Ultrasonographic predictors for the development of joint damage in rheumatoid arthritis patients: a single joint prospective study

P. Macchioni[1], M. Magnani[2,3], R. Mulè[4], S. Galletti[3], M. Catanoso[1], E. Pignotti[5], L. Boiardi[1], R. Meliconi[4,6], C. Salvarani[1]

[1]Servizio di Reumatologia, Arcispedale S. Maria Nuova IRCCS, Reggio Emilia, Italy; [2]Dipartimento Emergenza Urgenza, Ospedale Maggiore, Bologna; [3]Modulo Dipartimentale Imaging con Ultrasuoni, [4]Modulo di Reumatologia, and [5]Direzione Scientifica, Istituto Ortopedico Rizzoli (IOR), Bologna; [6]Dipartimento di Medicina Clinica, University of Bologna, Bologna, Italy.

Abstract

Objectives

This paper aims to evaluate if any ultrasonographic aspect of metacarpo-phalangeal (MCP) joint can be predictors for the development of new joint damage, at single joint level, in rheumatoid arthritis (RA) patients.

Methods

Two hundred and forty MCP joints of 24 patients with RA were prospectively evaluated both clinically and by ultrasound (US) at time 0, at six months and 12 months, in order to collect the following variables: presence of synovial hypertrophy and power-Doppler (PD) vascularisation both graded on a semiquantitative (0–3) scale, and the number and dimension of bone erosions. X-ray examinations were carried out at time 0 and at 12 months and lesions were graded using the Sharp/van der Heijde (S/vdH) method at single joint level. Potential prognostic determinants for joint damage obtained at the first examination and during follow-up were entered in a conditional logistic regression analysis.

Results

Fifteen out of seventeen (88%) of the new eroded joints on x-rays examination had persistent PD vascularity and 14/17 (82%) had persistent synovial thickening (p=0.001 and p=0.02, vs. non-eroded joints, respectively). In multiple conditional logistic regression analysis, the most important factor associated with the development of radiological joint damage was the presence of a synovial PD score ≥2 on two or more US evaluations (OR 8.51 [95%CI 1.84–39.48] for Rx new erosions and OR 8.30 [95%CI 1.97–38.9] for increased S/vdH local joint score). Both baseline synovial score ≥2 and presence of Rx erosions were also significantly associated with the development of radiological joint damage. Two predictive models for x-ray erosions and total single joint level S/vdH damage score were constructed consisting of 2 baseline plus one longitudinal variable with a ROC AUC of 0.916 (95%CI 0.867–0.965) and 0.886 (95%CI 0.814–0.957).

Conclusion

At the single joint level, the presence of US determined synovial thickness and PD signal at baseline and the persistent PD signal over time have relevant prognostic value for the development of articular damage in the same MCP joints of RA patients.

Key words

ultrasound, erosions, joints, rheumatoid arthritis, prospective study

Pierluigi Macchioni, MD
Mirco Magnani, MD
Rita Mulè, MD
Stefano Galletti, MD
Mariagrazia Catanoso, MD
Elettra Pignotti, BD
Luigi Boiardi, MD, PhD
Riccardo Meliconi, MD
Carlo Salvarani, MD

Please address correspondence to:
Carlo Salvarani,
Servizio di Reumatologia,
Arcispedale S.Maria Nuova,
Viale Risorgimento 80,
42100 Reggio Emilia, Italy.
E-mail: salvarani.carlo@asmn.re.it

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Introduction

The new paradigm of early aggressive therapy for rheumatoid arthritis (RA) based on biological agents has prompted the search for better approaches to monitor the impact of therapy and to define prognosis.

Standard clinical and radiographic methods utilised for the assessment of RA disease activity and severity both have significant limitations. B-mode and power-Doppler ultrasonography (US, PDUS), however, can visualise both destructive and inflammatory joint changes, and numerous recent studies have demonstrated that US is superior to standard radiological methods and equivalent to MRI in the evaluation of these lesions (1-8). Moreover, the combination of clinical evaluation and PD - US could be used in predicting progression of undifferentiated RA to RA (9).

In terms of diagnosis, studies comparing US and clinical findings in the assessment of joint inflammation have provided partially conflicting results. For example, some recent studies have reported a significant discrepancy between clinical and B-mode/PDUS findings in the evaluation of joint inflammation of the metacarpo-phalangeal (MCP) joints in RA patients (10, 11). However, all studies have for the most part demonstrated a significantly greater sensitivity of US compared to the standard clinical examination for the detection of joint synovitis (6, 12, 13).

In terms of prognosis, while some studies have reported a correlation between synovial joint inflammation, evaluated by clinical examination or MRI, and the development of joint erosions (14-19), other studies found no such association. Some authors, therefore, hypothesise that inflammation and erosive bone lesions may not be strictly associated (20, 21).

