement with PDUS synovitis than patient-reported swollen joints at each PDUS signal grade. However, tender joints also detected more false positive results (absence of PDUS synovitis) than swollen joints (results not shown). The proportion of physician tender joints at each semi-quantitative grade remained low, but had less false positives than patient-reported tender joints. However, the proportion of physician-reported swollen joints was better than patient-reported swollen joints at each PDUS grade, notably at grade 2 PDUS synovitis. Overall, the number of joints were not identified as affected, but had PDUS activity, reduced as the semi-quantitative grade increased for both patient-reported tender and swollen joints, as well as physician-reported swollen joints (Fig. 1).

Patient-reported joints vs. active inflammation by PDUS

The level of association of patient-reported tender and swollen joints with PDUS synovitis was similar with LR, ranging from 1.73 to 1.99 (Table II). When compared to tender joints, patient-reported swollen joints were not as sensitive to detect active inflammation when the cut-off for PDUS synovitis ≥ grade 1, with a sensitivity of 0.30 (95%CI 0.25–0.36). However, tender joints were less specific (0.76, 95%CI 0.73–0.80) when compared to swollen joints with higher false positive results. The association was re-evaluated with ≥ grade 2 as the cut-off for PDUS synovitis. The LR of swollen joints with active inflammation was higher at 2.27 (95%CI 1.77–2.9) due to improved sensitivity. On the other hand, patient-reported tender joints did not improve with similar sensitivity, specificity and likelihood ratio as that when the cut-off for PDUS synovitis was ≥grade 1. This was similar for physician tender joints. The LR of physician-swollen joints with active inflammation on PDUS was higher than patient-reported swollen joints for both PDUS cut-off (Table II).

Patient-reported joints vs. active inflammation by PDUS according to radiographic damage

The level of association of patient-reported joints with active inflammation according to radiographic damage is illustrated in Table III. Patient-reported swollen joints in the presence of significant erosive disease had the lowest association with active inflammation with a LR of 1.36 (95%CI 0.81–2.28), when the cut-off for PDUS synovitis was grade 1. Similarly, when the association was re-evaluated with grade 2 signal as the lowest cut-off for PDUS synovitis, the relationship remained poor (LR 1.32, 95%CI 0.75–2.32). However, patient-reported swollen joints when there was no significant erosive disease had a stronger associa-

Table II. Sensitivity, specificity and likelihood ratio of joints with active inflammation (PDUS synovitis as gold standard).

	Sensitivity* 95%CI	Specificity** 95%CI	Positive likelihood ratio^ 95%CI
Clinical *vs*. PDUS synovitis (≥grade 1)			
Patient tender joint	0.42 (0.36–0.48)	0.76 (0.73–0.80)	1.73 (1.45–2.07)
Patient swollen joint	0.30 (0.25–0.36)	0.85 (0.83–0.87)	1.99 (1.58–2.50)
Physician tender joint	0.25 (0.20–0.31)	0.87 (0.85–0.89)	1.91 (1.47–2.47)
Physician swollen joint	0.43 (0.37–0.49)	0.85 (0.83–0.87)	2.91 (2.39–3.56)
Clinical *vs*. PDUS synovitis (≥grade 2)			
Patient tender joint	0.47 (0.39–0.55)	0.75 (0.72–0.77)	1.84 (1.52–2.24)
Patient swollen joint	0.36 (0.29–0.44)	0.84 (0.82–0.86)	2.27 (1.77–2.91)
Physician tender joint	0.27 (0.21–0.35)	0.86 (0.84–0.88)	2.00 (1.49–2.68)
Physician swollen joint	0.52 (0.44–0.60)	0.84 (0.82–0.86)	3.29 (2.69–4.01)

*Sensitivity: number of clinically reported joints with PDUS signal divided by the total number of joints reported to be clinically involved.
**Specificity: number of joints not reported as clinically involved without PDUS signal divided by the total number of joints not reported as clinically involved.
^Positive likelihood ratio: the probability of clinically reported joint having PDUS signal divided by the probability of joints not reported as clinically involved with PDUS signal.

tion with PDUS signal with a LR of 2.54 (95%CI 1.93–3.34), with the association similar to that of physician reported swollen joints and PDUS. On the other hand, patient-reported tender joints had similar sensitivity, specificity and likelihood ratio irrespective of radiographic damage and level of PDUS signal cut-off for active inflammation. Likewise, similar results were observed for physician tender joints. However, physician-reported swollen joints were better than patient-reported swollen joints with or without significant radiographic damage at both PDUS cut-off.

