Six-joint ultrasound in rheumatoid arthritis: a feasible approach for implementing ultrasound in remission

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ABSTRACT

Objective. *Subclinical disease activity in rheumatoid arthritis (RA) detected by imaging methods is predictive for flares and damage. Lack of time is the major limitation for not screening for subclinical disease in routine practice. We aimed to determine the most feasible protocol to screen patients with no clinical disease activity by ultrasound (US).*

Methods. *A hundred consecutive RA patients with no clinical activity according to the physician had an US scan for 38 joints. The prevalence of power Doppler (PD) signal in each joint was determined and different combinations of joints were assessed for their ability to capture this information. The most practical combination with a good sensitivity was tested in another group of 50 RA patients.*

Results. *Having any PD signal was not linked to the disease activity parameters whereas presence of PD of ≥2 was associated with higher DAS28CRP. Sixty patients had at least one joint with PD of grade ≥2 (60%). A combination of the wrists and 2nd–3rd MCP joints bilaterally (PD-6 joints) was able to detect 45/60 (75%) cases with PD signals and 45% of the whole patient population. The correlation between PD-38 and PD-6 joints was excellent (r=0.820, p<0.0001). PD-6 joints in the 2nd cohort was also able to detect 22/50 (44%) of the whole group.*

Conclusion. *Subclinical disease activity could be detected in 60% of RA patients when 38 joints screened by US. Limiting the screening to wrists, 2nd–3rd MCPs bilaterally was acceptable as it detected 75% of cases with subclinical disease and increased the feasibility.*

Introduction

There has been a major improvement in the outcome of patients with rheumatoid arthritis (RA) in the last decade, partially due to the advances on imaging. Imaging studies using either ultrasound (US) or magnetic resonance imaging showed that physical examination can be inadequate to diagnose synovitis as both being more sensitive (1). A number of studies showed that anti-CCP positive patients without clinically detected arthritis have a higher risk of developing RA if they have power Doppler (PD) positivity at baseline leading to US having an increasing role in the diagnosis of RA (2). Additionally, US plays a role in follow up as patients in clinical remission have a higher risk of having flares at follow up if they have PD positivity and joints with PD positivity at baseline with a 12 fold higher risk of developing erosions at 1 year (3-7). US has the advantage of being a non-invasive method with no radiation which allows the scanning of multiple sites in a patient at multiple time points (8). For these advantages, it has been increasingly used in the field of rheumatology.

However, there are also limitations of using US in daily practice. A survey showed that the leading cause for not doing US in patients with RA was the lack of time (9). Therefore, it is important to identify the minimum number of joints that should be scanned to increase the feasibility. By using a standardised report form, developed by the Targeted Ultrasound Initiative (TUI), an international organisation of ultrasonographers aiming at implementing the use of US in routine management of RA patients (10), it was demonstrated that rheumatologists scan different number of joints depending on the indication, (*i.e.* diagnosis of RA or disease activity evaluation) (11). In the present study, we focused on RA patients in stable disease state, in order to identify the minimum number of joints to scan for detecting subclinical inflammation, as a guide for physicians.

Methods

First step: Determining the optimum joint combination

• *Patient selection*

Consecutive patients who had RA according to the 2010 ACR/EULAR RA classification criteria were screened (12). They were assessed for clinical disease activity by using DAS28CRP, by the same rheumatologist (EKG). Patients who were in clinical remission or low disease activity state (DAS-28CRP <2.7) and who do not require any treatment change according to the clinician's opinion were recruited for

the 1st step. The demographics of the patients were documented and their rheumatoid factor (RF) and anti-CCP status were recorded from their files. The study was approved by local ethics committee (Marmara University Ethics Committee, no. 09.2013.0142) and all patients gave informed consent prior to the study.

• *Ultrasound assessments*

All patients had an US scan within 1 week of their clinical assessment, by an experienced rheumatologist in musculoskeletal US (SZA) blinded to the clinical examination findings. All scans were performed in a darkened room, using a MyLab 70 XVG (Esaote Biomedica, Genoa – Italy), equipped with a broadband 6–18 MHz linear probe. Thirty-eight joints per patient were scanned: 1–5 metacarpophalangeal (MCP) and 1–5 proximal interphalangeal (PIP) joints, wrist, elbow, knee, ankle, and 1–5 metatarsophalangeal (MTP), bilaterally. PD setting was standardised with a pulse repetition frequency of 500 Hz and low wall filter. The colour gain was increased to the highest value where PD signals under the bony cortex were not generated. Particular attention was paid not to apply too much pressure with the probe on the anatomic structures.