The correlation between US abnormalities and the development of radiological damage has also been assessed in two studies at patient level. One study found a significant positive correlation between synovial thickening and PD signal at baseline in the metacarpophalageal joints and the development of radiological damage to joints of the hands and feet at 54 weeks in a group of early RA patients treated with conventional agents, but not in the group treated with infliximab (22). Another study – a multicentre longitudinal study of 367 RA patients treated with anti-tumour necrosis factor – found that the time-integrated US joint count for PD signal had predictive value for the development of radiographic erosions and the progression of the total radiographic score (23).

Only two studies have analysed whether B-mode synovial hyperplasia and/or synovial hypervascularity, as assessed by PDUS, can predict the development of joint erosions at a single joint level. The first (11) found an association between progression of structural changes in individual joints and baseline positive PD signal, scores for PD and synovial hypertrophy when analysing RA patients receiving conventional treatment and considered to be in clinical remission state. The other (24), a recent longitudinal US study on single joints by Fukae *et al*., demonstrated a positive correlation between baseline presence of joint vascularity and the development of erosions 6 months later. The same group found a negative correlation between the reduction of quantitative PD and the development of structural damage.

However, no longitudinal study has yet evaluated the potential relationship between both US determined synovial hyperplasia and PD vascularity with the development of radiological erosions at single joint level.

Our prospective, single-joint study attempted to address these points by analysing the MCP joints of a group of RA patients before and over the course of one year of treatment, in order to determine whether US joint examination could predict progressive radiographic joint damage.

Patients and methods

Twenty-four RA outpatients, diagnosed according to the American College of Rheumatology (ACR) criteria for RA (25) consecutively seen, entered the prospective 12-month period study. The study was approved by the local ethics committees and informed consent was obtained from all patients before study entry. At baseline all patients had ac-

tive disease (more than 5 inflamed joints, ESR>40 mm/first hour and/or CRP>2.0 mg/dl, DAS28>4.0) and none were treated with any disease modifying anti-rheumatic drug (DMARD). Patients with longer disease duration were not on DMARDs because of previous low or absent disease activity. After the first visit, patients were started on steroids (16 patients) and one of the following DMARDs chosen by the attending rheumatologist: methotrexate (10 patients, weekly dosage range 10–20 mg), leflunomide (11 patients, 20 mg/day), sulfasalazine (3 patients, dosage range 2–3 g/day). Low-dose steroid and DMARD dosage were modified according to the clinical response as defined by EULAR response criteria or in the event of adverse effects without knowledge of the US findings. Two rheumatologists (RM, MGC), who were blinded to the US results, performed clinical assessments every 6 months, including tender and swollen joint counts (of 68 and 48 total joints, respectively). Joints were categorised as inflamed when tenderness and swelling were present at the same time, according to Thompson *et al*. (26). Each joint was graded on a 0–3 scale, with 0 indicating that the joint was never inflamed, and 1, 2 or 3, indicating that the joint was clinically active at 1, 2, or at every examination, respectively. The four variables disease activity score (DAS)28 were calculated at each visit (27).