Relationship between joint counts vs. PDUS score and disease activity

The relationship of patient-reported TJC or patient-reported SJC failed to reach statistical significance with PDUS score with r=-0.103 and r=0.234, respectively. Only physician SJC was statistically correlated with PDUS score (r=0.373, p=0.008).

Despite this, patient-reported SJC did correlate with other surrogate markers of disease activity such as CRP (r=0.427, p=0.002), physician DAS28 (r=0.668, p<0.001), PDUS-DAS28 (r=0.676, p<0.001), patient-reported level of global pain on VAS (r=0.459, p=0.001), patient global on VAS (r=0.459, p=0.001) and level of disability by modified HAQ (r=0.336, p=0.001). Likewise, patient-reported TJC correlated with all the mentioned variables, except CRP. There was also a negative association of patient-reported TJC and level of radiographic damage measured by the Larsen score (r=-0.284, p=0.046) (Table IV).

In terms of the reliability of composite disease activity measures, patient-reported DAS28, when compared to PDUS-DAS28, had excellent reliability with ICC of 0.90 (95%CI 0.82–0.94). Likewise, for physician reported DAS28, the ICC was 0.97 (95%CI 0.95–0.98) compared to PDUS-DAS28.

Sensitivity analysis

A sensitivity analysis was performed looking at whether the level of disease activity state affected agreement of tender or swollen joints with PDUS (either grade 1 or grade 2 as the cut-off for PDUS synovitis), as shown in Table V. Both patient-reported tender and swollen joints were more likely to correspond with PDUS synovitis,

Table III. Sensitivity, specificity and likelihood ratio of 1100 joints with active inflammation according to radiographic damage.

	Significant erosion#			No significant erosion#		
	Sensitivity* (95%CI)	Specificity** (95%CI)	Positive likelihood ratio^ (95%CI)	Sensitivity* (95%CI)	Specificity** (95%CI)	Positive likelihood ratio^ (95%CI)
Clinical *vs*. PDUS synovitis (≥grade 1)						
Patient tender joint	0.46 (0.34-0.58)	0.76 (0.67–0.83)	1.89 (1.24-2.88)	0.40 (0.33–0.47)	0.77 (0.74–0.80)	1.73 (1.39–2.16)
Patient swollen joint	0.30 (0.20–0.42)	0.78 (0.70–0.85)	1.36 (0.81-2.28)	0.33 (0.27–0.41)	0.83 (0.80–0.86)	1.96 (1.51–2.55)
Physician tender joint	0.30 (0.20–0.42)	0.81 (0.73–0.87)	1.54 (0.90–2.65)	0.23 (0.18–0.30)	0.87 (0.85–0.89)	1.82 (1.31–2.53)
Physician swollen joint	0.70 (0.58–0.80)	0.64 (0.55-0.73)	1.98 (1.47–2.65)	0.33 (0.27–0.41)	0.84 (0.82–0.87)	2.15 (1.64–2.80)
Clinical *vs*. PDUS synovitis (≥grade 2)						
Patient tender joint	0.45 (0.31–0.60)	0.72 (0.64–0.79)	1.61 (1.04–2.49)	0.47 (0.38–0.56)	0.75 (0.72–0.77)	1.89 (1.52–2.35)
Patient swollen joint	0.30 (0.18–0.45)	0.77 (0.69–0.83)	1.32 (0.75–2.32)	0.38 (0.29–0.47)	0.85 (0.83–0.87)	2.54 (1.93–3.34)
Physician tender joint	0.30 (0.18–0.45)	0.79 (0.72–0.85)	1.46 (0.82–2.60)	0.26 (0.19–0.35)	0.87 (0.84–0.89)	1.95 (1.35–2.82)
Physician swollen joint	0.70 (0.55–0.82)	0.59 (0.50–0.67)	1.70 (1.28–2.26)	0.43 (0.34-0.53)	0.84 (0.81–0.86)	2.73 (2.08–3.58)

*Sensitivity: number of clinically reported joints with PDUS signal divided by the total number of joints reported to be clinically involved.
**Specificity: number of joints not reported as clinically involved without PDUS signal divided by the total number of joints not reported as clinically involved.
^Positive likelihood ratio: the probability of clinically reported joint having PDUS signal divided by the probability of joints not reported as clinically involved with PDUS signal.
#Significant erosion: Larsen grade ≥3, missing values n=300.

