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# Ultrasound-detected activity in rheumatoid arthritis on methotrexate therapy: Which joints and tendons should be assessed to predict unstable remission?

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**Abstract** The aim of the study was to investigate the predictive value of different reduced joint ultrasound (US) assessments of synovitis and tenosynovitis in relation to unstable remission in a cohort of rheumatoid arthritis (RA) patients on methotrexate therapy. Forty-seven RA patients (38 women, 9 men), being treated with methotrexate (MTX), in clinical remission as judged by their consultant rheumatologist were evaluated for disease activity according to the Disease Activity Score (DAS) 28 at baseline and 6 months. Sustained remission and unstable remission were defined according to the baseline and 6-month DAS28 and changes in RA therapy during the follow-up. Each patient underwent at baseline a B-mode and power Doppler (PD) assessment of 44 joints and 20 tendons/tendon compartments by a rheumatologist blinded to the clinical and laboratory data. B-mode synovial hypertrophy (SH), synovial PD signal, B-mode tenosynovitis, and Doppler tenosynovitis were scored 0–3. The presence and index of synovial PD signal in 44 joints [odds ratio (OR) 8.21 ($p = 0.016$) and OR 2.20 ($p = 0.049$), respectively] and in 12 joints [OR 5.82 ($p = 0.041$) and OR 4.19 ($p = 0.020$), respectively], the presence of SH in wrist and MCP joints [OR 4.79 ($p = 0.045$)], and the presence of synovial PD signal in wrist–MCP–ankle–MTP joints [OR 4.62 ($p = 0.046$)] were predictors of unstable remission. The 12-joint or wrist–hand–ankle–MTP US assessments can predict unstable remission in RA patients in apparent clinical remission being treated with MTX.

**Keywords** Ultrasound · Doppler · Synovitis · Tenosynovitis · Rheumatoid arthritis · Remission

## Introduction

In recent years, remission has become a realistic therapeutic goal in rheumatoid arthritis (RA) management thanks to early diagnosis and treatment, effective drugs, both old and new, tight clinical control, and the treat-to-target concept [1, 2]. In this current scenario, therapeutic decisions should target sustained remission in RA clinical practice. Thus, accurate assessment of remission state is of utmost importance for therapeutic decision making regarding RA patients [1, 2].

Remission in RA can be established and measured by different instruments [e.g., Disease Activity Score (DAS), DAS28, Simple Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI)] or by the new remission criteria in RA by the ACR and European League Against Rheumatism (EULAR) [3]. These instruments are either criteria or composite scores, which are combinations of clinical and laboratory parameter surrogates for inflammation. However, clinical parameters (e.g., tender and swollen joints) may not accurately reflect real joint synovitis in RA patients. Over the last decade, musculoskeletal ultrasound (US) on B-mode has widely demonstrated greater sensitivity than clinical assessment for detecting synovitis and tenosynovitis in RA target joints [4–7]. Moreover, US on Doppler mode detects pathological synovial blood flow, which reflects joint inflammatory activity [8–10].

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Several recent studies have shown the capability of US to detect B-mode synovitis and synovial Doppler activity in a high percentage of RA patients in clinical remission treated with either synthetic or biological disease-modifying antirheumatic drugs (DMARDs) [11–23]. However, the most important capability aspect is that US-detected subclinical synovitis, mainly synovial Doppler signal, has shown predictive value in relation to radiographic damage progression [13, 21, 23] and disease flare or relapse [14, 17, 19, 23]. In the above studies, US assessment has ranged from a reduced number of wrist and hand [11, 13, 15, 17–21] joints to a comprehensive examination of 42 [12, 16] or 44 joints [14]. In addition, these studies have evaluated only intra-articular US-detected synovitis but not tenosynovitis which is an important component of joint inflammation in RA [24].

We have previously shown that a feasible US assessment of wrist, ankle, and second through fifth metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints was highly sensitive for detecting residual B-mode and Doppler intra-articular synovitis as compared with a comprehensive US assessment in RA patients in clinical remission [22]. However, the optimal number and which joints and/or tendons should be assessed for predicting RA clinical outcomes in patients in clinical remission has not been addressed.

The objective of the present prospective study was to investigate the predictive value of different reduced joint US assessments of synovitis and tenosynovitis in relation to unstable remission in a cohort of RA patients in clinical remission being treated with methotrexate (MTX).

## Patients and methods

Forty-seven consecutive patients (38 women, 9 men) with RA according to the American College of Rheumatology 1987 criteria [25] and treated with MTX for at least 2 years were prospectively recruited from the outpatient rheumatology clinic for a period of 3 months. Inclusion criteria consisted of being in clinical remission judged by their usual consultant rheumatologist and having had neither disease flare nor changes in therapy including corticosteroid and MTX doses in the previous 6 months.

The patients underwent clinical, laboratory, and musculoskeletal US examination at baseline and 6 months. Therapeutic decisions throughout the follow-up period were not taken according to the study assessments but were made by the patients' usual consultant rheumatologist, according to their clinical practice, without knowledge of the results of the clinical protocol and the US findings.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the Hospital General Universitario Gregorio Marañón (Madrid, Spain). Informed consent was obtained from all patients before study enrollment.