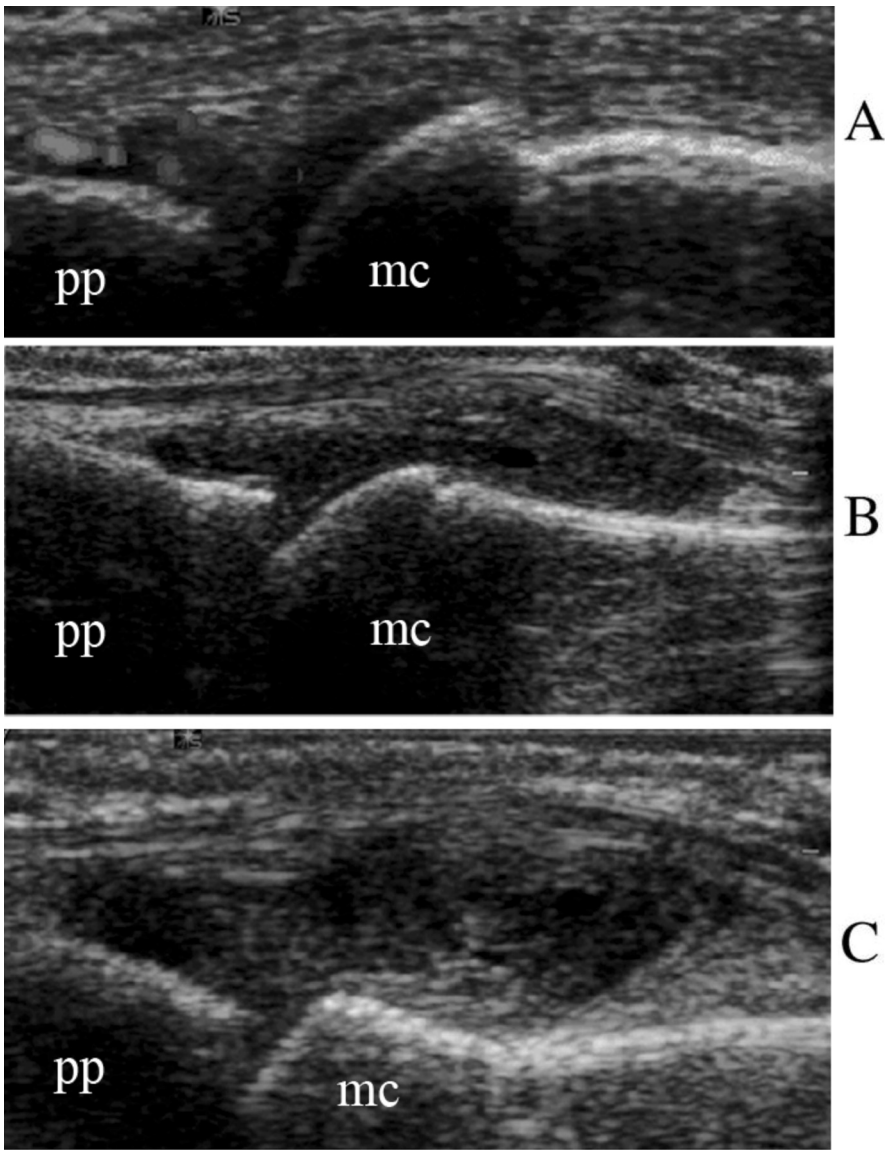

Fig. 1. Longitudinal dorsal ultrasound scan of the metacarpo-phalangeal joints with different grades of synovial hypertrophy.
A) synovial hypertrophy grade +; **B**) synovial hypertrophy grade ++; **C**) synovial hypertrophy grade +++; mc: metacarpal bone; pp: proximal phalnx.

Radiographic evaluation

Anteroposterior radiographs of the hands and feet of all patients were obtained at baseline and at week 52. Radiographs were scored in chronologic order for both erosions and joint space narrowing, according to the modified Sharp/van der Heijde (S/vdH) method (28), by 2 independent observers (LB, CS), who were blinded to the identity, treatment, and clinical status of the patients. The mean score assigned by the 2 observers was used in all subsequent analyses.

Damage was expressed as the Sharp damage score (erosion score, narrowing score, and total score) at baseline for each individual joint. The radiographic result at 1 year was coded as a binary variable to express, in each joint, the presence or absence of progression (defined as an increase in the mean score of both observers of at least 1) in the erosion or narrowing score.

High-frequency ultrasonography and power Doppler imaging

We used a Sonoline Antares unit with a VFX 13-5 multi-D linear array transducer (Siemens Medical Systems, Ultrasound Group, Issaquah, WA, USA).

At baseline and at weeks 26 and 52, patients underwent US assessment of all 10 MCP joints, which were scanned over the dorsal and palmar surface in the transverse and longitudinal planes. The same sonographer (PM, MM) independently scanned the joints of the same patients at every visit. Synovial hypertrophy was defined according to reference 29 as an abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal (29).

The images were stored and evaluated semiquantitatively for synovial thickness in the longitudinal plane by two assessors (PM, MM) unaware of the

identity of the patients (Fig. 1) who assigned a score of 0–3 according to Szkudlarek *et al*. (30).

The presence and number of bone erosions on the surface of the metacarpal head (cortical defects seen in two perpendicular scanning planes) according to definition for ultrasonographic pathology (29) were also evaluated for each joint at every US examination. All MCP joints were scanned on the dorsal and palmar surface, the 1st, 2nd and 5th MCP joints were also evaluated on the lateral (radial for the 1st and 2nd, ulnar for the 1st and 5th) surface. Erosive change was evaluated for proximal phalanges as well.

All MCP joints were also scanned in the PD mode, and the images demonstrating maximal synovial vascularity were stored for analysis.

Power Doppler parameters were adjusted at the lowest permissible pulse repetition frequency (PRF) to maximise sensitivity. This setting resulted in PRF ranging from 500 Hz to 1,000 Hz, depending on the joint scanned. Low wall filters were used. The dynamic range was 20–40 dB. Colour gain was set just below the level at which colour noise appeared underlying bone (no flow should be visualised at bony surface). This setting resulted in gains from 18 dB to 30 dB.

For each ultrasonographic scan, the PD signal of the synovial membrane was graded on a 0–3 scale (30) (0=normal, undetectable PD vessel signals in ultrasonographic synovial thickening area; 1=single vessel PD signal; 2=moderate hyperaemia, less than 50% of the synovial thickening area; 3=marked hyperaemia if intrasynovial PD flow signal distribution was detectable in more than 50% of the synovial thickening area, Fig. 2).

The persistence of US signs of inflammation in each single joint was measured utilising the semiquantitative score for synovial thickening and the semiquantitative score of PD signal.

For each parameter, persistence of inflammation was scored as follows: 0 if the semiquantitative score was always =0, 1 if the semiquantitative score was >0 in only one US evaluation, 2 if the semiquantitative score was >0 in two US evaluations, and 3 if the semiquantitative score was >0 in all three US evaluations.

