High-resolution B-mode and Doppler Sonography

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ABSTRACT

Objective: Intra-articular and extra-articular soft tissue abnormalities of joints affected by RA can be assessed in detail by high-resolution ultrasonography (US). This study investigated whether US can provide information on signs of inflammation in the wrists and metacarpophalangeal (MCP) joints in patients with RA that are not available with the clinical examination.

Methods: One hundred twenty wrists and 480 MCP joints of 60 patients (12 men, 48 women) with different grades of RA were assessed with US in B-mode and Power Doppler (PD) application, conventional radiography, and clinical examination for signs of bone destruction and joint inflammation. Involvement and severity of inflammation, as well as vascularization, were scored according to a 3-grade scale. The results were correlated with benchmarks of the clinical investigation. Clinical status was determined by the Disease Activity Score (DAS).

Results: 36.5% of the 600 joints were found to be swelling by clinical examination. Synovial swelling was seen in 41.3% of the joints by B-mode US and hypervascularization was observed in 92.7% by power Doppler application. Erosions were detected by radiography and US in 47% and 85% of joints, respectively.

Conclusions: US detects more abnormalities than does clinical examination and radiography. Over and above that, US enables detection of inflammatory changes of rheumatoid joints and provides simple grading of disease activity.

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by symmetric joint inflammation and destruction that often involves the small joints of the hands, with progressive deformity and disability of the joints. Synovial inflammation is accompanied by hyperemia, and during disease progression, angiogenesis appears to be the principal prerequisite for damage to cartilage and bone.1 Rather than treating the rheumatoid synovium as an inert structure through which inflammatory cells pass, it should be viewed as a multicentric tumor-like mass that invades and destroys.

New aggressive and powerful treatments that permit fast and effective suppression of inflammation and a significant decrease in vascularity in RA demand sensitive and specific methods for detecting disease signs, and monitoring disease activity. Finger joints are frequently the first affected by RA, and methods of assessment of these joints are important at the onset of the disease.

Clinical examination, one of the important methods to diagnose and monitor RA, is not optimal due to poor reproducibility and accuracy.2 Visualization of bone erosions through various imaging methods are essential in diagnosis and monitoring of RA. Though radiography is used, it is not sensitive enough to detect early stages of the disease.3,4 Magnetic resonance imaging (MRI) has been tested in patients with RA, and its value has been confirmed in studies of large joints5,6 and finger joints7 compared with histologic evaluation of biopsy specimens. However, MRIs are not used to assess RA patients due to the expensive equipment required and the need for highly qualified personnel.

Musculoskeletal ultrasonography (US) is an imaging technique that is now routinely used by a growing number of rheumatologists throughout the world. With US equipment now available, such as high-frequency linear-array transducers, it is possible to visualize and grade signs of inflammation and destruction in the small joints.8 Power Doppler ultrasonography (PDUS) was first introduced for cardiology investigations in the 1980s.9,10 Since it proved useful in cardiology, PDUS was soon applied to other medical diagnostic problems.11-19 It is the Doppler imaging technique that encodes an estimate of the integrated Doppler power spectrum in color, rather than the mean Doppler frequency shift as in conventional color Doppler US methods.20 PDs expand standard color capability. While conventional color Doppler US is well suited to evaluate high-velocity flow in large vessels, it is less effective in detecting low-velocity blood flow at the microvascular level.21-23
With PDUS, B-mode image information is enhanced by the depiction of the vascularity of soft tissue, and US diagnosis as a whole appears to be even more sensitive for the differentiation of synovitis and joint effusion, and for quantification of the degree of inflammation.\textsuperscript{24-29} This may allow detection of RA, especially in the early stages of the disease, and improve treatment options.\textsuperscript{30}

Few reports comparing US with clinical examination in RA exist. The primary outcome of the present study was to compare wrist and digital synovitis assessed by clinical and US methods. Secondary outcomes were to compare US and radiographs to assess erosions on distal metacarpophalangeal (MCP) (second through fifth) and proximal interphalangeal (second through fifth), and to evaluate the ability of US to discriminate between active and inactive synovitis.

Patients and Methods

A total of 120 wrists and 480 MCP joints of 60 patients with RA were examined. The patients were recruited from the outpatient clinic at Bichat Hospital in Paris, France. The diagnosis of RA in all patients fulfilled the American College of Rheumatology (formally, the American Rheumatism Association) 1987 revised criteria.\textsuperscript{51} Standard clinic and laboratory evaluations were performed according to the recommendations by Villaverde et al.\textsuperscript{32} Laboratory studies included testing for rheumatoid factor (RF), anti-cyclic citrullinated antibody (CCP), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and medication use was allowed. Patients with severe deformity of the wrist or finger joints were excluded.

The median age of the patients was 54 years (range 26 to 79), and the ratio of women to men was 4:1. The median disease duration was 11.5 years (range 0.25 to 32), and the group was comprised of four patients with early disease (disease duration < two years), and 56 patients with established disease (disease duration > two years). Nineteen patients were being treated with a disease-modifying anti-rheumatic drug (DMARD) associated with an anti-tumor necrosis factor-alpha (TNF-a) treatment.