### Clinical and laboratory assessment

Patient demographics and RA features, including the presence of rheumatoid factor (RF) [nephelometry; >20 IU], anti-citrullinated peptide antibodies (ACPAs) [second-generation commercial enzyme-linked immunosorbent assay (Immunoscan RA; Euro-Diagnostica, Malmö, Sweden; >25 IU], and radiographic structural damage in hands or feet, were recorded at study entry. Patients were evaluated at baseline and 6 months for disease activity according to the DAS28 [26] by two of the investigators (IDlT, LME) who reached consensus on joint tenderness and swelling assessment prior to the study. These investigators were blinded to US findings. At each visit, 28 joints, including the left and right glenohumeral, elbow, and wrist joints, metacarpophalangeal (MCP) joints, proximal interphalangeal joints of the hands, and knee joints were assessed for tenderness and swelling. Tender joint counts and swollen joint counts were recorded. Patients rated their overall disease activity on a 100-mm visual analog scale at each visit. Data on serum markers of inflammation [C-reactive protein (CRP) level [normal 0–0.5 mg/dL] and erythrocyte sedimentation rate (ESR) [normal 10–20 mm/h] were obtained from laboratory tests performed on the day of each clinical evaluation. In addition, functional ability was assessed with a self-assessment Spanish version of the Health Assessment Questionnaire (HAQ) [27].

### US assessment

Each patient underwent B-mode and power Doppler (PD) assessments at baseline and 6 months by a rheumatologist experienced in musculoskeletal US (EN), blinded to the clinical, laboratory, and radiographic data, on the day of the clinical evaluations. To reduce the possibility of bias, the patients were asked not to talk about their clinical data to the US examiner. We also maximized the level of darkness in the examination room.

The US assessment consisted of a systematic longitudinal and transverse multiplanar examination of 44 joints (i.e., 36 joint regions) and 20 tendons/tendon compartments using a real-time scanner (Mylab 70 XVG, Esaote, Genoa, Italy) equipped with two multifrequency linear array transducers, a 6- to 18-MHz transducer for superficial areas and a 4- to 13-MHz transducer for deep areas.

The following bilateral joints were investigated for the presence of intra-articular B-mode synovial hypertrophy (SH) and synovial PD signal: glenohumeral (i.e., posterior and axillary recesses and biceps sheath), elbow (i.e.,

anterior and posterior recesses), wrist (i.e., radiocarpal, midcarpal, distal radioulnar, and ulnar–carpal joints; dorsal recesses), second through fifth metacarpophalangeal (MCP) (i.e., dorsal and palmar recesses), second through fifth proximal interphalangeal (PIP) of the hands (i.e., dorsal and palmar recesses), hip (i.e., anterior recess), knee (i.e., anterior and parapatellar recesses), ankle joints (i.e., tibiotalar joint, anterior recess and subtalar joint, medial and lateral recesses), and second through fifth metatarsophalangeal joints (i.e., dorsal recess). We considered wrist SH or synovial PD signal positive if they were detected in the radiocarpal, midcarpal, distal radioulnar, or the ulnar–carpal joints. We also considered ankle SH or synovial PD signal positive if they were detected in either the tibiotalar or the subtalar joints.

The following bilateral hand–wrist and foot–ankle tendons–tendon compartments with synovial sheath were evaluated for the presence of B-mode tenosynovitis (TS) and tenosynovial PD signal: second through sixth wrist extensor compartments, second through fifth finger flexor digitorum superficialis and profundus tendons, and tibialis posterior tendon.

B-mode and PD machine settings were optimized before the study and standardized for the whole study. These settings were as follows: B-mode frequency of 10–18 MHz, B-mode gain of 56–62 %, Doppler frequency of 6.3–14.3 MHz, Doppler gain of 45–62 %, low-wall filters, and pulse repetition frequency of 500–750 Hz, depending on the depth of the anatomic area.

B-mode SH was defined according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) as the presence of abnormal hypoechoic (relative to subdermal fat) intra-articular tissue that is nondisplaceable and poorly compressible [28]. At each intra-articular synovial recess, B-mode SH was scored semiquantitatively on a scale of 0–3 (0, absent; 1, mild; 2, moderate; and 3, marked). Synovial PD signal was also scored on a semiquantitative scale of 0–3 [0, absent (no synovial flow); 1, mild ($\leq$3 PD signals); 2, moderate (>3 PD signals in less than half of the synovial area); and 3, marked (signals in more than half of the synovial area)] [29, 30]. Each joint was scored for B-mode SH and synovial PD signal on a scale from 0 to 3. These scores corresponded to the maximum score for SH and PD signal, respectively, obtained from any one of the synovial sites evaluated at each joint. The wrist and ankle SH and PD signal scores corresponded to the maximum score for these parameters, respectively, obtained from any of the joints evaluated at the above joint regions.