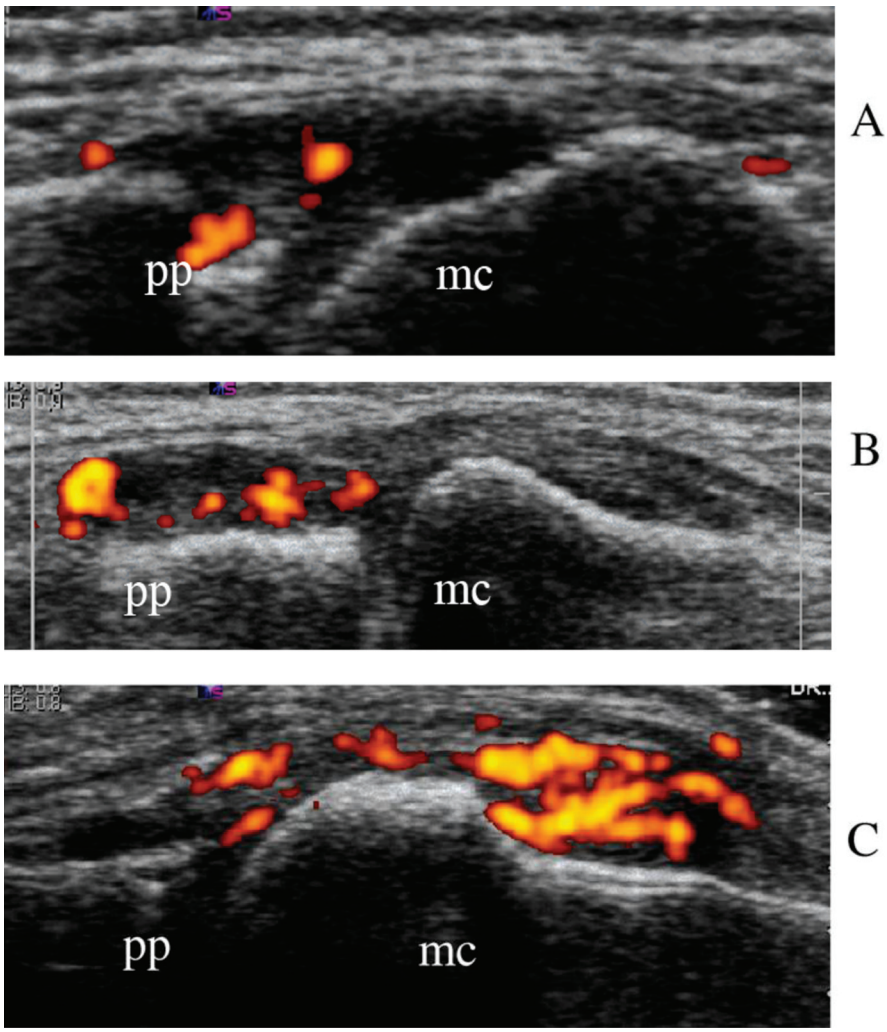

Fig. 2. Longitudinal dorsal ultrasound scan of the metacarpo-phalangeal joints with different grades of synovial hyperplasia and power-Doppler signal.
A) power-Doppler signal +; **B**) power-Doppler signal ++; **C**) power-Doppler signal +++; mc: metacarpal bone; pp: proximal phalanx.

Images of each single joint were stored independently by the two sonographers working in two different offices. At the end of the study, the images of all the joints were evaluated and graded together by the two sonographers, who were unaware of the identity of the patient and of the timing of scans.

Statistical analysis

Joints in which radiographic erosive damage had developed by the end of follow-up were compared with those without new damage using logistic regression for ordinal variables and Student's *t*-test for continuous variables. Joints categorised according to ultrasonographic scores (synovial and power-Doppler scores) were compared using chi-square test. As a measure of uncertainty, we used standard deviation (SD), unless otherwise stated.

All clinical (pain, swelling, or both) and ultrasonographic variables were then entered as possible explanatory variables in a conditional logistic regression analysis with joint outcome (damage or no damage) at one-year follow-up as the dependent variable (31). Using a backward selection procedure, the most significant independent variables were identified using a *p*-value greater than 0.10 as the removal criterion. Because of the small number of joints developing damage in the conditional logistic regression analysis, the values of some variables were redefined as 0 or 1. In particular, syno-

vial score, PD score, persistence of high synovial score, and persistence of high PD score were redefined as 0 for the former 0 or 1, and 1 for the former 2 or 3. Two final parsimonious models were obtained for the development at singular joint level of x-ray erosions, and total S/vdH damage score.

A simplified version of the models was constructed for clinical use by substituting the odds ratios (ORs) with weighted scores. For ORs between 1.5 and 6 the score was 1, and for ORs >6 the score was 2.

To evaluate the prognostic performance of these indexes a receiver operating characteristic (ROC) curve was constructed for discrimination between erosive *vs*. non erosive disease and damage *vs*. no damage. The area under the ROC curve (AUC) values provided a measure of the overall discriminative ability of the model. The ROC area and its standard error were estimated using a non-parametric approach. The ROC curve was obtained by applying the model to each individual joint.

