Subclinical ultrasound synovitis in a particular joint is associated with ultrasound evidence of bone erosions in that same joint in rheumatoid patients in clinical remission

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Abstract

Objective

The main aim of this study was to investigate the relationship between ultrasound (US) findings indicative of joint inflammation and US features characterising bone erosions at joint level in patients with rheumatoid arthritis (RA) in clinical remission.

Methods

Twenty-four consecutive patients with RA in clinical remission according to EULAR criteria (DAS28<2.6) underwent a complete clinical assessment. An experienced sonographer blind to the clinical data performed the US examinations to detect and score signs of joint inflammation and bone erosions from second to fifth metacarpophalangeal (MCP) joints of both hands. All joints were scanned both on dorsal and volar aspects. The second and fifth MCP joints were scanned also in lateral aspects.

Results

The patients were mainly female (79.2%), with a mean age of 63.2 years ±12.3 standard deviation (SD) and a mean disease duration of 114.5 months ±53.9 SD. Half of the patients were rheumatoid factor positive and 45.8% were anti-citrullinated protein antibody positive. A total of 192 MCP joints and 480 aspects were assessed. Of these joints, 105 (54.7%) were found inflamed by grey-scale US, 57 (29.7%) were power Doppler (PD) positive, and bone erosions were detected in 42 (21.7%) joints. PD signal was found in 30 (53.6%) of the 56 eroded aspects and in only 41 (9.7%) out of the 424 aspects without bone erosions. Both the GS and PD mean scores were statistically higher in the joints with US bone erosions compared to those without erosions.

Conclusion

A higher prevalence of PD signal was found in the joints where bone erosions were detected. This is the first study providing evidence supporting the association between US bone erosions and the persistence of subclinical inflammation in RA patients in clinical remission.

Key words
rheumatoid arthritis, clinical remission, ultrasound, bone erosions, power Doppler, synovitis.

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Received on July 2, 2015; accepted in revised form on February 1, 2016.

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Funding: this work was funded by a grant given to F. Vreju by the EULAR.

Competing interests. none declared.

Introduction

The final goal in rheumatoid arthritis (RA) is to achieve remission, in order to prevent joint damage and functional impairment (1-7). Thus, accurate assessment of the disease activity and sensitive detection of bone erosions are essential for monitoring treatment efficacy in patients with RA. Active disease appears to be the cause for structural joint damage and bone erosions are considered the result of persistent synovitis (8-11). However, bone erosions may occur also in patients achieving clinical remission. After two years of follow-up, Molenaar *et al*. detected radiographic evidence of newly developed bone erosions in 15% of RA patients in persistent remission, suggesting that a residual subclinical inflammation may be missed using only clinical and laboratory data (1). In the recent years, therefore the use of imaging techniques has been claimed to state true disease remission (12-14).

In the last decade, evidence has been gained in favour of the use of ultrasound (US) as a sensitive imaging tool to detect joint inflammation both in early RA and in established disease, and both in active disease and in clinical remission (15-19). Furthermore, the results of some studies suggest that US findings may identify patients with a high risk of early relapse (19). Different rates in achieving clinical remission between longstanding and early RA were found (20, 21). Thus, there are factors promoting the persistence of inflammation, which require further investigations and might include the presence of joint damage.

The main aim of the present study was to investigate the relationship between US findings indicative of bone erosion and both clinical and US features indicative of joint inflammation in patients with RA in clinical remission.

Methods

Patients

The study included 24 RA patients fulfilling the American College of Rheumatology diagnostic criteria, who were in clinical remission according to the European League Against Rheumatism definition of remission: disease activity score 28 (DAS28) less than 2.6 (22, 23) for at least 3 months.

All patients, were consecutively recruited from the inpatient and outpatient clinics of the Rheumatology Department, Università Politecnica delle Marche, Ancona, Italy. Patients receiving conventional DMARDs and/or biologic agents were included in the study. The study was conducted according to the Declaration of Helsinki and local regulations. Approval for the study was obtained from the local ethics committee, and patients gave their informed consent to participate.

Clinical assessment

All patients underwent a complete clinical examination carried out by two expert rheumatologists (FS and AC). Joints were evaluated by inspection, palpation and during active and passive movements, in order to detect joint swelling and tenderness. For each patient, the dominant hand was recorded. Laboratory data including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) were obtained and DAS28 was calculated in all patients. The ESR normal values were less than 15 mm/hour for males and less than 20 mm/hour for females.

