Ultrasound of target joints for the evaluation of possible inflammatory arthropathy: associated clinical factors and diagnostic accuracy

S. Chaiamnuay, R. Lopez-Ben, G.S. Alarcón

[1]Division of Clinical Immunology and Rheumatology, Department of Medicine, [2]Department of Diagnostic Radiology. The University of Alabama at Birmingham, Birmingham, Alabama, USA.

Abstract

Objective

To examine the clinical features associated with an ultrasound (US) diagnosis of synovitis and/or erosions in patients suspected of inflammatory arthritis, and the factors associated with this evolution in patients with a normal initial US.

Patients and methods

Cross-sectional: the records of 144 patients who underwent US for suspected inflammatory arthropathy were categorized into synovitis and/or erosions present or not.

Longitudinal: of 58 patients without synovitis and/or erosions, 30 could be located and 19 agreed to be studied (two were asymptomatic and refused, nine could not be reached).

Analyses: univariable descriptive analyses were performed. Age, gender, variables significant ($p<0.05$) in the univariable analyses, and those clinically relevant were examined by logistic regression for the cross-sectional study. The metric properties of US compared to overall clinical assessment were also examined.

Results

Age, gender, ethnicity and symptoms' duration were comparable in patients with and without synovitis and/or erosions. Wrist swelling (history) and the number of swollen wrist/hand joints were associated with synovitis and/or erosions by US; morning stiffness, sicca symptoms and low back pain were negatively associated with synovitis and/or erosions. Four patients evolved into an inflammatory arthropathy but no features distinguished them from those who did not evolve into an inflammatory arthropathy. The sensitivity, specificity, and overall accuracy of US, compared to the clinical assessment were 98.9%, 94.1% and 98.1%, respectively.

Conclusions

US is an adequate tool for the assessment of inflammatory arthropathy; however, patients with a single negative US at initial clinical presentation still need to be followed for the eventual development of an overt arthropathy.

Key words

Ultrasound, inflammation, arthritis, outcome.

Sumapa Chaiamnuay, MD
Robert Lopez-Ben, MD
Graciela S. Alarcón, MD, MPH

Please address correspondence and reprint requests to:
Dr. Graciela S. Alarcón,
830 Faculty Office Tower,
510 20th Street South, Birmingham,
Alabama 35294-3408, USA.
E-mail: graciela.alarcon@ccc.uab.edu

Received on October 8, 2007; accepted in revised form on April 14, 2008.

Competing interests: none declared.

Introduction

Over the last few years, ultrasonography (US) has become a useful tool in the evaluation of patients with inflammatory arthritis (1, 2); it is more sensitive than physical examination and radiographs in detecting early inflammatory and destructive joints changes although somewhat less sensitive than magnetic resonance imaging (MRI) (3-6). The identification of these patients may allow clinicians to initiate the most appropriate treatment, including early aggressive therapies in order to minimize joint destruction and functional losses (7, 8); however, the ultimate influence of this technology in clinical practice or in the conduct of clinical trials has yet to be defined (2, 9, 10).

Known clinical and serological measures identified at initial evaluations as predictors of poor radiographic outcomes in patients with inflammatory arthritis include disease duration (11), the number of swollen joints (12), serum rheumatoid factor positivity (11, 13), anti-cyclic citrullinated peptide antibodies (14), higher levels of C-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR) (11, 13, 15), the presence of the rheumatoid or shared epitope (12, 13, 16) and the presence of increased levels of RANK (and low levels of osteoprotegerin) in the synovium (15). However, the factors associated with abnormal US findings, either at first evaluation or subsequently, have not been examined to date.

In this study we investigated the clinical and serological features associated with the presence of joint inflammation by US in patients referred to a tertiary care rheumatology clinic for the evaluation of possible inflammatory arthritis. By performing a long-term follow up on patients with an initial normal US exam in this population we aimed at defining the accuracy of this exam in the context of the eventual diagnoses.

Patients and methods

The study was approved by the Institutional Review Board and it was performed according with the Declaration of Helsinki's guidelines for the conduct of research in humans.

This is a two-part study: cross-sectional and longitudinal.