To assess interobserver reliability for real time image acquisition, the two independent investigators (MM, PM) performed the US examinations of MCP joints of 5 patients (50 joints) on the same day. Kappa coefficients were calculated for semiquantitative US parameters of synovial thickening, PD score and erosive score. Intra-reader agreement was assessed by calculating a kappa coefficient between two subsequent evaluations for the same semiquantitative US parameters (synovial thickening, PD score and erosive score) of 120 randomly selected stored joints with a two-month interval. Kappa coefficients were classified as follows: <0 poor, 0.00–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, 0.81–1.00 excellent. Statistical analysis was performed using the standard software package SPSS 17.0 (SPSS Inc, Chicago, IL, USA) and the SAS System for Windows Release 8.0.

Results

Baseline characteristics of the patients and clinical response to treatment

Tables I and II summarise the baseline characteristics and the clinical response to treatment of the 24 patients who entered the study.

All patients were treated with one or more DMARDs. At the end of the study period, all patients had a significant reduction in the disease activity score (DAS28) (Table II), and attained at least an ACR response of 20% at week 52.

Baseline and follow-up ultrasound and radiological evaluation

Twelve (50%) of the twenty-four patients had radiological erosions at hands and feet examination at baseline, and 14 patients at the end of follow-up.

Considering only the MCP joints, 27 out of the 240 (11%) showed evidence of radiological erosions at baseline, while 17 joints developed new erosive damage or had worsening of pre-existing erosions after one year ($p<0.001$). There were 51 (21%) MCP joints with erosions at US examination at baseline, while 35 joints developed new erosions or had progression in US erosive damage at the end of follow-up ($p<0.001$). US examination detected the presence of synovial hypertrophy in 78% of the MCP joints at the first US examination with a significant reduction after one year of treatment (53%, $p<0.001$). The number of joints with positive PD signal showed a significant decrease by the end of follow-up (from 58% to 39%, $p<0.001$).

Univariate conditional logistic regression model to distinguish joints with development of new erosions

There was a positive relationship between baseline synovial semiquantitative score and the development of new erosions detected with radiological examination after 52 weeks. Only 3.4% of

Table I. Baseline characteristics of the 24 patients.

M/F	6/18
RF positive	19
Anti-CCP positive	15 (23 pt)
Median age (years, range)	59.5 (27–78)
Median disease duration (months, range)	9 (1–115)
Steroid use	13 (54%)
Radiographic erosive disease	12 (50%)
Median baseline (range) number of x-ray eroded joint/patient	0 (0–12)

Table II. Clinical and laboratory characteristics of the 24 patients and response to treatment.

	Baseline	6 months	12 months
Morning stiffness (minutes)	120 (120)	27 (46) (< 0.001)*	22 (25) (< 0.001)*
Pain (VAS)	66.3 (20.7)	28.7 (19.7) (< 0.001)*	33 (25.7) (< 0.001)*
Patient disease activity (VAS)	63.7 (22.9)	26.1 (17.0) (< 0.001)*	34.7 (28.1) (0.001)*
Physician disease activity (VAS)	57 (17.1)	24.7 (17.6) (< 0.001)*	29.2 (24.1) (< 0.001)*
Tender joint count	15.2 (8.1)	3.7 (5.7) (< 0.001)*	5.6 (7.1) (< 0.001)*
Swollen joint count	9.8 (6.4)	2.7 (2.9) (< 0.001)*	2.7 (4.2) (< 0.001)*
HAQ	1.75 (0.70)	0.74 (0.74) (< 0.001)*	0.78 (0.84) (< 0.001)*
Erythrocyte sedimentation rate (mm/1st hour)	31.3 (19.5)	18 (14.6) (0.01)*	22.9 (16.7) (0.67)*
C-reactive protein (mg/dl)	2.56 (2.53)	0.9 (1.2) (0.002)*	1.36 (1.75) (0.032)*
DAS28 (4 v)	5.72 (1.09)	3.18 (1.11) (< 0.001)*	3.59 (1.64) (< 0.001)*

Mean values (SD) *: *p*-value *vs*. baseline.

the joints with a baseline synovial score =0 developed new radiological erosions, compared with 35% with a baseline synovial score =3. The OR (95%CI) for synovial score 2–3 *vs*. synovial score 0–1 was 9.21 (3.0–28.27). Baseline PD synovial score predicted the development of radiological damage 12 months later (Table IIIa) (OR [95%CI] for synovial PD score 2–3 *vs*. synovial PD score 0–1= 6.79 [2.34–19.66]).

With regard to US evaluation during follow-up, we found a significant correlation between persistently high synovial score, on the one hand, and the development of x-ray erosions and increased total S/vdH score, on the other (Table IIIb). The persistence of an articular PD score ≥2 was significantly associated with the progression of erosive damage determined by x-rays. Eighty-eight per cent of new x-ray erosions and 87.5% of the joints with increased total S/vdH score developed in joints with persistent (on 2 or more examinations) PD score ≥2. The percentage of joints that developed new damage was negligible in joints with only occasional presence of a PD score <2 (1.8% for new x-ray erosions, 3% for increased S/vdH score), (Table IIIb). The OR (95%CI) for synovial score >1 on two or more occasions *vs*. synovial score >1 never or only one time were 12.6 (95%CI 2.8–53.7) for x-ray erosions and 11.6 (95% 3.4–38.8) for S/vdH local damage.