Tenosynovitis on B-mode was defined according to OMERACT as abnormal anechoic and/or hypoechoic (relative to tendon fibers) tendon sheath widening which can be related both to the presence of tenosynovial abnormal fluid and hypertrophy [31]. Tenosynovitis on Doppler mode was identified according to OMERACT as the presence of peritendinous Doppler signal within the synovial sheath, seen in two perpendicular planes, excluding normal feeding vessels (i.e., vessels at the mesotenon or vinculae or vessels entering the synovial sheath from surrounding tissues) only if the tendon shows peritendinous synovial sheath widening on B-mode [31]. B-mode tenosynovitis was scored semiquantitatively on a scale of 0–3 (i.e., grade 0, normal; grade 1, minimal; grade 2, moderate; and grade 3, severe) [31]. PD tenosynovitis was also scored on a semiquantitative scale of 0–3 (i.e., grade 0, no Doppler signal; grade 1, focal; grade 2, multifocal; and grade 3, diffuse) [31]. Also, if in addition to abnormal peritendinous (i.e., intrasheath) signal there was abnormal intra-tendinous signal seen in two perpendicular planes (i.e., excluding intra-tendinous small isolated signals that can correspond to normal feeding vessels), the grades 1 and 2 were increased by 1 point, according to the OMERACT scoring system for Doppler tenosynovitis [31]. The time spent on the PDUS assessment was 30–40 min.

A global index for B-mode SH (SHI) (0-108) and a global index for synovial PD signal (PDI) (0-108) (the sum of the B-mode SH and synovial PD signal scores, respectively, obtained for each evaluated joint or joint region) were calculated for each patient. In addition, we calculated the SHI and PDI for different models of joint combinations as follows: large joints (i.e., bilateral glenohumeral, elbow, wrist, hip, knee and ankle joints), wrist and hand (i.e., bilateral wrist, second through fifth MCP, and second through fifth PIP joints), reduced wrist and hand (i.e., bilateral wrist and second through fifth MCP joints), and wrist–MCP–ankle–MTP (i.e., bilateral wrist, second through fifth MCP, ankle, and second through fifth MTP joints). We also calculated the above scores for the 12-joint US assessment (i.e., bilateral elbow, wrist, second and third MCP, knee and ankle joints) [32], the 7-joint US assessment (i.e., wrist, second and third MCP, second and third PIP of the clinically dominant hand, and second and fifth MTP of the clinically dominant foot) [33], and the 6-joint US assessment (i.e., bilateral wrist, second MCP, and knee) [34], which had been previously validated in published studies on RA therapy monitoring.

A global index for B-mode tenosynovitis (BTI) (0-60) and a global index for PD tenosynovitis (PTI) (0-60) (the sum of the B-mode tenosynovitis and PD tenosynovitis scores, respectively, obtained for each evaluated tendon or tendon compartment) were calculated for each patient.

### Clinical outcomes

Clinical remission at baseline or 6 months was defined as a DAS28 < 2.6 [35]. DAS28-determined sustained remission was defined as both a baseline and 6-month DAS28 < 2.6

without any change in RA therapy during the follow-up. Unstable remission was defined either as a baseline or 6-month DAS28 ≥ 2.6 having had no changes in RA therapy during the follow-up or as an increase in RA therapy because of disease relapse determined by the patients' usual consultant rheumatologist during the follow-up period (i.e., increase in corticosteroid or MTX dosage, initiation of other synthetic DMARD or a biologic DMARD) [36].

### Statistical analysis

Statistical analysis was performed using SPSS version 13.0 (SPSS, Chicago, IL, USA). Quantitative variables were presented as the mean ± SD and range. Categorical variables were presented as absolute frequencies and percentages. Comparisons between independent means were analyzed using Mann–Whitney test. Association between categorical variables was evaluated by Chi-square test. Multivariate logistic regression models were used to predict unstable remission from baseline clinical and PDUS variables. Variables with a *P* value less than 0.10 were used in multivariate models. Forced introductions as well as stepwise methods were used for variable selection. *P* values > 0.05 were considered significant.

## Results

### Demographics and clinical data at baseline and 6 months

The mean (SD, range) age of the patients was 61.6 (13.6, 28–82) years, and the mean (SD, range) disease duration was 9.4 (6.9, 1–20) years. Thirty-three (70.2 %) patients were RF positive and 35 (74.5 %) were ACPA positive. Thirteen (27.7 %) patients showed radiographic erosions. At baseline, the treatment for RA was MTX [47 (100 %) patients; mean (SD, range) dose, 12.3 (3.9, 5–20 mg/week)] and oral prednisone [14 (29.8 %) patients; mean (SD, range) dose, 3.9 (1.9, 2.5–7.5 mg/day].

Of the 47 patients included in the study, DAS28 criterion of sustained remission was fulfilled in 15 (31.9 %) and unstable remission criteria were fulfilled in 32 (68.1 %) patients. Eight (17 %) patients suffered relapse during the follow-up: three (6.4 %) patients began a biological DMARD, and in five (10.6 %) patients, the MTX dose was increased (5–10 mg/week) because of clinical worsening of disease activity. Clinical data from these eight patients at 6 months were excluded from the analysis.