Cross-sectional study

Two hundred and five patients referred for evaluation of inflammatory arthropathy to the tertiary care rheumatology clinic at the University of Alabama at Birmingham between January 2002 and December 2004 who also underwent an US examination of the joints of the hands and feet were identified from the Radiology Department's database. Of them, 61 patients were excluded (56 already had an established diagnosis of an inflammatory arthropathy, two were less than 18 years of age when US was performed and three were referred with a different presumptive diagnosis). Thus, the medical records of the remaining 144 patients were reviewed and the following data extracted: age, gender, ethnicity, symptoms' duration at the time of evaluation, duration of morning stiffness, presence of joint pain and swelling by history and physical examination, extra-articular symptoms, medication usage, history of other comorbidities, laboratory data (complete blood cell count, rheumatoid factor positivity and titer, anti-nuclear antibodies, ESR and CRP) and radiographs and US reports.

Longitudinal study

A total of 58 patients who had a negative initial US (absence of synovitis or erosions) were identified from the above cross-sectional portion of this study. As per the United States Health Insurance Portability and Accountability Act's (HIPAA) regulations, patients could not be contacted directly by telephone, thus they were invited to participate in this follow-up study via an explanatory postcard. Thirty patients responded; of them, two did not want to participate as their symptoms had completely resolved and nine could not be contacted by telephone; thus, 19 patients were studied. Clinical (history and physical examination) and then imaging evaluations (hand radiographs and US) were performed within two to 48 hours. Joints assessed in both imaging modalities included the wrist joints and the metacarpophalangeal and proximal

interphalangeal joints; the time between the initial US and these subsequent clinical and imaging evaluations varied from eight to 24 months.

Hand radiographs were obtained using standard techniques (Kilo volt peak 54, miliampere-second 2.5, fine detail film-screen combination). US exams were performed using 15 MHz high-resolution linear array transducers with small footprints; scans of the joints were performed in the dorsal and palmar/plantar planes. Individual optimization of Doppler gain and gate for detecting low-velocity flow was done; the initial and follow-up US were performed and interpreted by a musculoskeletal radiologist with extensive experience in musculoskeletal ultrasonography. Individual scanning parameters were optimized for musculoskeletal detail for the US machines utilized (Sequoia, Accuson, Mountain View, CA and HDI 3000, Advanced Technologies Laboratories, Bothell, WA). No sonographic contrast agents were utilized as their use is not routine practice in the United States. The US examination included bilateral wrists, second and fifth metacarpophalangeal joints, fifth metatarsophalangeal joints, and the most swollen PIP (one in each hand), for a total of ten joints per patient. These target joints were selected on the basis of their likelihood of involvement in early rheumatoid arthritis (RA) as well as their easy accessibility to the US probe (17-19). Erosions were defined as cortical defects greater than 2 mm in diameter, visualized in two planes and having an irregular floor (17;20). Synovitis was defined as increase in joint fluid and/or hypoechoic synovial proliferation with increased blood flow by Power Doppler and it was graded as previously described on a 1 to 4 scale (20-22).

Analyses

Cross-sectional study

Patients were categorized into two groups, those with and without synovitis and/or erosions by US and their demographic and clinical characteristics compared using Chi-square and Students' tests, as appropriate. Significant variables in these analyses ($p \leq 0.05$) and those felt to be clinically relevant were further examined by logistic regression with abnormal findings by US being the dependent variable; age and gender were included regardless of their level of significance in the univariable analyses. For highly correlated variables (fibromyalgia, myalgias, depression, insomnia, fatigue and low back pain), only the most significant (smallest *p*-value) was entered into the model.

Longitudinal study

Patients were categorized into two groups, those with and without progression to inflammatory arthropathy. Progression was defined as worsening of symptoms, presence of joint swelling on physical examination, erosions on hand radiographs and/or synovitis and/or erosions by US. The baseline characteristics between these two groups were compared using Chi-square (Fisher's exact) and Students' *t*-tests, as appropriate.

Finally, the metric properties of US in the diagnosis of inflammatory arthropathy were examined; to this end, the overall patients' comprehensive clinical assessment of their final working diagnosis was arbitrarily considered the gold standard.

All analyses were performed using SPSS version 14.0 (Chicago, IL 60606).

Table I. Clinical, laboratory and radiographic features of patients suspected of an inflammatory arthropathy as a function of the presence of synovitis and/or erosions by ultrasound.