No relationship was found between radiological development of erosion or increased S/vdH score and baseline or follow-up clinical detected abnormalities (pain and swelling) at singular joint level (data not shown).

Table IIIa. Univariate conditional logistic regression model to distinguish joints developing damage: baseline evaluation.

Baseline synovial score	% new x-ray erosion at 52 weeks (% of total new eroded joints)	% increased local S/vdH score (% of total new damaged joints)
0	3.4 (12)	5.7 (12.5)
1	2.2 (12)	2.5 (12.5)
2	16.7 (35)	37.0 (41.7)
3	35.0 (41)	47.1 (33.3)
OR (95%CI)*	9.21 (3.00–28.27)	8.62 (3.42–21.73)
p-value*	<0.001	<0.001
Baseline PD score (PDS)	**% new x-ray erosion at 52 weeks**	**% increased S/vdH score**
0	2.0 (12.0)	2.9 (12.5)
1	7.0 (17.6)	13.3 (25.0)
2	20.0 (58.8)	23.1 (50.0)
3	12.5 (12.0)	15.8 (12.5)
OR (95%CI)*	6.79 (2.34–19.66)	5.05 (2.17–11.76)
p-value*	<0.001	<0.001

*OR and *p*-values were calculated by conditional logistic regression utilising only two classes instead of four. Baseline synovial score and baseline PD score are recategorised as 0 for the former 0 or 1, and 1 for the former 2 or 3.

Table IIIb. Univariate conditional logistic regression model to distinguish joints developing damage: follow-up examination.

Synovial score ≥2	% new x-ray erosion at 52 weeks (% of total new eroded joints)	% increased local S/vdH score (% of total new damaged joints)
Never	1.5 (5.9)	2.4 (12.0)
Once	4.3 (11.8)	13.8 (16.0)
Twice	8.0 (11.8)	14.3 (24.0)
Always	14.6 (70.6)	27.3 (48.0)
OR (95%CI)*	4.39 (1.27–15.11)	2.90 (1.15–7.24)
p-value*	0.021	0.024
PD score ≥2	**% new x-ray erosion at 52 weeks**	**% increased S/vdH score at 52 weeks**
Never	1.3 (5.9)	1.2 (4.2)
Once	2.3 (5.9)	4.1 (8.3)
Twice	12.9 (23.5)	22.6 (29.2)
Always	22.0 (64.7)	25.9 (58.3)
OR (95%CI)*	12.60 (2.80–53.70)	11.57 (3.45–38.85)
p-value*	0.001	<0.001

*OR and *p*-values were calculated by conditional logistic regression utilising only two classes instead of four. Synovial score and PD score are redefined as 0 for the former "never" or "once", and 1 for the former "twice" or "always."

Multivariate conditional logistic regression anlaysis

In multiple conditional logistic regression analysis, factors associated with the development of Rx erosions were an ultrasound baseline synovial thickening score ≥2 and the presence of synovial PD score ≥2 on two or more US evaluations and the presence in the same joint of pre-existing Rx erosions (Table IV). After the substitution of the OR value with the values described in the *Patients and Methods* section, we obtained a score for each joint ranging from 0 to 5 useful for prognostic purpose. A ROC curve of the score is reported in Figure 3a.

Using a cut-off value >2 in the weighted score, the positive predictive value was 30.7% and the negative predictive value was 99.5%, with a LR+=4.397 and a LR-=0.075. Sensitivity was 94.1% and specificity was 78.6%.

The same three independent factors were also associated with the progression of damage at the individual joint level according to the S/vdH method: the presence of radiological erosions at baseline, an ultrasound baseline synovial thickening score ≥2, and the persistence of synovial PD score ≥2 on two or more US evaluations (Table IV). The value of the weighted score has a range from 0 to 4. Using a cut-off value >2, the positive predictive value was 48% and the negative predictive value

Table IV. Multivariate conditional logistic regression model to distinguish joints developing damage and coring algorithm.

	OR (CI) for local x-ray erosions	Points for local x-ray erosions*	OR (CI) for x-ray local S/vdH total damage	Points for local S/vdH total damage*
Baseline presence of x-ray erosion (range 0–1)	8.43 (2.37–29.9)	2	4.38 (1.70–11.33)	1
Baseline US synovial score (range 0–1)	5.36 (1.70–16.84)	1	3.58 (1.27–10.13)	1
Longitudinal PD score (range 0–1)	8.51 (1.84–39.48)	2	8.30 (1.77–38.90)	2
Baseline PD score (range 0–1)				
Baseline Thompson (range 0–1)				

* weighted value for scoring index.

