Musculoskeletal Ultrasonography in Healthy Subjects and Ultrasound Criteria for Early Arthritis (The ESPOIR Cohort)

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ABSTRACT. ***Objective.*** To confirm the occurrence of bone erosions and synovitis in healthy subjects detectable by ultrasound (US) and to establish US criteria for early arthritis.

Methods. Our study involved 127 healthy subjects matched with a cohort of patients with early arthritis (the ESPOIR cohort). The second and fifth metacarpophalangeal (MCP) joints and the fifth metatarsophalangeal (MTP) joint of both hands and feet were assessed with US to detect bone erosion; and the second, third, fourth, and fifth MCP and the fifth MTP were evaluated for synovial thickening in B-mode US and synovial vascularity in power Doppler. Bone erosion and synovitis were defined according to the Outcome Measures in Rheumatology Clinical Trials consensus.

Results. Bone erosion and grade 2–3 synovial thickening in B-mode were detected in 11% and 9% of healthy subjects. To consider the diagnosis of early arthritis, a cutoff at 1 case of synovial thickening in B-mode enabled discrimination between patients with early arthritis and healthy subjects, with a good sensitivity of 74.8% (95% CI 67.2%–82.3%) and a high specificity of 90.5% (95% CI 85.4%–95.6%). If higher specificity is required to confirm the diagnosis of early arthritis, cutoff at 2 cases of synovial thickening in B-mode or at 2 cases of bone erosion gave optimal results, with specificity of 98.4% (95% CI 96.2%–100%) and 100%, respectively, and lower sensitivity of 59.8% (95% CI 51.2%–68.3%) and 17% (95% CI 10.5%–23.5%) (area under the curve = 0.85 for synovitis and 0.63 for bone erosion). Neither the combination of power Doppler signal plus bone erosion, nor bone erosions plus synovial thickening on the same joint, were seen in healthy subjects.

Conclusion. A single case of bone erosion or synovial thickening in B-mode is common in healthy subjects. However, more than 1 case of synovial thickening in B-mode or bone erosion is a strong argument for the diagnosis of early inflammatory arthritis. (First Release Feb 1 2011; J Rheumatol 2011;38:613–20; doi:10.3899/jrheum.100379)

Key Indexing Terms:
ULTRASOUND BONE EROSION EARLY ARTHRITIS
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Rheumatoid arthritis (RA) is an inflammatory disease that may cause severe joint destruction and functional disability[1]. Initiation of effective treatment before the onset of articular destruction may prevent structural progression. Conventional radiography is considered the "gold standard" for assessing destructive skeletal changes in RA. However, magnetic resonance imaging (MRI) and ultrasonography (US) are more sensitive than clinical assessment for the detection of synovitis and more sensitive than radiography for the detection of bone erosion in RA[2,3]. US examination allows the detection of bone erosion earlier than radiography[4]. The resolution of US images has considerably improved in the past few years and recent studies have shown that "abnormal" features could be observed even in healthy subjects[4,5,6,7].

Our objectives were, first, to confirm the presence of cortical bone erosion and synovitis in healthy subjects; and, second, to specify US criteria for early inflammatory arthritis by using a case-control study.

MATERIALS AND METHODS

A case-control study was performed comparing patients with early-onset arthritis to an age-matched and sex-matched control group of healthy subjects.

The ESPOIR cohort is a French multicenter cohort of patients with early arthritis[8]. There were 813 patients included in the cohort, in which cases of undifferentiated arthritis or RA were diagnosed < 6 months previously.

US examination was performed on 127 patients. All these patients were matched to healthy subjects according to gender and age (± 5 years). There were 127 healthy subjects. The exclusion criteria for these subjects were a history of foot or hand pain, a rheumatological pathology due to crystal deposits, arthritis in 1 or more joints, or surgery on any of the investigated joints. Healthy subjects consisted of hospital staff members and patients who were hospitalized with sciatica. Consent was obtained prior to their inclusion in the study.

Healthy subjects were examined by the same experienced ultrasonographer using Mylab 70 Esaote equipment (Esaote, Genoa, Italy) with a high-frequency 16 MHz linear probe. ESPOIR cohort patients were examined by operators in 4 centers in France [10–13 MHz linear array transducer, 8.3 MHz frequency, and 750 Hz pulse repetition frequency for power Doppler (PD) detection].

Each joint was scanned in both longitudinal and transverse planes from the palmar to the dorsal sides, in B-mode and in Doppler mode. The second and fifth metacarpophalangeal (MCP) and fifth metatarsophalangeal (MTP) of both hands and feet were assessed with US to find bone erosion. The second, third, fourth, and fifth MCP and the fifth MTP were examined to find synovial thickening in B-mode and flow signal on PD US. MCP1 and MTP1 of the hands and the feet often contain joint effusions, synovial thickening, and osteophyte formation in the asymptomatic population. Therefore these joints were excluded from our case study to determine synovitis and bone erosion.