The study was approved by the local ethics committee, and signed informed consent was obtained from each patient. The US and clinical examination were performed on the same day; ESR, determined by using the Westergren method; and CRP, measured by using nephelometry, were performed within two weeks of the main examinations, and radiographs of the hands (posteroanterior projection) were obtained within six weeks of the US examinations.

Clinical Examination

Prior to undergoing evaluation by US, all patients were assessed for clinical disease activity by a consultant rheumatologist. Swollen and tender joints, and morning stiffness were determined. Functional evaluation of disease activity was performed by using the Health Assessment Questionnaire (HAQ).\textsuperscript{33} as well as visual analogue scales (VAS) with values ranging from 0 to 100 mm for pain, fatigue, and patient and physician global assessments of disease activity. The composite disease activity score (DAS) 3,\textsuperscript{34} often used for assessing rheumatoid disease activity, and DAS 28\textsuperscript{35} were calculated for each patient. As US evaluation of the wrists and MCP joints (second through fifth) was performed, a DAS based on these 10 joints (DAS 10) in each patient (excluding elbows, shoulders, knees and the first MCP joints) was also calculated by using the same formula used to calculated the validated DAS 28 where $j$ ten, was the number of tender joints; $j$ swol, the number of swollen joints; and GADA pt, the patient’s score for global assessment of disease activity.

Ultrasonography

US was performed with an Esaote unit using a 10 to 15 MHz linear-array transducer. B-mode and PD applications were done using a standardized technique. During the scan, the patient was seated in front of the scanning table opposite the investigating physician, with his or her hands placed flat on the table surface. Synthetic plastic blocks were used to improve contact between the surface of the transducer and the hands and fingers, and to reduce near-field artifacts. B-mode was performed in the dorsal, lateral, medial and palmar aspects of the second through fifth MCP joints of both hands, and in the dorsal aspect of radiocarpal joints. Wrist scanning was performed in the sagittal plane over the dorsal surface of the radius, lunate bone, and capitate bone (Figure 1.1 and Figure 1.2). MCP joint scanning was performed in the sagittal plane over the dorsal surface of the joint. The assessed changes in the MCP joints and wrists were defined as follows: joint effusion was defined as the compressible anechoic intracapsular area, synovitis as a hypoechoic synovial thickening (non-compressible hypoechoic intracapsular area and absence of Doppler signal), and bone erosion as pathologic changes in the bone surface of the area adjacent to the joint, visualized in two planes.

The US examinations were conducted to detect the presence or absence of bone erosions (Figure 2), and for the presence or absence of signs of inflammation (joint effusion and synovial thickening; Figure 3). Furthermore, the synovial
measurements were systematically carried out perpendicular to the great axis and at the point of greatest thickness. A cut-off for US positivity was defined as synovitis involving a synovial thickness of at least 1 mm in radiocarpal joints and at least 0.5 mm in MCP joints.36

PD settings were standardized with a pulse repetition frequency of 750 Hz. For optimum sensitivity, the PDUS gain was set elevating its level until the color box was almost uniformly filled with the first indication of color, and with only the minimum amount of the next highest signal just beginning to appear. Using this method of adjustment,26 depth dependency, effects of blood pressure and medication, as well as heart rate and blood viscosity can be expected to have the same influence on the synovial tissue, and are therefore of minor importance for the measurement. We can perform this procedure either with the scan wiped clean of gel and contacting only air, or after applying the gel-covered transducer to the patient at the region of interest, which in the present study was the MCP joints and radiocarpal joint.

Power Doppler ultrasonography (PDUS) measurements were carried out when they were positive (Figure 4), and the signal was scored according to a semiquantitative scale where a score of 0 meant absence of signal in the synovitis; 1, signal in less than 1/3 of the synovitis; 2, signal in 1/3 to 2/3 of the synovitis; and 3, signal in more than 2/3 of the synovitis.37 All US examinations were performed by the same rheumatologist, who was trained in musculoskeletal US. The US was performed without knowledge of the clinician’s assessment or radiographic data.

Statistical Analysis
The data collected on 10 joints through physical examinations were correlated with the presence of synovitis in the same 10 joints measured by B-mode sonography, using Pearson’s correlation test. Counting variables were transformed according to the square root function to satisfy the supposition of a normal distribution of Pearson’s linear correlation method. In clinical practice, PDUS interpretation leads, in most cases, to qualitative statements. In this study, the assessment of the presence of erosions on radiographs of the hands was also qualitative. The relationship of both variables was analyzed using the Chi-square test. Fisher’s exact test was used to compare the presence of bone erosions on radiographs and US.