Synovitis/erosions	Absence (n=58)	Presence (n=86)	*p*-value[§]
Total symptom duration, months, mean (SD)	31.3 (33.6)	34.1 (46.5)	
Morning stiffness, minutes, mean (SD)	110.7 (105.2)	63.4 (63.9)	0.001
History of, n (%)			
Wrist pain	24 (41.4)	42 (48.8)	
MCP* pain	41 (70.7)	62 (72.1)	
Wrist swelling	6 (10.3)	28 (41.2)	0.002
MCP swelling	22 (39.7)	40 (46.5)	
Physical examination			
Wrist tenderness, n (%)	17 (29.3)	34 (39.5)	
Wrist swelling, n (%)	9 (15.5)	30 (34.9)	0.013
Number of hand (MCPs and PIPs†) and wrist joints with tenderness, mean (SD)	6.7 (7.9)	5.9 (6.8)	
Number of hand (MCPs and PIPs) and wrist joints with swelling, mean (SD)	2.4 (4.0)	5.1 (3.7)	0.008
Sicca symptoms, n (%)	22 (37.9)	15 (17.4)	0.007
Low back pain, n (%)	23 (39.7)	13 (15.1)	0.001
Fibromyalgia, n (%)	11 (19.0)	6 (7.0)	0.036
Rheumatoid factor positivity, n (%)	19 (33.0)	27 (31.7)	
C-reactive protein, mg/dL, mean (SD)	3.5 (15.3)	1.8 (2.9)	
Presence of soft tissue swelling on hand films, n (%)	7 (12.2)	25 (29.3)	0.041

*MCPs for metacarpophalangeal joints, †PIPs for proximal interphalangeal joints, §Only *p*-values ≤0.05 are shown.

Results

Cross-sectional study

Univariable analyses. Of the 144 patients evaluated there were 86 with synovitis and/or erosions and 58 without them. Age, gender, ethnicity and duration of symptoms were comparable in both groups. Patients with synovitis and/or erosions were more likely to have wrist swelling by history and physical examination (41.2 and 34.9 *vs.* 10.3 and 15.5%, p=0.002 and 0.013, respectively) and a higher number of swollen wrist and hand joints by physical examination [mean (standard duration, SD) 5.1(3.7) *vs.* 2.4 (1.0), p=0.008]; they were also more likely to have evidence of soft tissue swelling on hand radiographs than those with neither synovitis nor erosions (29.3% *vs.* 12.2%; p=0.041). In contrast, patients with neither synovitis nor erosions were more likely to have a longer duration of morning stiffness,

[110.7 (105.2) *vs*. 63.4 (63.9) minutes, p=0.001], more sicca symptoms (37.9 *vs*. 17.4%, p=0.007), low back pain (39.7 *vs*. 15.1%, p=0.001) and fibromyalgia (19.0 *vs*. 7.0%, p=0.041). Rheumatoid factor positivity (and titers) and CRP levels were comparable in the two groups. These results are summarized in Table I. The diagnoses in these patients are depicted on Table II. Of importance, the proportion of patients who were diagnosed with an inflammatory arthropathy was much higher in those with positive US examinations (87.2% *vs*. 27.6%) and the opposite was true for the non-inflammatory conditions (72.4% *vs*. 12.8%), $p \leq 0.0001$.

Table II. Final clinical diagnoses in patients with suspected inflammatory arthropathy and ultrasound (US).

US findings Diagnoses	No synovitis/ no erosion, n	Synovitis/ no erosion, n	Erosion and/or synovitis, n
Inflammatory arthropathies			
Rheumatoid arthritis	4	25	31
Seronegative spondyloarthropathies	1	1	2
Undefined polyarthritis	7	12	2
Systemic lupus erythematous	3	2	0
Polymyalgia rheumatica	1	0	0
Subtotal	16	40	35
Non-inflammatory arthropathies			
Osteoarthritis	11	4	3
Fibromyalgia	9	2	0
Hepatitis C-related arthralgias	1	0	0
Polyarthralgias- unidentified cause	21	2	0
Subtotal	42	8	3
Total	58	48	38

Multivariable analyses

A history of wrist swelling and the number of swollen hand and wrist joints by physical examination were independently associated with the presence of synovitis and/or erosions by US [Odds ratios (OR) 3.204 and 1.104; 95% Confidence Intervals (CI) 1.132-9.072 and 1.020-1.194; p-values=0.028 and 0.014, respectively)] whereas the duration of morning stiffness, sicca symptoms and low back pain were negatively associated with the presence of synovitis and/or erosion (OR=0.994, 0.366 and 0.355; 95% CI 0.989-1.000, 0.148-0.900 and 0.141-0.893 p=0.035, 0.029 and 0.028, respectively). These data are shown in Table III.

Table III. Multivariable logistic regression analyses of factors associated with the presence of synovitis and/or erosions on ultrasound of target joints*.