Table IV. Correlation of tender and swollen joint counts with surrogate markers of disease activity and other clinical features.

	PDUS score		DAS28		PDUS-DAS28		CRP		Patient global VAS		Patient pain VAS		Modified HAQ		Larsen score	
	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value
Patient TJC	-0.103	0.475	0.697*	<0.001	0.693*	<0.001	0.275	0.053	0.399*	0.004	0.498*	<0.001	0.449*	0.002	-0.284^	0.046
Patient SJC	0.234	0.101	0.668*	<0.001	0.676*	<0.001	0.427*	0.002	0.459*	0.001	0.561*	<0.001	0.336^	0.021	-0.111	0.441
Physician TJC	0.031	0.830	0.895*	<0.001	0.890*	<0.001	0.414*	0.003	0.378*	0.007	0.445^	0.002	0.459*	0.007	-0.102	0.482
Physician SJC	0.373*	0.008	0.615*	<0.001	0.529*	<0.001	0.303^	0.032	0.198	0.169	0.115	0.454	0.193	0.194	0.260	0.068

*$p<0.01$; ^$p<0.05$.
PDUS: power Doppler ultrasonography; DAS: disease activity score; CRP: C-reactive protein; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire.

Table V. Sensitivity analysis of the association of tender and swollen joints with active inflammation (PDUS) according to disease activity.

	DAS28≤3.2			DAS28>3.2		
	Sensitivity* (95%CI)	Specificity** (95%CI)	Positive likelihood ratio^ (95%CI)	Sensitivity* (95%CI)	Specificity** (95%CI)	Positive likelihood ratio^ (95%CI)
Clinical *vs*. PDUS synovitis (≥grade 1)						
Patient tender joint	0.20 (0.13–0.30)	0.94 (0.91–0.96)	3.39 (1.85–6.23)	0.52 (0.44–0.54)	0.67 (0.63–0.70)	1.55 (1.30–1.84)
Patient swollen joint	0.09 (0.05–0.18)	0.97 (0.94–0.98)	2.68 (1.11–6.49)	0.39 (0.32–0.46)	0.79 (0.76–0.82)	1.87 (1.48–2.35)
Physician tender joint	0.08 (0.04–0.16)	0.99 (0.98–1.00)	7.82 (2.54-24.08)	0.34 (0.27–0.41)	0.79 (0.75–0.82)	1.57 (1.22–2.03)
Physician swollen joint	0.38 (0.28–0.48)	0.93 (0.91–0.95)	5.77 (3.73–8.93)	0.45 (0.38–0.53)	0.80 (0.76–0.82)	2.22 (1.77–2.77)
Clinical *vs*. PDUS synovitis (≥grade 2)						
Patient tender joint	0.24 (0.14–0.39)	0.93 (0.91–0.95)	3.68 (1.92–7.05)	0.55 (0.46–0.64)	0.66 (0.62–0.69)	1.59 (1.32–1.93)
Patient swollen joint	0.12 (0.05–0.26)	0.96 (0.94–0.98)	3.31 (1.27–8.64)	0.44 (0.35–0.53)	0.78 (0.76–0.81)	2.05 (1.61–2.62)
Physician tender joint	0.08 (0.03–0.20)	0.98 (0.97–0.99)	5.33 (1.67–17.07)	0.36 (0.27–0.45)	0.78 (0.75–0.81)	1.62 (1.22–2.17)
Physician swollen joint	0.44 (0.31–0.58)	0.92 (0.89–0.94)	5.33 (3.46–8.22)	0.56 (0.46–0.65)	0.79 (0.76–0.82)	2.64 (2.12–3.29)

*Sensitivity: number of clinically reported joints with PDUS signal divided by the total number of joints reported to be clinically involved.
**Specificity: number of joints not reported as clinically involved without PDUS signal divided by the total number of joints not reported as clinically involved.
^Positive likelihood ratio: the probability of clinically reported joint having PDUS signal divided by the probability of joints not reported as clinically involved with PDUS signal.