The mean (SD, range) DAS28 was 2.4 (1.2, 0.5–5.4) at baseline and 2.6 (1.2, 0.5–5.1) at 6 months. At baseline, 27 (57.4 %) patients showed a DAS28 < 2.6 [mean DAS28 (SD, range) 1.6 (0.7, 0.5–2.5)] and 20 (42.6 %) patients showed a DAS28 ≥ 2.6 [mean DAS28 (SD, range) 3.6 (0.7, 2.8–5.4)]. At 6 months, the DAS28 was <2.6 in 21 (53.8 %) patients [mean DAS28 (SD, range) 1.8 (0.6, 0.5–2.7)] and ≥2.6 in 18 (46.2 %) patients [mean DAS28 (SD, range) 3.9 (0.5, 3.2–5.1)]. The mean (SD, range) HAQ was 0.71 (0.75, 0–2.5) at baseline and 0.70 (0.75, 0–2.5) at 6 months. The mean (SD, range) ESR and CRP were 10.9 mm/h (8.3, 2–37) and 0.7 mg/dL (1.2, 0.1–6.5), respectively, at baseline and 12.8 mm/h (9.4, 2–39) and 0.5 mg/dL (0.4, 0–2), respectively, at 6 months.

### US findings at baseline and 6 months

At baseline, B-mode SH was detected in 24 (88.8 %) patients with DAS28 < 2.6 and 20 (100 %) patients with DAS 28 ≥ 2.6 ($p = 0.202$). Synovial PD signal was detected in 14 (51.9 %) patients with DAS28 < 2.6 and 11 (55 %) patients with DAS 28 ≥ 2.6 ($p = 0.592$). B-mode tenosynovitis was detected in 10 (37 %) patients with DAS28 < 2.6 and eight (40 %) patients with DAS 28 ≥ 2.6 ($p = 0.556$). PD tenosynovitis was detected in seven (25.9 %) patients with DAS28 < 2.6 and four (20 %) patients with DAS 28 ≥ 2.6 ($p = 0.256$).

At baseline, there were no significant differences between DAS28-determined active and inactive patients in the B-mode and PD indices for synovitis and tenosynovitis: mean SHI [7.31 ± 8.67 (range 1–32) vs. 7.22 ± 6.22 (range 0–23), $p = 0.471$], mean PDI [3.00 ± 6.38 (range 0-23) vs. 1.70 ± 3.05 (range 0–13), $p = 0.989$], mean BTI [1.48 ± 3.03 (range 0–12) vs. 0.50 ± 1.03 (range 0–4), $p = 0.810$], and mean PTI [0.48 ± 1.20 (range 0–4) vs. 0.31 ± 1.01 (range 0–4), $p = 0.789$].

At 6 months, B-mode SH was detected in 19 (90.5 %) patients with DAS28 < 2.6 and 17 (94.4 %) patients with DAS 28 ≥ 2.6 ($p = 0.581$). Synovial PD signal was detected in 13 (38.1) patients with DAS28 < 2.6 and nine (50 %) patients with DAS 28 ≥ 2.6 ($p = 0.410$). B-mode tenosynovitis was detected in six (28.6 %) patients with DAS28 < 2.6 and seven (38.9 %) patients with DAS 28 ≥ 2.6 ($p = 0.461$). PD tenosynovitis was detected in two (9.5 %) patients with DAS28 < 2.6 and five (27.8 %) patients with DAS 28 ≥ 2.6 ($p = 0.233$).

At 6 months, there were no significant differences between active and inactive patients according to the DAS28 in the global PDUS indices: mean SHI [9.47 ± 8.65 (range 0–32) vs. 4.71 ± 3.96 (range 0–14), $p = 0.095$], mean PDI [4.24 ± 6.56 (range 0–23) vs. 0.62 ± 0.97 (range 0–3), $p = 0.199$], mean BTI [1.65 ± 3.26 (range 0–12) vs. 0.67 ± 1.53 (range 0–6), $p = 0.601$], and mean PTI [0.65 ± 1.37 (range 0–4) vs. 0.24 ± 0.89 (range 0–4), $p = 0.467$].

Representative ultrasound images of B-mode and Doppler synovitis and tenosynovitis are shown in Figs. 1, 2, and 3.

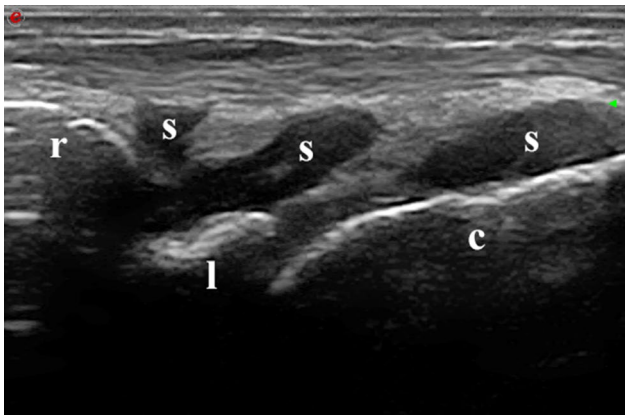


**Fig. 1** Longitudinal ultrasound image of the dorsal aspect of the radiocarpal and midcarpal joints that show B-mode synovial hypertrophy (s) in a rheumatoid arthritis patient in clinical remission. *r* radius, *l* lunate, *c* capitate