Synovitis was defined by the presence of synovial hypertrophy (SH) and PD according to the definition developed by the OMERACT (Outcome Measures in Rheumatology) US taskforce (13). A semiquantitative scoring system was used. Grey-scale SH was scored between 0–3; 0 being none, 1: mild, 2: moderate, 3: marked synovial thickening. For PD signals: score 0: no signal, score 1: one or two vessels (including one confluent vessel) for small joints and two or three signals for large joints, score 2: PD signal more than score 1 but less than 50% of the area; score 3: PD signal covering >50% of the grey-scale synovitis.

• *Statistical analysis*

The prevalence of PD signals was determined in each joint, analysing separately for the severity of the Doppler signal. The data are given as per joint and per patient. Patients with different degrees of PD signals were compared for disease activity parameters to find a cut off for PD signals that has a clinical value. An overall PD score was calculated by adding the PD scores of each joint that was included in that combination. All comparisons on continuous variables in patients with or without PD signals were made using a Mann-Whitney U-test. Different sets of joints were calculated to find out the best combination with PD positivity. Correlations of PD scores of different joint combinations and DAS28 CRP was calculated with Spearmen's correlation coefficient. SPSS v. 23 was used for statistical comparisons.

Second step: Testing the optimum combination of joints in a control group

The optimum combination was tested in another group of 50 RA patients. The same clinical approach and US assessment was performed, with the exception of using a limited scanning protocol including 300 joints in 50 patients (6 per patient).

Table I. The frequency of having a PD signal and GS synovitis according to the joints in the first cohort of patients. n=200 of each joint. Numbers are given as n (%).

	Any PD	PD at least grade 2	PD grade 3	Any GS	GS at least grade 2	GS grade 3
1st MCP	12 (6)	7 (3.5)	3 (1.5)	34 (17)	25 (12.5)	2 (1)
2nd MCP	55 (27.5)	36 (18)	4 (2)	113 (55.5)	71 (35.5)	18 (9)
3rd MCP	30 (15)	20 (10)	2 (1)	69 (34.5)	30 (15)	10 (5)
4th MCP	12 (6)	6 (3)	0 (0)	39 (19.5)	23 (11.5)	3 (1.5)
5th MCP	27 (13.5)	11 (5.5)	1 (0.5)	66 (33)	24 (12)	8 (4)
IP	4 (2)	3 (1.5)	0 (0)	21 (10.5)	16 (8)	3 (1.5)
2nd PIP	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)
3rd PIP	4 (2)	2 (1)	1 (0.5)	5 (2.5)	5 (2.5)	1 (0.5)
4th PIP	0 (0)	0 (0)	0 (0)	3 (1.5)	3 (1.5)	1 (0.5)
5th PIP	2 (1)	1 (0.5)	1 (0.5)	2 (1)	2 (1)	1 (0.5)
Wrist	25 (12.5)	15 (7.5)	1 (0.5)	69 (34.5)	36 (18)	3 (1.5)
Elbows	1 (0.5)	1 (0.5)	0 (0)	24 (12)	11 (5.5)	4 (2)
Knees	0 (0)	0 (0)	0 (0)	16 (8)	10 (5)	1 (0.5)
Ankles	1 (0.5)	1 (0.5)	0 (0)	22 (11)	11 (5.5)	4 (2)
1st MTP	38 (19)	29 (14.5)	1 (0.5)	47 (23.5)	26 (13)	7 (3.5)
2nd MTP	17 (8.5)	11 (5.5)	2 (1)	35 (17.5)	29 (14.5)	4 (2)
3rd MTP	14 (7)	11 (5.5)	1 (0.5)	23 (11.5)	17 (8.5)	4 (2)
4th MTP	9 (4.5)	9 (4.5)	4 (2)	24 (12)	16 (8)	3 (1.5)
5th MTP	10 (5)	9 (4.5)	3 (1.5)	17 (8.5)	9 (4.5)	4ì (2)

Results

Step 1

Patient characteristics, subclinical disease activity and determining the cut off level for Doppler signal:

For the first step, 100 patients were included and 3800 joints were examined in total. The median (range) of age, disease duration, duration of remission and DAS28CRP were 55 years (25–79), 7 (0.5–40) years, 19 months (4–72) months and 1.96 (1.46–2.63), respectively. 77% were females and 65% were seropositive for ACPA and/or RF. The mean (SD) sum of PD scores according to 38 joints was 4.63 (5.19).