US scanning technique

The scanning technique was agreed among the US experts authoring this study (LDG, EF, WG, MG, and FV).

The second through fifth metacarpophalangeal (MCP) joints were bilaterally examined both in dorsal and volar aspects. Moreover, the second and fifth MCP joints were scanned also in lateral aspects.

The first MCP joint was excluded because its anatomy is different from the other MCP joints. The multiplanar US examination was performed using a MyLab Twice (Esaote SpA, Genoa, Italy) equipped with a 6-18 MHz frequency linear probe according to the EULAR guidelines (24). Power Doppler (PD) examinations were carried out using a Doppler frequency of 9.1 MHz and a pulse repetition frequency of 750 Hz (25). All US examinations were per-

formed by an experienced sonographer (FV) who was blinded to clinical and laboratory data. Patients were asked not to talk about their clinical condition with the sonographer.

US assessment

US examinations were carried out to assess grey-scale (GS) and PD US findings indicative of joint inflammation, and to detect and score bone erosions.

US findings were assessed in terms of presence/absence according to the OMERACT preliminary definitions (26) and semiquantitative evaluation was performed using previously described scoring systems for joint inflammation (27). Both synovial fluid and synovial proliferation were considered findings indicative of joint inflammation. MCP joint effusion and synovitis were subjectively scored from 0 to 3 (0 = absence; 1 = mild; 2 = moderate; 3 = marked). The intra-articular PD signal was subjectively graded using a semiquantitative scoring system ranging from 0 to 3 (0 = absence, no intra-articular PD signal; 1 = mild, PD signal due to a single vessel; 2 = moderate, PD signal due to confluent vessels; 3 = marked, PD signals in more than half of the intra-articular area

The bone profile was assessed to report the presence/absence of bone erosions and to score them using the following scale from 0 to 4 (28):

– score 0 = absence of US findings indicative of bone erosion;
– score 1 = very small erosion, <1 mm;
– score 2 = small erosion, 1–1.9 mm;
– score 3 = moderate erosion, 2–4 mm;
– score 4 = large erosion, >4 mm.

Moreover, the extent of the bone damage was described as focal or multifocal, and the PD signal within the bone erosion, was recorded, in terms of presence/absence. When more than one erosion in an aspect was present, we considered the score for the widest of them.

Statistical analysis

Statistical analyses were performed with the software programme GraphPad Prism 5.00. All data were expressed as the mean ± standard deviations (SD) unless specified otherwise. Simple correlations were estimated by

Table I. Demographic and clinical data of the 24 rheumatoid patients recruited in this study.

Characteristic	Value
Gender - Women, number (%)	19 (79.2%)
Age, years (mean±SD)	63.2 ± 12.3
Disease duration, months (mean±SD)	114.5 ± 53.9
RF positive (%)	12 (50%)
ACPA positive (%)	11 (45.8%)
RF and ACPA negative (%)	11 (45.8%)
DAS28 (mean±SD)	2.50 ± 0.1
ESR, mm/1h (mean±SD)	10.08 ± 3.2
CRP, mg/dl (mean±SD)	0.59 ± 0.41
HAQ (mean±SD)	0.36 ± 0.13

ACPA: anti-citrullinated protein antibodies; CRP: C-reactive protein; DAS28: disease activity score 28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; SD: standard deviation.

Table II. Prevalence of US findings and scores recorded in the 480 MCP joint aspects.

A. Joint inflammation

	Score				
	0	1	2	3	≥1
Grey-scale ultrasound	391	34	45	10	147
Power Doppler	409	34	28	9	71

B. Bone erosions

	Score					
	0	1	2	3	4	≥1
Bone erosions	424	22	22	7	5	56

Table III. Double entry table showing the relationship between presence/absence of intra-articular power Doppler signal and presence/absence of at least one bone erosion recorded in the 480 joint aspects.

	PD signal +	PD signal -	Total
Bone erosion +	30	26	56
Bone erosion –	41	383	424
Total	71	409	480

PD: intra-articular power Doppler.