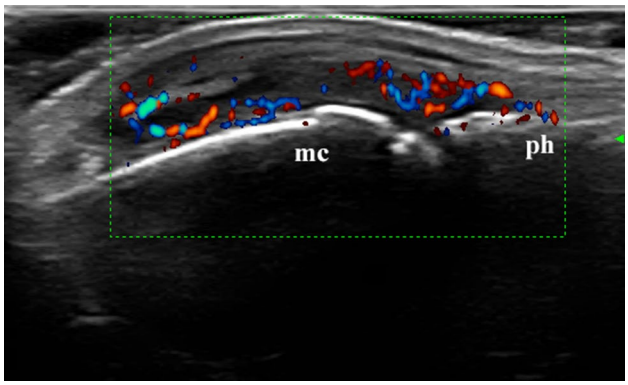


**Fig. 2** Longitudinal ultrasound image of the dorsal aspect of a metacarpophalangeal joint that shows B-mode synovial hypertrophy with power Doppler signal in a rheumatoid arthritis patient in clinical remission. *mc* metacarpal bone, *pp* proximal phalanx

## Comparison of baseline US parameters between patients with sustained remission and patients with unstable remission

Table 1 displays the prevalence of clinical and laboratory baseline findings as well as the prevalence of baseline B-mode SH and synovial PD signal in the comprehensive and reduced joint US assessments, B-mode tenosynovitis, and PD tenosynovitis in patients with sustained remission and those with unstable remission. There were no significant differences between these groups in the following: sex, treatment with prednisone, positivity for RF or ACPAs, the presence of radiographic erosions, the presence of B-mode synovitis either in the comprehensive US

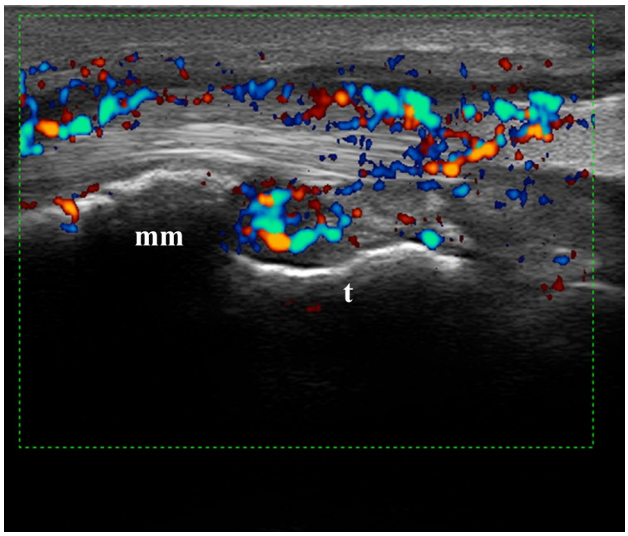


**Fig. 3** Longitudinal ultrasound image of the tibialis posterior tendon that shows B-mode and Doppler tenosynovitis in a rheumatoid arthritis patient in clinical remission. *mm* medial malleolus; *t* talus

assessment or in most reduced joint US assessments, and the presence of B-mode tenosynovitis. However, there was a significant association between unstable remission and the presence of B-mode synovitis in bilateral wrist and second through fifth MCP joints ($p = 0.036$) with a likelihood ratio of 4.52 ($p = 0.034$). There was also a significant association between unstable remission and the presence of synovial PD signal in 44 joints ($p = 0.014$; likelihood ratio, 6.38; $p = 0.012$), the presence of synovial PD signal in bilateral wrist–second through fifth MCP–ankle–second through fifth MTP joints ($p = 0.037$; likelihood ratio, 4.51; $p = 0.034$), the presence of synovial PD signal in 12 joints $p = 0.037$; likelihood ratio, 4.51; $p = 0.034$), and the presence of PD tenosynovitis ($p = 0.007$; likelihood ratio 10; $p = 0.002$).

Table 2 shows the mean values of clinical and laboratory baseline data, baseline SHI and PDI derived from the comprehensive and the reduced joint US assessments, and baseline BTI and PTI in patients who were in sustained remission and those who had unstable remission. The mean baseline MTX dose; 44-joint PDI, SHI, and PDI for the wrist–MCP–PIP US assessment; SHI and PDI for the wrist–MCP US assessment; PDI for the wrist–MCP–ankle–MTP US assessment; PDI for the 12-joint US assessment; PDI for the 6-joint US assessment; and PTI were significantly higher in the unstable remission group than in the sustained remission group. In contrast, the other B-mode and PD US baseline indices, though they were higher in the patients with unstable remission than in patients with sustained remission, did not significantly differ between both