Table VI. Sensitivity analysis of the association of tender and swollen joints with active inflammation (PDUS) according to patient reported level of global pain.

	Global pain VAS < 50mm			Global pain VAS ≥ 50mm		
	Sensitivity* (95%CI)	Specificity** (95%CI)	Positive likelihood ratio^ (95%CI)	Sensitivity* (95%CI)	Specificity** (95%CI)	Positive likelihood ratio^ (95%CI)
Clinical *vs*. PDUS synovitis (≥grade 1)						
Patient tender joint	0.24 (0.18–0.31)	0.90 (0.87–0.92)	2.30 (1.61–3.28)	0.40 (0.30–0.51)	0.76 (0.72–0.80)	1.67 (1.20–2.52)
Patient swollen joint	0.36 (0.29–0.44)	0.83 (0.80–0.85)	2.07 (1.59–2.71)	0.60 (0.49–0.70)	0.62 (0.57–0.67)	1.58 (1.27–1.98)
Physician tender joint	0.20 (0.14–0.26)	0.91 (0.89–0.93)	2.16 (1.45–3.22)	0.38 (0.28–0.50)	0.81 (0.77–0.85)	2.03 (1.43–2.89)
Physician swollen joint	0.42 (0.35–0.50)	0.86 (0.83–0.88)	2.93 (2.26–3.80)	0.45 (0.34–0.56)	0.83 (0.79–0.86)	2.59 (1.86–3.62)
Clinical *vs*. PDUS synovitis (≥grade 2)						
Patient tender joint	0.26 (0.18–0.35)	0.89 (0.86–0.91)	2.29 (1.55–3.38)	0.56 (0.41–0.70)	0.77 (0.72–0.80)	2.38 (1.73–3.27)
Patient swollen joint	0.39 (0.30–0.48)	0.82 (0.79–0.84)	2.10 (1.57–2.80)	0.70 (0.55-0.81)	0.61 (0.56–0.66)	1.79 (1.42–2.25)
Physician tender joint	0.22 (0.15–0.31)	0.90 (0.88–0.92)	2.28 (1.48–3.51)	0.42 (0.28–0.57)	0.80 (0.76–0.83)	2.07 (1.38–3.09)
Physician swollen joint	0.49 (0.39–0.58)	0.84 (0.81–0.87)	3.08 (2.37–4.01)	0.58 (0.43–0.72)	0.82 (0.78–0.85)	3.18 (2.30–4.41)

*Sensitivity: number of clinically reported joints with PDUS signal divided by the total number of joints reported to be clinically involved.
**Specificity: number of joints not reported as clinically involved without PDUS signal divided by the total number of joints not reported as clinically involved.
^Positive likelihood ratio: the probability of clinically reported joint having PDUS signal divided by the probability of joints not reported as clinically involved with PDUS signal. VAS: visual analogue scale (0–100mm).

when disease activity was low (DAS28 ≤3.2), for both definitions of PD synovitis, with LR of 3.58 (95%CI 1.92–7.05) and 3.31 (95%CI 1.27–8.64), respectively. A similar result was also observed with physician-reported tender and swollen joints.

The level of global pain of the patient also affected agreement of patient-reported tender or swollen joints with PDUS (grade 1 as cut-off). Patient-reported tender and swollen joints had a lower level of association with active inflammation when patient-reported global pain was ≥50mm on VAS, with mean LR for patient-reported tender or swollen joints <2 (Table VI). When PDUS cut-off for PDUS synovitis was grade 2, this observation was only seen for patient-reported swollen joints. On the other hand, the association of physician-reported tender or swollen joints with PDUS was not affected by level of patient reported global pain.

Discussion

This study further provides important information on the relationship and potential role of self-reported joints in the evaluation of disease activity. Patients may be able to identify joints that are significantly inflamed (PDUS grade 2 or 3) at the joint level, with the association being stronger for swollen joints, especially when there was no radiographic damage. In the presence of significant erosive disease, patient-derived swollen joints performed poorly. Although tender joints were more sensitive than swollen joints, they were less specific with higher false positives, and most apparent when there was no radiographic damage. At the patient level there was no significant relationship of patient-reported joint counts and PDUS score, although significant correlations with other more traditional surrogate markers of disease activity were seen. Despite the relationship of patient-reported joints with active inflammation being affected by the level of disease activity and degree of global pain, reliability was excellent between patient-derived DAS28 with that derived by PDUS.