Table IV. Double entry table showing the relationship between intra-articular power Doppler score and the bone erosion score (**A**) or type (**B**) recorded in the 480 joint aspects

A

		PD signal +			
		Score 3	Score 2	Score 1	Total
Bone erosion +	Score 4	1	0	0	1
	Score 3	1	1	1	3
	Score 2	3	9	2	14
	Score 1	0	8	4	12
	Total	5	18	7	30

B

		PD signal +			
Bone erosion +		Score 3	Score 2	Score 1	Total
	Multifocal	3	5	1	9
	Focal	2	13	6	21
	Total	5	18	7	30

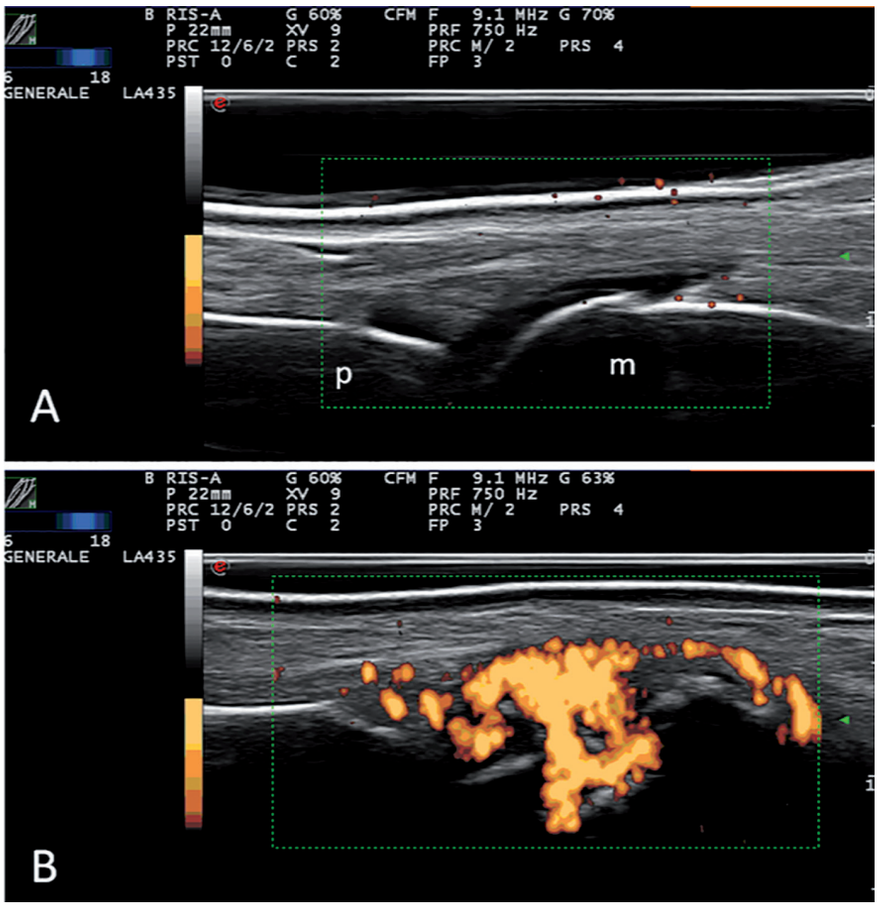

Fig. 1. Second metacarpophalangeal joint of the dominant hand. **A**. Dorsal longitudinal scan showing the presence of a minimal abnormal amount of synovial fluid on the dorsal aspect of the metacarpal head. No power Doppler signal was detectable even using very high level of Doppler gain (70%) which generated small artefactual Doppler spots. **B**. Lateral longitudinal scan revealing marked intra-articular power Doppler signal at synovial proliferation invading the bone erosion on the lateral aspect of the metacarpal head. **m** = metacarpal head; **p** = proximal phalanx.

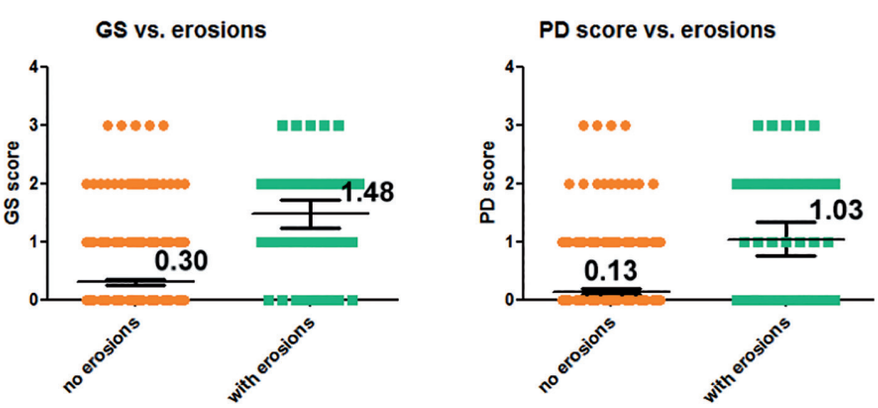

Fig. 2. GS and PD scores in patients with erosions, compared to those in patients without erosions.