**Table 1** Prevalence of clinical, laboratory, and US baseline parameters in patients with sustained remission and patients with unstable remission

| Clinical, laboratory, and US baseline parameters | Patients with sustained remission $n = 15$ | Patients with unstable remission $n = 32$ | $p$ |
|---|---|---|---|
| Sex, men, *n* (%) | 4 (26.7) | 5 (15.6) | 0.302 |
| Presence of RF, *n* (%) | 10 (66.7) | 23 (71.9) | 0.484 |
| Presence of ACPAs, *n* (%) | 10 (66.7) | 25 (78.1) | 0.310 |
| Oral prednisone, *n* (%) | 5 (33.3) | 9 (28.1) | 0.421 |
| Presence of radiographic erosions, *n* (%) | 3 (20) | 10 (31.3) | 0.332 |
| Presence of SH in 44 joints, *n* (%) | 13 (86.7) | 31 (96.9) | 0.235 |
| Presence of synovial PD signal in 44 joint, *n* (%) | 4 (26.7) | 21(65.6) | 0.014 |
| Presence of SH in large joints, *n* (%) | 10 (66.7) | 24 (75) | 0.396 |
| Presence of synovial PD signal in large joints, *n* (%) | 0 (0) | 7 (21.9) | 0.054 |
| Presence of SH in wrist–MCP–PIP joints, *n* (%) | 8 (53.3) | 25 (78.1) | 0.084 |
| Presence of synovial PD signal in wrist–MCP–PIP joints, *n* (%) | 4 (26.7) | 16 (50) | 0.116 |
| Presence of SH in wrist–MCP joints, *n* (%) | 7 (46.7) | 25 (78.1) | 0.036 |
| Presence of synovial PD signal in wrist–MCP joints, *n* (%) | 4 (26.7) | 16 (50) | 0.116 |
| Presence of SH in wrist–MCP–ankle–MTP, *n* (%) | 12 (80) | 30 (93.8) | 0.178 |
| Presence of synovial PD signal in wrist–MCP–ankle–MTP, *n* (%) | 4 (26.7) | 19 (59.4) | 0.037 |
| Presence of SH in 12 joints, *n* (%) | 11 (73.3) | 28 (87.5) | 0.212 |
| Presence of synovial PD signal in 12 joints, n (%) | 4 (26.7) | 19 (59.4) | 0.037 |
| Presence of SH in seven joints, *n* (%) | 6 (40) | 21 (65.6) | 0.090 |
| Presence of synovial PD signal in seven joints, *n* (%) | 3 (20) | 13 (40.6) | 0.144 |
| Presence of SH in six joints, *n* (%) | 10 (66.7) | 26 (81.3) | 0.229 |
| Presence of synovial PD signal in six joints, *n* (%) | 4 (26.7) | 17 (53.1) | 0.082 |
| Presence of B-mode tenosynovitis, *n* (%) | 3 (20) | 15 (46.9) | 0.072 |
| Presence of PD tenosynovitis, *n* (%) | 0 (0) | 11 (34.4) | 0.007 |

*n* number, *US* ultrasound, *RF* rheumatoid factor, *ACPAs* anti-citrullinated peptide antibodies, *SH* synovial hypertrophy, *PD* power Doppler, *MCP* metacarpophalangeal, *MTP* metatarsophalangeal

groups. Neither clinical nor laboratory baseline parameters, with the exception of the dose of MTX, showed significant differences between the two groups of patients.

### Predictive value of baseline US parameters in relation to unstable remission

Thirty two multivariate logistic regression models have been run to test predictive capacity of baseline US quantitative indices and US dichotomic findings (presence/absence) to predict instability in remission, initially adjusted by several covariates. None of the covariates, age, disease duration, presence and values of RF and ACPAs, HAQ value, oral prednisone, MTX dose, and presence of radiographic erosions was associated to the stability of remission. Table 3 shows the odds ratio of unstable remission that reached statistical significance in logistic regression models including the above clinical and laboratory variables and baseline US variables. The presence and index of synovial PD signal in 44 joints and in 12 joints, the presence of SH in wrist and MCP joints, and the presence of synovial PD signal in wrist–MCP–ankle–MTP joints were predictors of unstable remission. The predictive value for the presence of PD tenosynovitis could not be estimated due to statistical reasons (no patients with sustained remission showed PD tenosynovitis).

## Discussion

Currently available evidence supports the growing conviction that treatment for RA should target sustained clinical remission in both early and established disease [1, 2]. However, a number of published studies on RA have shown that sustained remission is uncommon in clinical practice [37–39] and that unstable remission and disease relapse are associated with adverse outcomes [40]. Thus, accurate and strict monitoring of RA activity is always recommended [1, 2]. In this cohort study, we included RA patients, being treated with MTX, in sustained clinical remission as