To our knowledge, this is the first study to evaluate the relationship between patient joint assessments to active inflammation by PDUS. Although previous studies have failed to find a correlation with other surrogate markers of inflammation (29) and with PDUS score in this study, there is a potential relationship at the joint level and a significant correlation with disease activity at the patient level. The sensitivity of patient-reported joints to detect true synovitis is low, however, the high specificity suggests that tender or swollen joints reported by patients could be an alert signal that there may be clinically relevant inflammation. Patient perception of joint involvement may help identify synovitis that is active, especially when there is significant PDUS flow (*i.e.* grade 3).

Limitations of our study were as follows. Firstly, patients were not instructed to indicate if joints were active, but to identify what was regarded as swollen or tender to avoid potential confusion. Secondly, there was no longitudinal follow-up, with a cohort consisting of patients who are older, with a longer disease duration and significant radiographic damage. Hence, the clinical relevance of detecting PDUS synovitis in this particular cohort is unclear and cannot be generalisable to early RA cohorts. Despite no longitudinal follow-up, it is agreed that PDUS is a valid gold standard to use for active inflammation. It is clinically more relevant for RA than grey-scale US (7) with the presence of a higher PDUS grade predictive of persistence of inflammatory arthritis (30). Persistence of PDUS activity has also been associated with radiographic progression in longitudinal studies (11-14), and scoring systems for disease activity scores incorporating PDUS have been validated against clinical assessment (23, 31). Ideally, the study should also have had two independently blinded US assessments, since US may be liable to inter-observer variation (9, 32), however the reproducibility of US assessments in this particular study at least that of intra-observer reliability was considered satisfactory.

The analysis at the individual joint level was liable to potential problems of clustering. The subsequent analysis at the patient level was used to address this potential bias. Sensitivity analysis did indeed confirm that the level of disease activity (*i.e.* high TJC or SJC), or global pain can affect the relationship between patient-reported joints and active inflammation by PDUS with a better association in minimal to low disease activity states, as well as in patients with lower levels of reported global pain. Considering recent evidence that PDUS is predictive of disease relapse and radiological progression in low levels of disease activity (14), this is a relevant observation. In addition, self-reported joint counts are potentially useful in patients who are in clinical remission, when compared to joint counts performed by trained assessors (16).

Patients had difficulty accurately detecting active inflammation in the context of significant erosive disease. This could be due to the altered patient perception of swelling and pain in a joint that was already damaged. Hence, the use of patient-reported joints should only be considered in patients without significant erosive disease in minimal to low disease activity states. The level of global pain reported by the patient also appears to influence the level of association of patient-reported joints and active inflammation as seen through the sensitivity analysis, especially with swollen joints, which was not observed in physician-reported joints. It may be difficult to apply self-assessment of joints in patients with high levels of reported global pain. Although there was also a relationship with patient-reported global level of disease and disability as measured by the modified HAQ, other important patient quality of life measures and impact of disease assessments (33) should be assessed in future studies.

There are several advantages of patient-reported tender and swollen joints as measures of disease activity: patients are involved in their treatment, the same person does the measurement, and it is time efficient. It also provides opportunity for home monitoring between clinic visits and, therefore, increases the frequency of disease activity monitoring, potentially improving the clinical outcome of disease. Despite the lack of correlation of

patient-reported joint counts with the PDUS score, it was reassuring to see that other surrogate markers of disease activity, *e.g.* CRP and DAS28, were significantly correlated.

Conclusion

In conclusion, there is a potential role of patient-reported disease activity and assessment of active inflammation in the setting of minimal to low disease activity without erosive disease, provided the level of patient reported global pain is not high. Future studies may direct the application of self-assessed joints in this setting, but further studies with longitudinal follow-up of a different cohort in particular, that of early RA, evaluating with other patient reported quality of life measures, will be required to determine the exact clinical impact and generalisability as a patient reported outcome measure.

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