Variables	Odds ratio (95% CI‡)	p-value
History of wrist swelling	3.204 (1.132-9.072)	0.028
Number of swollen hand§ and wrist joints by physical examination	1.104 (1.020-1.194)	0.014
Duration of morning stiffness	0.994 (0.989-1.000)	0.035
Sicca symptoms	0.366 (0.148-0.900)	0.029
Low back pain¶	0.355 (0.141-0.893)	0.028

*Age, gender and ethnicity were adjusted for in the model; ‡CI: confidence interval; §includes metacarpophalangeal and proximal interphalangeal joints; ¶ highly associated with fibromyalgia, myalgias, depression, insomnia and fatigue, thus this was the only variable included in the model.

Longitudinal study

Of the 19 patients included in this part of the study, four patients had progressed to a defined inflammatory arthropathy (two patients developed RA and one each developed psoriatic arthritis and systemic lupus erythematosus, SLE) within one to three months of the initial evaluation; these diagnoses were based on clinical findings and laboratory tests. None of the demographic, clinical or laboratory features at initial evaluation distinguished these patients from those who did not evolve to a defined inflammatory arthropathy. In contrast, at follow-up those patients who had evolved into a defined inflammatory arthropathy were more likely to have wrist swelling by physical examination (50% *vs*. 0%, p=0.035); one of the RA patients, however, was not symptomatic during the second assessment. The initial and subsequent imaging data for these four patients are depicted in Table IV; none of the four patients developed any radiographic abnormalities, one of the four had stable negative findings with no US abnormalities whereas one patient with RA had developed erosions; three of the four including the one with erosions had developed synovitis on follow-up US [two had hypoechoic synovial proliferation with increased blood flow by Power Doppler (1+and 2+) and one had effusion (1+)]. Taken together the data from both, the cross-sectional and longitudinal studies, and including the two patients who declined the follow up assessment as they were no longer symptomatic, the sensitivity, specificity and overall accuracy of US in the evaluation of patients suspected of an inflammatory arthropathy when compared to clinical assessment were 98.9%, 94.1% and 98.1%, respectively. These data are noted in Table V.

Discussion

The two parts of our study had a different purpose. The first one was to assess the factors associated with the presence of abnormal US findings in patients suspected of an inflammatory arthropathy and referred for evaluation to a tertiary center rheumatology clinic. The second part was to determine if a negative initial US assessment should be considered definitive or if patients should be followed further. Not surprisingly, we have shown that a history of swollen wrists and the number of swollen wrist and hand joints by physical examination were predictive of US findings; in fact the majority of patients with positive US findings went on to be diagnosed with RA after their initial evaluation (65%). Of interest, few patients who were clinically diagnosed with osteoarthritis

Table IV. Initial and final imaging evaluations in patients who developed an inflammatory arthropathy.

Patient	Clinical diagnosis*	Radiograph		Ultrasonography		Interval between assessments (months)
		Initial	Subsequent	Initial	Subsequent	
1	RA	Normal	Normal	Normal	Erosions/Synovitis (1+SP by PD)	8
2	SLE	Normal	Normal	Normal	Synovitis(1+SP by PD)	16
3	RA	Normal	Normal	Normal	Normal	16
4	Psoriatic arthritis	Normal	Normal	Normal	Synovitis (1+Ef)	20

*RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; PD: Power Doppler; SP: Synovial proliferation; Ef: Effusion.

Table V. Diagnosis of inflammatory arthropathy: ultrasound *vs*. overall clinical assessment.

Assessment		Clinical diagnoses of inflammatory arthropathy		Total
		Presence	Absence	
Synovitis and/or erosions by Ultrasound	Presence	89	0	9
	Absence	1	17	18
Total		90	17*	107

Sensitivity: 98.9%
Specificity: 94.1%
Positive predictive value: 98.9%
Negative predictive value: 94.1%
Overall accuracy: 98.1%

*Two patients who were asymptomatic and thus declined the assessment are included in the total.

(OA) had erosions indicating the now recognized inflammatory nature of this arthritide (23); these patients, however, had no additional stigmata that will suggest the presence of RA. We were not surprised about the fact that non-articular symptoms (associated with low back pain) were negatively associated with US findings (*vide infra*). However, we were surprised at finding morning stiffness to be negatively associated with US positive findings. Our results for the second part of the study are less conclusive given the small number of patients included (*vide infra*). Taken together, however, we believe the metric properties of US in terms of aiding in the diagnosis of an inflammatory arthropathy are quite good.