**Table 2** Clinical, laboratory, and US baseline parameters in patients with sustained remission and patients with unstable remission

| Clinical, laboratory, and US baseline parameters | Patients with sustained remission $n = 15$ | Patients with unstable remission $n = 32$ | $p$ |
|---|---|---|---|
| Age, mean, (SD), (range) years | 58.2 (12.8) (28–77) | 63.2 (14.1) (30–82) | 0.274 |
| Disease duration, mean, (SD), (range) years | 9.1 (7.9) (1–20) | 9.4 (6.6) (1–20) | 0.405 |
| RF, mean, (SD), (range), IU | 51.8 (53.2) (20–213.4) | 94 (130.1) (20–561) | 0.583 |
| ACPAs, mean, (SD), (range), IU | 551.7 (928.5) (25–3200) | 549.1 (738.3) (25–3200) | 0.502 |
| HAQ, mean, (SD), (range) | 0.47 (0.63) (0–2) | 0.80 (0.78) (0–2.5) | 0.187 |
| MTX dose, mean, (SD), (range), mg/week | 10.2 (3.7) (5–15) | 13.3 (3.6) (7.5–20) | 0.013 |
| 44-joint SHI, mean, (SD), (range), (0–108) | 4.93 (3.67) (0–12) | 10.66 (9.89) (0–44) | 0.069 |
| 44-joint PDI, mean, (SD), (range), (0–108) | 0.53 (1.06) (0–3) | 4.72 (7.93) (0–38) | 0.005 |
| Large joints SHI, mean, (SD), (range), (0–36) | 1.67 (1.54) (0–5) | 2.16 (2.23) (0–9) | 0.658 |
| Large joints, PDI, mean, (SD), (range), (0–36) | 0 (0) (0) | 0.31 (0.64) (0–2) | 0.053 |
| Wrist–MCP–PIP joints, SHI, mean, (SD), (range), (0–54) | 1.47 (1.81) (0–6) | 6.19 (8.46) (0–41) | 0.036 |
| Wrist–MCP–PIP joints, PDI, mean, (SD), (range), (0–54) | 0.40 (0.83) (0–3) | 3.50 (7.33) (0–39) | 0.042 |
| Wrist–MCP joints, SHI, mean, (SD), (range), (0–30) | 1.27 (1.79) (0–6) | 4.38 (5.78) (0–26) | 0.033 |
| Wrist–MCP joints, PDI, mean, (SD), (range), (0-30) | 0.40 (0.83) (0–3) | 2.69 (5.16) (0–27) | 0.045 |
| Wrist–MCP–ankle–MTP, SHI,, mean, (SD), (range), (0–60) | 3.13 (3.04) (0–10) | 7.19 (7.23) (0–27) | 0.085 |
| Wrist–MCP–ankle–MTP, PDI,, mean, (SD), (range), (0–60) | 0.53 (1.06) (0–3) | 3.81 (6.05) (0–26) | 0.013 |
| 12-joint SHI, mean, (SD), (range), (0–36) | 2.47 (1.85) (0–6) | 5.31 (4.64) (0–19) | 0.076 |
| 12-joint PDI, mean, (SD), (range), (0–36) | 0.33 (0.62) (0–2) | 2.53 (3.61) (0–17) | 0.009 |
| 7-joint SHI, mean, (SD), (range), (0–21) | 0.80 (1.15) (0–3) | 2.28 (2.96) (0–11) | 0.068 |
| 7-joint PDI, mean, (SD), (range), (0–21) | 0.27 (0.59) (0–2) | 1.57 (2.97) (0–13) | 0.101 |
| 6-joint SHI, mean, (SD), (range), (0–18) | 2.00 (1.81) (0–6) | 3.13 (3.03) (0–12) | 0.332 |
| 6-joint PDI, mean, (SD), (range), (0–18) | 0.33 (0.62) (0–2) | 1.53 (2.29) (0–11) | 0.038 |
| BTI, mean, (SD), (range), (0–60) | 0.53 (1.55) (0–6) | 1.69 (2.62) (0–12) | 0.069 |
| PTI, mean, (SD), (range), (0–60) | 0 (0) (0) | 0.97 (1.67) (0–6) | 0.011 |

*n* number, *US* ultrasound, *RF* rheumatoid factor, *ACPAs* anti-citrullinated peptide antibodies, *DAS* Disease Activity Score, *SDAI* Simple Disease Activity Index, *HAQ* Health Assessment Questionnaire, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MTX* methotrexate, *SHI* index for B-mode synovial hypertrophy, *PDI* index for synovial power Doppler signal, *BTI* index for B-mode tenosynovitis, *PTI* index for power Doppler tenosynovitis, *MCP* metacarpophalangeal, *MTP* metatarsophalangeal

**Table 3** Association of clinical and US baseline parameters with unstable remission

| US baseline parameters | OR | CI 95 % | $p$ |
|---|---|---|---|
| Presence of synovial PD signal in 44 joint | 8.21 | 1.49–45.41 | 0.016 |
| 44-joint PDI | 2.20 | 1.01–4.82 | 0.049 |
| Presence of SH in wrist–MCP joints | 4.79 | 1.04–22.17 | 0.045 |
| Presence of synovial PD in wrist–MCP–ankle–MTP joints | 4.62 | 1.03–20.74 | 0.046 |
| Presence of synovial PD signal in 12 joints | 5.82 | 1.07–31.61 | 0.041 |
| 12-joint PDI | 4.19 | 1.26–13.96 | 0.020 |

*US* ultrasound, *OR* odds ratio, *CI* confidence interval, *PD* power Doppler, *SH* synovial hypertrophy, *SHI* index for B-mode synovial hypertrophy, *PDI* index for synovial power Doppler signal

judged by their usual consultant rheumatologist. However, in spite of the apparent sustained remission, only 32 % of the patients fulfilled DAS28 remission criterion both at baseline and 6 month time points. We used the DAS28 as criterion of clinical remission because of its continuing widespread use in therapeutic decision making in clinical practice.