According to the extensive scanning protocol on 38 joints, 79 patients had at least one joint with any PD signal and 60 patients had at least one joint with grade ≥2 PD signal (60%). Comparison of patient characteristics according to different PD grades showed that patients with grade ≥2 PD signals in any of the joints had higher DAS-28CRP and VAS patient global scores then patients who do not have the same PD signals (DAS28CRP: 2.15 (0.33) *vs*. 1.93 (0.29); p=0.001. VAS: 21.2 (11.5) *vs*. 14.7 (11.7); p=0.006) which was not observed for tender or swollen joint counts and CRP. None of the comparisons was found significant when the threshold was drawn as having any PD or grade 3 PD signal (data not given). For that reason, we accepted the definition of grade≥ 2 PD for having a positive signal and the rest of the analysis was used by using that threshold.

The positivity of Doppler findings according to different combination of joints:

The 2nd MCP joints were the most com-

Table II. Number of scanned joints per patient, number of PD positive patients by using different combinations and correlations with PD38 joints and DAS28CRP.

	All joints	All MCPs	2-3 MCPs	Wrists+all. MCPs	Wrists+2-3. MCPs	All MTPs	All MTPs +MCPs	Wrists+2-3. MCPs+all	Wrists-2-5th MTPs MCPs+ ankles+2-5th MTP
Number of scanned joints per patient	38	10	4	12	6	10	20	16	20
Number of positive patients	60	42	38	49	45	33	57	53	50
Correlations with PD38 (correlation coefficient)*		0.788	0.745	0.851	0.820	0.634	0.973	0.982	0.918
Correlations with DAS28CRP (correlation coefficient and *p*-values)	0.292 0.003	0.226 0.024	0.259 0.009	0.273 0.006	0.296 0.003	0.080 0.4	0.234 0.019	0.287 0.004	0.286 0.004

*p-value is <0.0001 for all comparisons.

monly affected joints (Table I). When testing for combination of different sets of joints PIP joints, elbows and ankles were excluded as these joints were positive in the minority (≤2 % of the joints). Scanning only 2nd–3rd MCP joints depicted 38 out of 60 patients showing a sensitivity of 63% (Table II). A combination of wrists and 2nd–3rd MCP joints (PD-6 joints) was able to detect 45 in 60 cases with a sensitivity of 75%. The combination of 20 joints [wrists-ankles 2–5th MCP and 2–5th MTP joints (14)] as suggested by Naredo *et al*. was also tested and found to be positive in 50 patients with a sensitivity of 83%.

There was a significant but poor correlation between DAS28CRP and PD-38 joints (r=0.292, p=0.003) which was almost identical to the correlation between DAS28CRP and PD-6 joints (r=0.296, p=0.003) (Table II). None of the other joint combinations tested had a higher correlation than PD-6 joints. The correlation between PD-38 joints and PD-6 joints was excellent (r=0.820, p<0.0001). All combinations other than the combination that only included MTP joints were able to differentiate DAS28CRP remission (n=73) *versus* low disease activity state (n=27) for having higher overall PD scores in patients with low disease activity (data not given). Therefore PD-6 joint was tested in the second cohort.

Step 2

The demographic features of the external validation cohort of 50 RA patients were similar to the first cohort (Mean (SD) age: 54 years (26–81), disease duration 5 (0.5–25), duration of remission: 24 (1–132) months; DAS28CRP: 1.87 (0.96–2.7): 76 % female; 62.7% seropositive). Within 6 joints (wrists, 2nd and 3rd MCP joints) grade ≥2 PD signal was detected in 14 wrists (14%) of 11 patients (22%), 16 (16%) 2nd MCP joints of 14 (28%) patients and 5 (5%) 3rd MCP joints of 5 patients (10%). The US scanning of the combination these joints (PD-6 joints) was able to detect subclinical disease in 22/50 (44%) of the whole group.