Pearson's correlation coefficient. The Mann Whitney test was used to calculate statistically significant difference between joints with and without bone erosions, in terms of PD and GS findings. We considered $p<0.05$ as statistically significant.

Results

Demographic and clinical characteristics of the 24 RA patients in clinical remission enrolled in the present study are reported in Table I.

A total of 192 MCP joints were scanned and data were acquired in 480 aspects, both in GS and PD (Table II). GS US changes indicative of joint inflammation were found in 105 (54.7%) out of 192 joints, from which, 50 aspects in the dominant and 39 in the non-dominant hand. Intra-articular PD signal was detected in 57 (29.7%) out of 192 MCP joints, 32 in the dominant and 25 in the non-dominant hand.

Figure 1 shows a representative example of subclinical joint inflammation.

Table III shows the relationship between the presence/absence of intra-articular PD signal and US bone erosions as recorded in the 480 aspects. PD signal was found in 30 (53.6%) out of the 56 eroded aspects and in only 41 (9.7%) out of the 424 aspects without bone erosions. At least one bone erosion was found in 30 (42.3%) of the 71 PD positive aspects and in only 26 (6.4%) out of the 409 aspects with no PD signal.

The median PD score was 1 in the joints with bone erosions compared to 0 in the joints without erosions ($p<0.001$). The median GS score was 2 in the joints with bone erosions, compared to 0 in those without erosions ($p<0.001$) (Fig. 2).

We found that 23 (62%) out of 37 aspects with a PD score ≥2 had at least one bone erosion. PD signal was detected in 18 (53%) out of the 34 aspects found positive for bone erosions with an erosion score ≥2 (Table IVA). Moreover, a higher percentage of aspects with high PD score was found in aspects with multifocal erosions: of the 9 aspects where multifocal erosions were found, 3 of them (33%) showed a PD score of 3, while of the 21 aspects with focal erosions only 2 (10%) out of 21 showed a PD score of 3 (Table IVB). There is a tendency to a positive correlation between both the PD presence and PD score and the type (*i.e.* focal or multifocal) of the erosions and (r= 0.35, $p<0.001$ and r=0.41, $p<0.001$).

The presence of PD signal (r=0.31, $p<0.001$) and the PD score (r=0.38, $p<0.001$) tend to correlate with the erosion score. In the same time, there is a higher correlation between the GS score and the erosion score (r=0.47, $p<0.001$).

Discussion

The results of the present study provide evidence for a positive association between US inflammatory changes and the presence of US bone erosions in RA patients in clinical remission.

This evidence can be explained making two hypotheses. In the first, the bone erosions are the natural consequence of the persistent joint inflammation. We can think that US can detect subclinical findings of joint inflammation in the areas most aggressively hit by the disease and/or where the inflammation has started earlier. In the second hypothesis, bone erosions sustain joint inflammation (29). The presence of bone (and maybe cartilage) degradation elements, as result of joint damage, can trigger immunological pathways causing further joint inflammation. Of note, these two hypotheses are not in contrast and we can assume the establishing of a vicious circle in which the joint inflammation leads to joint damage with the consequent release of bone and cartilage fragments sustaining the joint inflammation.

The possibility that local factors, such as the presence of bone erosion, can contribute to maintain joint inflammation is not new (30) and it may have practical relevant consequences. In fact this can guide imaging monitoring of the disease activity at joint level. In the setting of clinical remission, joints with bone erosions could be considered the sites to scan with the higher probability to find subclinical inflammation. Those areas may be the targets to select for tailoring imaging monitoring in RA patients in clinical remission. This approach may make feasible the use of US or MRI, which are largely considered more sensitive than the clinical examination, but not sustainable in daily clinical practice, especially in a limited resources context.

The main limitations of the present study include. First, the small number of recruited patients with a relatively late disease. Second, US findings were acquired by only one operator even if experienced in musculoskeletal US. Third, the detection of bone erosions by US was not confirmed by other imaging techniques (*i.e.* CT scan).

In conclusion, the results of this study suggest that there is a positive correlation between the US bone erosions and US signs of subclinical synovitis in RA patients in clinical remission. Further investigations aimed at confirming the results of this study in a larger cohort of patients with earlier stages of the disease are required.

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