In terms of the negative association of US findings and duration of morning stiffness, considered indicative of joint inflammation and a criterion for the classification of RA (24), our data suggest that clinicians should not put too much weight on it when evaluating patients for possible inflammatory arthropathy as it can occur in other diseases such as OA; in fact, it is part of The Western Ontario and McMaster Universities OA Index (25). Furthermore, patients with fibromyalgia also frequently complain of morning stiffness (26). Of note, OA and fibromyalgia were the two most common diagnoses in those patients with negative US findings (21% and 16%, respectively). We must also add that there is a lack of consistency in recording the duration of morning stiffness; a large intra-individual variation has been reported depending if it is recorded by the patient or ascertained by interview (27).

A history of low back pain, a correlate of fibromyalgia, and of sicca symptoms were found to be negatively associated with US findings. Fibromyalgia was the second most common diagnosis in patients with negative US. None of the patients who complained of sicca symptoms was later diagnosed as having Sjögren's syndrome; it is possible that sicca symptoms in these patients were associated with the use of anticholinergic agents, not an infrequent occurrence in patients with depression, fibromyalgia and insomnia. However, this information was not readily available in the records examined.

Should patients referred for evaluation of a possible inflammatory arthropathy but who have a negative US evaluation be followed as they still may evolve into a defined diagnosis? Four out of 19 (or 21 including the two patients that were no longer symptomatic) patients assessed did in fact evolved and this occurred shortly after the initial evaluation. Of note, three of these four patients had findings suggestive of inflammatory arthropathy at our follow-up US (one with erosions and three with synovitis). *Sensu strictu*, the remaining patient represents a false negative result; however, it is conceivable there would have been no evidence of synovitis and/or erosions even if histopathological data were available. Furthermore, the amount of Doppler signal and the degree of synovitis by histopathology may not correlate very well (28). The sensitivity, specificity and overall accuracy of US at initial clinical presentation compared to final clinical assessment in our study suggest that this method is valuable; however, only about one third of the potential eligible patients were assessed and this is an obvious drawback of this part of our study. Given this, it is not surprising that we failed to identify any predictive features of evolution into an inflammatory arthropathy. Nevertheless, our data suggests that a single comprehensive (included US) negative evaluation for inflammatory arthropathy does not exclude its eventual occurrence and that patients should be observed for a few more months for the appearance of overt clinical findings that may guide the clinical diagnosis; in fact, the final diagnoses in our four patients were clinically-based and not made by US. As noted before, current HIPAA regulations prelude us from contacting all patients and even in those we were able to contact we could only schedule an assessment on about two thirds of them.

Our study has some limitations. First, the clinical data extracted from the medical records in terms of possible factors associated with a positive US might not be totally accurate or complete; however, these data came from the same academic practice and documentation follows the same guidelines. Second, we studied patients referred for possible inflammatory arthropathies rather than with a single arthritide, our results may not be applicable to each one of them. Finally, the number of patients in the longitudinal study was small, which may have prevented us from identifying the predictive features of the evolution to an inflammatory arthropathy in patients who had an initial negative US evaluation.

In conclusion, US in patients suspected of an inflammatory arthropathy aids in the identification of patients with defined inflammatory arthropathies. Not surprisingly factors associated with such occurrence include history of wrist swelling and the number of swollen hand and wrist joints; however morning stiffness, sicca symptoms and fibromyalgia-related symptoms are negatively associated with positive US findings. Patients with a negative initial comprehensive evaluation (including US) should be followed as clinical features of a defined inflammatory arthropathy may still ensue over time.

Acknowledgments

We are grateful to our patients for their participation in the longitudinal aspects of the study, to the University of Alabama at Birmingham, Department of Diagnostic Radiology and Division of Clinical Immunology and Rheumatology for defraying the cost of the imaging evaluations and to Ms. Maria Tyson for her expert assistance in the preparation of this manuscript.