The Kolmogorov-Smirnov normality test was applied to confirm the suppositions of Gaussian distribution. The 95% confidence interval was calculated for Pearson’s correlation coefficient according to Fisher’s Z transformation. A strong linear correlation coefficient was defined as ≥ 0.70; moderate correlation coefficient between 0.5 and 0.7; weak to moderate correlation coefficient between 0.3 and 0.5; and weak correlation coefficient as less than 0.3. Medians (DAS 10) were compared between two independent groups (absence of Doppler signal and presence of Doppler signal) using
Student’s t-test. All significant probabilities (p values) shown are of bilateral type, and values lower than 0.05 were considered statistically significant. P values between 0.05 and 0.10 were considered marginally significant.

Results
In all 60 patients, standard documentation using high-resolution imaging techniques was performed in five regions in each hand. The mean investigation time was 10 minutes for each hand, and was reduced during the course of the study.

After refinement of instrumentation and optimization of image documentation, the following standard cuts were shown to be useful: dorsal longitudinal and transversal cuts for the radiocarpal joints, and longitudinal and transversal cuts dorsally and ventrally for the MCP joints (second through fifth). The metacarpal articulations were imaged with 10’ to 15’ of palmar flexion, and the wrist was imaged dorsally in a neutral position.

Correlation with Clinical and Image Data
On enrollment, 36.5% of the joints were classified as swollen. More than 25% of the swollen joints were third MCP joints, 24.6% were second MCP joints, and 24.2% were radiocarpal joints. On US examination, the joints most frequently involved were the radiocarpal joints (32.6%), followed by the second MCP joints (22.5%).

When B-mode sonography was compared with the clinical findings, there was a significant correlation (r = 0.6, p < 0.0001; Figure 5). Differences between sonographic findings (joint erosions and changes of soft tissue accompanied by hypervascularization) and radiographic findings of bone erosions were observed. Erosions were detected by radiography in 47% of joints and by sonography in 85% (p = 0.0024). Hypervascularization was found in 92.7% of swollen joints, using PD.

Fifty-six percent and 76% of the patients showed bone erosions on x-ray and presence of Doppler signal on US, while 50.4% showed only erosions on x-ray (p = 0.0469).

Finally, when we compared the medians of DAS 10 between the groups of patients with synovial hypervascularization (presence of Doppler signal) and without synovial hypervascularization (absence of Doppler signal), we observed a statistically significant difference between the groups (p < 0.0001).

Discussion
RA is a major inflammatory condition and the fundamental event is synovial proliferation. The growth of fibroblast-like synoviocytes and metalloproteinase production by fibroblast-like synoviocytes contribute to cartilage and bone damage associated with a dramatic expansion of the blood-vessel volume. This hypervascularized tissue containing fibroblastic elements is referred to as pannus.38,39

Visualizing inflammatory tissue is an important element not only in the diagnosis but also in the monitoring of disease activity.

US has potential as a measurement tool in inflammatory arthritis and has been increasingly investigated. It is a safe, cheap, non-ionizing, dynamic method of imaging. Vascularization is characterized by PD10,17,22 to support the diagnosis of RA. With prominent vascularization, there is a correlation between the disease process, including inflammation, and increased blood flow of the vessels.

With US (B-mode application), we observed that 41.3% of the joints were involved, and that 32.6% were located in the radiocarpal joints. When these results were compared with clinical findings, clinical examination was associated with a lower detection rate with regard to joint swelling (36.5%). The rheumatologist who did the US examination was unaware of the patient’s clinical examination, thus an overestimate of syn-
Ovitis can be excluded in our study. There was a significant correlation between the US image and clinical examination of inflamed joints. Our results do not differ from those reported by other investigators. The lower sensitivity of clinical examination may account for the deterioration of RA patients despite clinically adequate control of the disease.

The 10-joint simplified PDUS assessment is not a validated estimation of the level of general articular inflammation. However, a 12-joint PDUS has been proven as a validated method to assess joint inflammation in RA by Naredo et al in a recent publication.

X-ray is the traditional tool used to assess joint damage in RA. Bone erosions, joint-space narrowing as an indirect sign of cartilage thinning, juxta-articular osteoporosis, cysts and, in severe cases, joint subluxations, malalignment or ankylosis, can be demonstrated. Nevertheless, it shows a relative insensitivity to early bone damage and a total insufficiency to assess soft-tissue changes, including synovitis. In early disease, x-ray status is not related to functional outcome measures like the HAQ score, while in established disease, the radiographical damage and the functional status are significantly correlated, the correlation coefficient being 0.3 to 0.5 (i.e., changes visualized by x-ray explain approximately 25% of disability in established RA).

Due to the visualization of all structures involved in the RA disease process, it is likely that more advanced imaging modalities, such as US, could capture disease manifestations responsible for patient disability. According to previous reports, lesion extent and severity can be delineated to better advantage with sonography compared with radiography. In our study, sonography also detected more lesions in the B-mode application than did conventional radiography, thus having more sensitive diagnostic value. This can be explained by the late detection of bone lesions using conventional radiography. The lesions found on radiographs correlated significantly with those detected by sonography using the B-mode and PD applications.

**Conclusions**

Sonography can be used to assess synovitis better than clinical palpation, as well as the inflammatory and destructive changes in RA hands. US is more sensitive than plain film radiography for detecting erosions of the small joints.

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