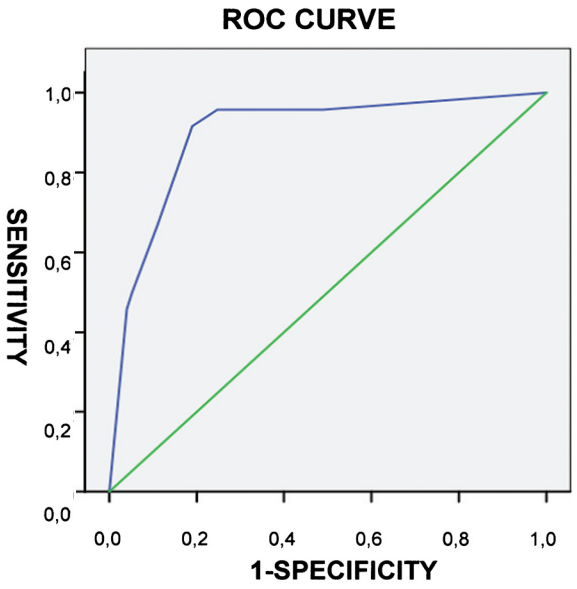

Fig. 3a. Receiver operating characteristic (ROC) curve using the weighted values of Table IV (baseline synovial hypertrophy, persistent PD signal and baseline local Rx erosions) in predicting the development of new Rx erosive damage.
The area under the curve is 0.898 (95%CI 0.832–0.964) with asintotic significance <0.001. A cut-off value of 3.0 has a sensitivity of 75.2% and sensibility of 95.8%.

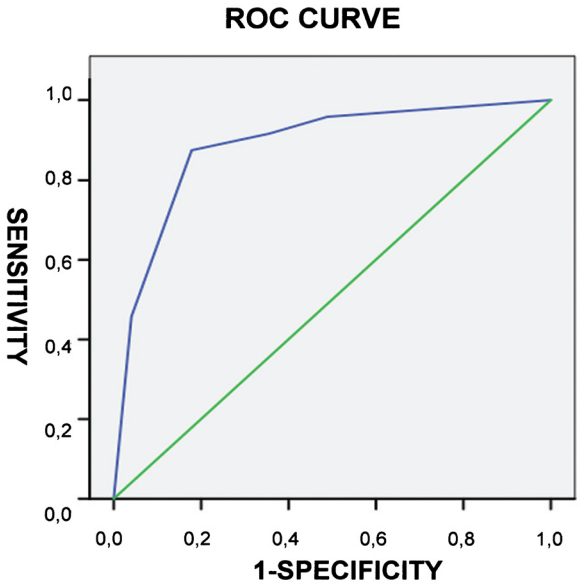

Fig. 3b. Receiver operating characteristic (ROC) curve using a conditional logistic regression analysis with baseline synovial hypertrophy, persistent PD signal and baseline presence of baseline local Rx erosions in predicting increase in S/vdH damage at individual joint level.
The area under the curve is 0.886 (95%CI 0.814–0.957) with asintotic significance <0.001. A cut-off value of 3.0 has a sensitivity of 87.5% and specificity of 82.2%.

was 98.8%, with a LR+=4.91 and a LR-=0.152. Sensitivity was 87.5% and specificity was 83.2%. The corresponding ROC curve for the prognostic index is reported in Figure 3b.
The variable "treatment" had no influence on the logistic regression analysis. We plotted ROC for each of the logistic regression equations and all models had excellent discriminative ability, with ROC AUC of 0.916 (95%CI 0.867–0.965) and 0.886 (95%CI 0.814–0.957) for x-ray determined erosions and local S/vdH total damage score respectively.

Intrareader and inter-reader assessment

Fifty MCP joints of 5 unselected patients were evaluated independently the same day by the two sonographers. Inter-observer agreement was k=0.86 for synovial semiquantitative thickening, k=0.79 for PD score, and k=0.74 for erosive US score (p<0.001 for the three variables).
One hundred and twenty unselected recorded images were evaluated at 2-month intervals by the same readers. Intraobserver agreement was k=0.84 for synovial semiquantitative thickening, k=0.865 for PD score, and k=0.79 for erosive US score (p<0.001 for the three variables).

Discussion

The conditional logistic regression analysis of our findings confirm that, among the various US variables, a synovial thickening >2 at baseline and a persistent PD score >2 of any single MCP joint are statistically significant in predicting prospective unfavourable outcomes.
Our study found that the most important factor associated with an increased risk of developing structural damage was the persistence of PD articular hypervascularity with score 2–3. Erosions and joint damage develop in a high percentage of joints when US signs of inflammation are not controlled by treatment. In contrast, the persistence of synovial thickening without PD signal did not appear to have any value as predictor of joint damage. Finally, the two regression equations have the best discriminative ability to define joints with

the worst outcome, as demonstrated by the ROC curve statistic. The simultaneous presence of baseline synovial score >2 plus the presence of RX baseline erosion and persistence of PD score >2 produce an AUC of 0.91 for increased value of S/vdH score.