The incidence of disease relapse at 6 months, defined as a change in RA therapy because of worsening of disease activity, was relatively low in our cohort (i.e., 17 %) in

accordance with results reported in some longitudinal studies on RA patients in remission [13, 23]. However, the incidence of DAS28-determined unstable remission in our population without treatment changes during the follow-up was high (i.e., 51 %) and also similar to that described in some remission RA cohorts [23]. We analyzed these patients together as a group with unstable remission because changes in RA treatment can depend on, in addition to the disease activity, the physician, the patient, and the moment and not necessarily indicate more RA activity than the DAS28 by itself. As previously reported [19], no baseline clinical or laboratory parameter showed association with unstable remission or disease relapse in our cohort.

Over the last years, there has been an increasing number of studies on US assessment of synovitis in RA patients in clinical remission according to different criteria and treated with either synthetic or biological DMARD [11–23]. In accordance with most of the published studies, we detected B-mode SH in the majority of patients in clinical remission according to the DAS28 and synovial PD signal in practically half of them at baseline and 6 months [11–19, 22]. In addition, as previously reported, there were no significant differences either in the SHI or the PDI between patients in DAS28 remission and those not in DAS28 remission [11, 16, 18, 22].

The capability of synovial Doppler signal to predict disease relapse in RA patients in clinical remission has been reported in recently published studies, which have assessed intra-articular synovitis in a variable number of joints [14, 17, 19, 23]. To the best of our knowledge, this is the first study that has evaluated the association of a comprehensive and several reduced joint and tendon US assessments with adverse outcomes in a cohort of RA patients in clinical remission treated with MTX. Our results confirm those from previous studies regarding the association of US-detected Doppler synovitis with unstable remission in RA patients in apparent clinical remission [14, 17, 19, 23]. Interestingly, among the reduced joint US assessments, the presence of B-mode synovitis in wrist and MCP joints; the presence of synovial PD signal in wrist, MCP, ankle and MTP joints, and the presence and grade of synovial PD in 12 joints showed predictive value in relation to unstable remission. Despite association between PD tenosynovitis and outcome, OR was not estimated due to statistical reasons.

Of particular note was that the presence of baseline Doppler tenosynovitis was significantly associated with unstable remission, and no patient in sustained remission showed this finding. Furthermore, the grade of Doppler tenosynovitis was able to discriminate between patients in sustained remission and patients with unstable remission. The inflammation of tenosynovial tissue plays an important role in early phases of the inflammatory process in RA [41–43]. Tenosynovitis can be detected by US in a relevant number of RA patients [7]. US has demonstrated high sensitivity [44] and specificity [45, 46] for detecting tenosynovitis as compared to magnetic resonance imaging. In addition, US-detected tenosynovitis has shown reproducibility [31], responsiveness [47], and predictive value in relation to erosive progression in RA [48]. Our results suggest a new aspect of the importance of tenosynovitis in RA, namely its association with unstable remission and relapse. This result, however, should be confirmed in other RA cohorts in clinical remission.

Some limitations in our study should be noted. The population size was relatively small. This may have limited the strength of some results and the predictive capability of the studied variables.

In conclusion, the results of this longitudinal study confirm those from previous studies regarding the association of US-detected Doppler synovitis with unstable remission in RA patients treated with synthetic DMARDs. The presence of B-mode synovitis in wrist and MCP joints and the presence of Doppler synovitis in these joints plus ankle and MTP joints showed predictive value in relation to unstable remission. The presence and grade of Doppler synovitis in 12 joints also showed predictive value in relation to this adverse outcome.

**Author contributions** Esperanza Naredo, Inmaculada De La Torre, Lara Valor, and Iustina Janta designed the study. Esperanza Naredo, Inmaculada De La Torre, Lara Valor, Iustina Janta, Lina Martínez-Estupiñán, Juan Carlos Nieto, Juan Gabriel Ovalles-Bonilla, Julia Martínez-Barrio, Natalia Bello, Michelle Hinojosa, María Montoro, Carlos Manuel González, Javier López-Longo, and Indalecio Monteagudo involved in data acquisition. Esperanza Naredo, Inmaculada De La Torre, Lara Valor, and Luis Carreño interpreted and analyzed the data. Esperanza Naredo, Iustina Janta, Inmaculada De La Torre, and Lara Valor prepared the manuscript.

**Compliance with ethical standards**

**Conflict of interest** Lara Valor has received speaker fees from Abbvie, Roche Farma, Bristol-Myers Squibb, and Pfizer. Juan Carlos Nieto-González has received speaker fees from Abbvie, Roche Farma, Pfizer, MSD. Francisco Javier López-Longo has received speaker fees from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, UCB, MSD, Actelion. Francisco Javier López-Longo has received research funding from Abbvie and GSK. Indalecio Monteagudo has received speaker fees from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, and UCB. Esperanza Naredo has received speaker fees from Abbvie, Roche Farma, Bristol-Myers Squibb, Pfizer, UCB, and Novartis.

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