Discussion

This study demonstrated that when screened for 38 joints by US, subclinical disease is present in 60% of cases with RA who are in clinical remission or low disease activity state and who do not require an increase in treatment. When compared with screening 38 joints, scanning 6 joints limited to wrists and 2nd-3rd MCP joints allowed detection of 75% of these cases with PD positivity. The limitation of the anatomical sites to MCP joints and wrists is time saving as positioning of the patient will only be required once. In another study by Naredo *et al*. highlighted that the wrist, MCP, ankle and MTP joints had the highest sensitivity for detecting subclinical disease (14). Our data showed that increasing the number of joints from 6 to 20 instead of limiting to one anatomical site had added value in only 5% of patients. Since the lack of time is a major a barrier for the rheumatologists for not doing US on a routine basis, we suggest that limiting the joint count to 6 would increase the use of US for patients in remission and therefore our understanding for subclinical disease.

One of the differences in the present study was measuring the severity of PD signals. The widely used semiquantitative scoring system to grade PD was also used in our study. Although mild Doppler signals (grade 1) are recorded, the common belief is that grade 1 signals can also be detected in healthy people (15), more easily can be confused with physiological vessels and usually does not lead to any management change when detected in patients with RA. Our data showed that the presence of grade 1 lesions was not linked to any clinical features. On the other hand having at least grade 2 signals had clinical relevance as those patients had higher DAS28CRP scores and VAS scores despite having stable disease according to the physician. For these patients, CRP and tender/swollen joint counts were not able to depict the statistically higher disease activity, which was instead detected by US. This is in contrast to the previous data, where PD positivity had no links to DAS28 remission, and thus supports the concept that the severity of Doppler signals for individual joints may be as important as total PD scores (7, 14, 16).

Currently there is no evidence to support the increase in therapy in patients who have PD signal despite being in clinical remission, although subclinical disease activity is associated with more frequent flares and more frequent erosions at follow up. Independent of this, the recognition of subclinical disease however may clarify which patients need close follow-up. By using a feasible protocol as suggested by our data, US can easily become a part of the patient care improving our understanding for subclinical disease.

To conclude, the scanning of the wrists, 2nd and 3rd MCP joints bilaterally is a feasible way for detecting subclinical disease in RA for the majority of patients. The threshold of grade 2 or more for Doppler signal detect patients that have higher disease activity despite having stable disease.

References

1. SZKUDLAREK M, NARVESTAD E, KLARLUND M, COURT-PAYEN M, THOMSEN HS, OSTERGAARD M: Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination. *Arthritis Rheum* 2004; 50: 2103-12.
2. RAKIEH C, NAM JL, HUNT L *et al*.: Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. *Ann Rheum Dis* 2015; 74: 1659-66
3. 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.
4. PELUSO G, MICHELUTTI A, BOSELLO S, GREMESE E, TOLUSSO B, FERRACCIOLI G: Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. *Ann Rheum Dis* 2011; 70: 172-5.
5. GENG Y, HAN J, DENG X, ZHANG Z: Deep clinical remission: an optimised target in the management of rheumatoid arthritis? Experience from an ultrasonography study. *Clin Exp Rheumatol* 2016; 34: 581-6.
6. 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.
7. 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.
8. NAREDO E, IAGNOCCO A: One year in review: ultrasound in arthritis. *Clin Exp Rheumatol* 2016; 34: 1-10.
9. ÇAKILILI ÖT, PAY S, İNANC N *et al*.: Use of musculoskeletal ultrasound in Rheumatoid arthritis in Turkey among rheumatologists: A national targeted ultrasound initiative survey. *Eur J Rheumatol* 2015; 2: 43-44.
10. WAKEFIELD RJ, D'AGOSTINO MA, NAREDO E *et al*.: After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? *Postgrad Med J* 2012; 88: 482-6.
11. AYDIN SZ, PAY S, INANC N *et al*.: Targeted Ultrasound Initiative (TUI) Steering Committee. Which joints and why do rheumatologists scan in rheumatoid arthritis by ultrasonography? A real life experience. *Clin Exp Rheumatol* 2017; 35: 508-11.
12. ALETAHA D1, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569-81.
13. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al*.: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-7.
14. NAREDO E, VALOR L, DE LA TORRE I *et al*.: Ultrasound joint inflammation in rheumatoid arthritis in clinical remission: how many and which joints should be assessed? *Arthritis Care Res* (Hoboken) 2013; 65: 512-7.
15. PADOVANO I, COSTANTINO F, BREBAN M, D'AGOSTINO MA: Prevalence of ultrasound synovial inflammatory findings in healthy subjects. *Ann Rheum Dis* 2016; 75: 1819-23
16. BALSA A, DE MIGUEL E, CASTILLO C, PEITEADO D, MARTIN-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.