Our findings are in agreement with those of a previous study which reported that the rapid control achieved with biological treatment of the clinical signs of synovitis reduced the rate of joint deterioration (22). In another recent study that analysed the predictive value of PD US parameters for radiological outcome in patients with RA, a strong correlation between time-integrated values of PD US and radiographic progression was found (23). These two studies found a significant correlation between the mean ultrasonographic score and the mean radiologic score for each patient, but this approach is not able to determine the role of any single joint abnormality as assessed by US as outcome predictor for damage at joint level.

Only two previous studies were conducted at individual joint level. In the first study, Brown *et al*. (11) evaluated baseline US parameters predictive of radiological damage 12 months later, comparing 10 joints with new erosive damage with 370 joints without radiological progression in a group 102 RA patients treated with conventional drug and defined by their consultant rheumatologist to be in clinical remission. The authors found that baseline PD positivity, baseline PD score and baseline synovial hypertrophy were all associated with significant odds of progression (OR [95% CI]:12.21 (3.34, 44.73; $p<0.001$), 4.0 (1.98, 8.08; $p<0.001$), 2.31 (1.06, 5.52; $p=0.032$ respectively). In agreement with our data, they did not find any significant correlation with baseline clinical findings (pain, swollen and tenderness).

In the second study, Fukaie *et al*. (24) examined longitudinally the correlation between PD signal at baseline and during treatment (both in quantitative and semiquantitative way) and the progression of the Genant-modifed Sharp score (GSS) in 190 MCP and 190 PIP joints of 19 RA patients with active disease treated with DMARDs. The authors demonstrated, in agreement with our study, that the level of quantitative PD signal at baseline significantly correlated with local progression of the GSS both at MCP and PIP joints 20 weeks later (Spearman's rho=0.466, $p=0.0001$ and Spearman's rho=0.362, $p=0.0001$ respectively). They demonstrated a similar positive correlation with the baseline semiquantitative score, but the data were not shown. During follow-up, the authors calculated an improvement rate (IR) for each single joint by comparing the quantitative PD signal of the 8th week with baseline values, considering only joints with positive PD signal at baseline. They demonstrated a negative correlation between the reduction of quantitative PD signal and structural deterioration only in MCP joints, but were unable to find a correlation between PD semiquantitative reduction and the progression of the GSS. Unfortunately, we do not know what happens in joints without baseline PD signal and we do not know in what percentage the progression of the local GSS is due to the development of erosions or to the reduction of the joint space. Moreover, in their study, these authors did not take into account, as we did, other clinical, laboratory and US variables (*e.g*. synovial hypertrophy) that are potentially correlated with this outcome.

Using a different approach and different statistical methods, we have found that semiquantitative PD score is a strong predictor of erosive changes. We think that PD semiquantitative approach is easier to perform than quantitative PD methods and could be preferred in clinical setting.

New ultrasound scoring methods have recently been proposed and validated to be used in the clinical setting to compliment the usual ACR and/or EULAR core set variables. US evaluation of synovitis has proved to be as relevant an outcome measure as physical examination. These scoring methods utilise a 0–3 point scale both for synovial thickening and for PD synovial vascularisation. In this way, we can obtain a patient US synovial and PD score summing up the value of each joint. A good correlation between these US indexes of articular inflammation and clinical and laboratory variables has been demonstrated (32-34).

In our study, we have demonstrated that for prognostic purposes a synovial thickening score <2 and PD score <2 have no influence on the development of radiological damage. At baseline, the independent presence of Rx erosions, baseline synovial score >1, baseline PD score >1 and the presence of clinically active joints (swollen and painful) are indicators of possible articular damage. These findings indicate the need of a rapid institution of DMARDs treatment. In our study, we have also shown that the only US variable useful during US follow-up joint examination is the persistence of a PD score >1 for more than 6 months. We think that the persistence of a PD score >1 in the same joints may induce the shift to a more aggressive treatment to avoid a further joint damage. We think that a scoring system which considers only joints at high risk of developing damage (*e.g*. PD score ≥2 or synovial score ≥2) may be a better method to evaluate the disease activity. As suggested by other authors (11, 23), we think that our results strongly support the use of US as a reliable method to evaluate the response to treatment. More specifically, in the management of RA patients we can evaluate the response to treatment by focusing on the control of synovial hypervascularity. Further studies are needed to specifically address this point.

Despite the lack of standardisation of PD US examination, different studies (23, 30, 35, 36) have reported, in agreement with our findings, very high inter- and intraobserver kappa values for semiquantitative PD scores.

Our study has some limitations, including the relatively small number of joints examined and the correspondingly small number of joints developing damage at the end of follow-up. These factors can reduce the power of the statistical methods that we have utilised. Another limitation could be that US joint assessment every 6 months, as we have done in our study, may underestimates its potential. However, previous studies did not demonstrate that DMARDs treatment is able to significantly reduce joint syno-

vial thickening and PD vascularity after 3 months of treatment (22, 23, 37). We think that a 6-month examination interval provides significant information on the disease evolution.

To summarise, US determined synovial hypertrophy and PD score at baseline and the persistence of a positive PD score over time in MCP joints may predict the rate of progression of joint damage. We believe that the time has come to routinely use US as a basic tool to evaluate the disease activity and the response to treatment in patients with RA.

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