References

1. OSTERGAARD M, EJBJERG B, SZKUDLAREK M: Imaging in early rheumatoid arthritis: roles of magnetic resonance imaging, ultrasonography, conventional radiography and computed tomography. *Best Pract Res Clin Rheumatol* 2005; 19: 91-116.
2. FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist. *Clin Exp Rheumatol* 2006; 24: 1-5.
3. SZKUDLAREK M, KLARLUND M, NARVESTAD E *et al*.: Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination. *Arthritis Res Ther* 2006; 8: R52.
4. MILOSAVLJEVIC J, LINDQVIST U, ELVIN A: Ultrasound and power Doppler evaluation of the hand and wrist in patients with psoriatic arthritis. *Acta Radiol* 2005; 46: 374-85.
5. MAGNANI M, SALIZZONI E, MULE R *et al*.: Ultrasonography detection of early bone erosions in the metacarpophalangeal joints of patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2004; 22: 743-8.
6. SZKUDLAREK M, NARVESTAD E, KLARLUND M *et al*.: Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination. *Arthritis Rheum* 2004; 50: 2103-12.
7. MACHOLD KP, STAMM TA, EBERL GJ *et al*.: Very recent onset arthritis-clinical, laboratory, and radiological findings during the first year of disease. *J Rheumatol* 2002; 29: 2278-87.
8. MACHOLD KP, NELL VP, STAMM TA *et al*.: Aspects of early arthritis. Traditional DMARD therapy: is it sufficient? *Arthritis Res Ther* 2006; 8: 211.
9. WAKEFIELD RJ, D'AGOSTINO MA, IAGNOCCO A *et al*.: The OMERACT Ultrasound Group: status of current activities and research directions. *J Rheumatol* 2007; 34: 848-51.
10. FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist VII. Ultrasound imaging in rheumatoid arthritis. *Clin Exp Rheumatol* 2007; 25: 5-10.
11. GUILLEMIN F, GERARD N, VAN LEEUWEN M *et al*.: Prognostic factors for joint destruction in rheumatoid arthritis: a prospective longitudinal study of 318 patients. *J Rheumatol* 2003; 30: 2585-9.
12. VAN ZEBEN D, HAZES JMW, ZWINDERMAN AH *et al*.: Factors predicting outcome of rheumatoid arthritis: Results of a followup study. *J Rheumatol* 1993; 20: 1288-96.
13. COMBE B, DOUGADOS M, GOUPILLE P *et al*.: Prognostic factors for radiographic damage in early rheumatoid arthritis. A multiparameter prospective study. *Arthritis Rheum* 2001; 44: 1736-43.
14. LINDQVIST E, EBERHARDT K, BENDTZEN K *et al*.: Prognostic laboratory markers of joint damage in rheumatoid arthritis. *Ann Rheum Dis* 2005; 64: 196-201.
15. GEUSENS PP, LANDEWE RB, GARNERO P *et al*.: The ratio of circulating osteoprotegerin to RANKL in early rheumatoid arthritis predicts later joint destruction. *Arthritis Rheum* 2006; 54: 1772-7.
16. WEYAND CM, HICOK KC, CONN DL *et al*.: The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. *Ann Intern Med* 1992; 117:801-6.
17. WAKEFIELD RJ, GIBBON WW, CONAGHAN PG *et al*.: The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis. A comparison with conventional radiography. *Arthritis Rheum* 2000; 43: 2762-70.
18. ALARCÓN GS, MORELAND LW, LOPEZ-BEN R: High resolution ultrasound for the study of target joints in rheumatoid arthritis. *Arthritis Rheum* 2002; 46: 1969-70.
19. GRASSI W, CERVINI C: Ultrasonography in rheumatology: an evolving technique. *Ann Rheum Dis* 1998; 57:268-71.
20. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al*.: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-7.
21. BAJAJ S, LOPEZ-BEN R, OSTER R *et al*.: Ultrasound detects rapid progression of erosive disease in patients in early rheumatoid arthritis: a prospective longitudinal study. *Skeletal Radiol* 2007; 36: 123-8.
22. NAREDO E, BONILLA G, GAMERO F *et al*.: Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. *Ann Rheum Dis* 2005; 64: 375-81.
23. BENITO MJ, VEALE DJ, FITZGERALD O *et al*.: Synovial tissue inflammation in early and late osteoarthritis. *Ann Rheum Dis* 2005; 64: 1263-7.
24. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
25. MCCONNELL S, KOLOPACK P, DAVIS AM: The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis Rheum* 2001; 45: 453-61.
26. BELLAMY N, SOTHERN RB, CAMPBELL J: Aspects of diurnal rhythmicity in pain, stiffness, and fatigue in patients with fibromyalgia. *J Rheumatol* 2004; 31: 379-89.
27. HAZES JM, HAYTON R, BURT J *et al*.: Consistency of morning stiffness: an analysis of diary data. *Br J Rheumatol* 1994; 33: 562-5.
28. KOSKI JM, SAARAKKALA S, HELLE M *et al*.: Power Doppler ultrasonography and synovitis. Correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipments. *Ann Rheum Dis* 2006; 65: 1590-95.