Bone erosion was defined according to the OMERACT consensus[9]. Bone erosion was measured at both edges of the cortical bone and was scored on a semiquantitative scale (width < 1 mm, 1 to 2 mm, 2 to 4 mm, > 4 mm; Figure 1A). The Wakefield Semiquantitative scoring system was used for erosion[4].

B-mode synovitis was scored according to a semiquantitative scale (range 0–3)[10]. The Szkudlarek semiquantitative scoring system was used for synovitis. Grades 0–1 were considered physiological and grades 2–3 pathological[7]. Synovial thickening alone in B-mode responding to grades 2–3 was recorded for ESPOIR cohort patients. For healthy subjects, grade 1 synovial thickening was also included for the descriptive study, while only grades 2–3 were used for comparative study.

Interobserver reliability was also calculated between the sonographer who performed US examinations on the control group of healthy people and one of the operators who carried out the ESPOIR cohort US examinations. The interrater reliability was evaluated using the results of US examinations carried out on 30 patients with RA or early arthritis. A blind test was carried out on these 2 operators in relation to the US examinations, which were performed on the same day, using the same equipment.

The interexaminer reliability of the 4 sonographers who performed US examination of patients with early arthritis in the ESPOIR cohort was assessed by means of a blind test carried out on selected images, clinical data, and other examiner results: 20 images in B-mode and 30 images of synovitis in PD mode were sent to each examiner. Examiners had to assess the presence or absence of synovial thickening in B-mode and score the synovitis in PD mode according to the semiquantitative score previously defined.

Statistical analysis. Interobserver agreement was calculated using the κ test. Statistical analysis included a comparison of bone erosion and synovitis between the healthy subject control group and patients.

Mann-Whitney U test and Fisher's exact test were applied to compare age and sex between healthy subjects with or without bone erosion.

A matched-paired t test and a McNemar's test were applied to compare age distribution, the expression of bone erosion, and synovitis between patients and controls. SPSS (version 12.0) was used to perform statistical analysis of the results; $p < 0.05$ was regarded as significant.

To confirm the ability of US to discriminate between patients with early arthritis and healthy subjects, an analysis of receiver-operation characteristic (ROC) curves was performed.

RESULTS

Descriptive study in healthy subjects. A total of 1270 joints from 127 healthy subjects were studied to look for synovial thickening in B-mode and synovial vascularity in PD (second, third, fourth, and fifth MCP, and fifth MTP of both hands and feet), and 762 joints for bone erosion (the second and fifth MCP and fifth MTP of both hands and feet).

The average age of subjects was 50 years (± 12.7 yrs). Patient characteristics are summarized in Table 1.

Bone erosion. Fourteen joints with bone erosion were found in 14 out of 127 healthy subjects (11%; Figure 1B, 1C). Eleven out of the 14 cases of bone erosion (78%) were scored grade 1 or 2 (< 2 mm; Figure 2A). Five cases of bone erosion were located on the second MCP, 1 on the fifth MCP, and 8 on the fifth MTP (Figure 2B). Three cases of erosion were located on dorsal scans, 6 on palmar scans, and 5 on radial scans. No healthy subject had > 1 case of bone erosion and none of them presented PD signal within the bone erosion.

Mean age was 50.2 years (± 12.8) for healthy subjects without erosions and 48.3 years (± 11.5) for healthy subjects with erosions. This difference was not statistically significant ($p = 0.51$). Median age (minimum-maximum) for subjects with erosion was 49 years (24.5–69.4). There was no statistical difference between male and female healthy subjects with or without joint erosions ($p = 0.742$).

"False erosions" (visible on 1 plane only, while the definition of joint erosion requires a cortical break detected on 2 planes) were found in 25 out of 127 (19.6%) scans of healthy subjects. Finally, vascular foramens (defined as a linear discontinuity of cortical bone with parallel edges and Doppler signal due to the presence of nutritional vessels) were identified on the scans of 15 healthy subjects (Figure 1G).

Joint synovitis. Thirty-seven joints with synovial thickening were identified in B-mode in 28 of the 127 healthy subjects (22%) if grade 1 synovial thickening was included (Figure 1D). Nineteen subjects had only 1 case of synovitis and 9 subjects had 2 cases of synovitis. Of the cases of synovitis, 23 (62%) had a grade 1 score (Figure 2C).

Counting only grade 2–3 synovial thickening (which was considered pathological)[7], 12 out of 127 healthy subjects (9%) had at least 1 synovial thickening. Ten cases of synovial thickening were located on the second MCP, 2 on the third MCP, 1 on the fourth MCP, and 1 on the fifth MCP. No synovitis was detected on the fifth MTP in any healthy subject (Figure 2D). Synovial vascularity in PD was observed in only 5 healthy subjects (Figure 1E). The mean age of healthy subjects without synovitis was 49.3 years (± 12.6),

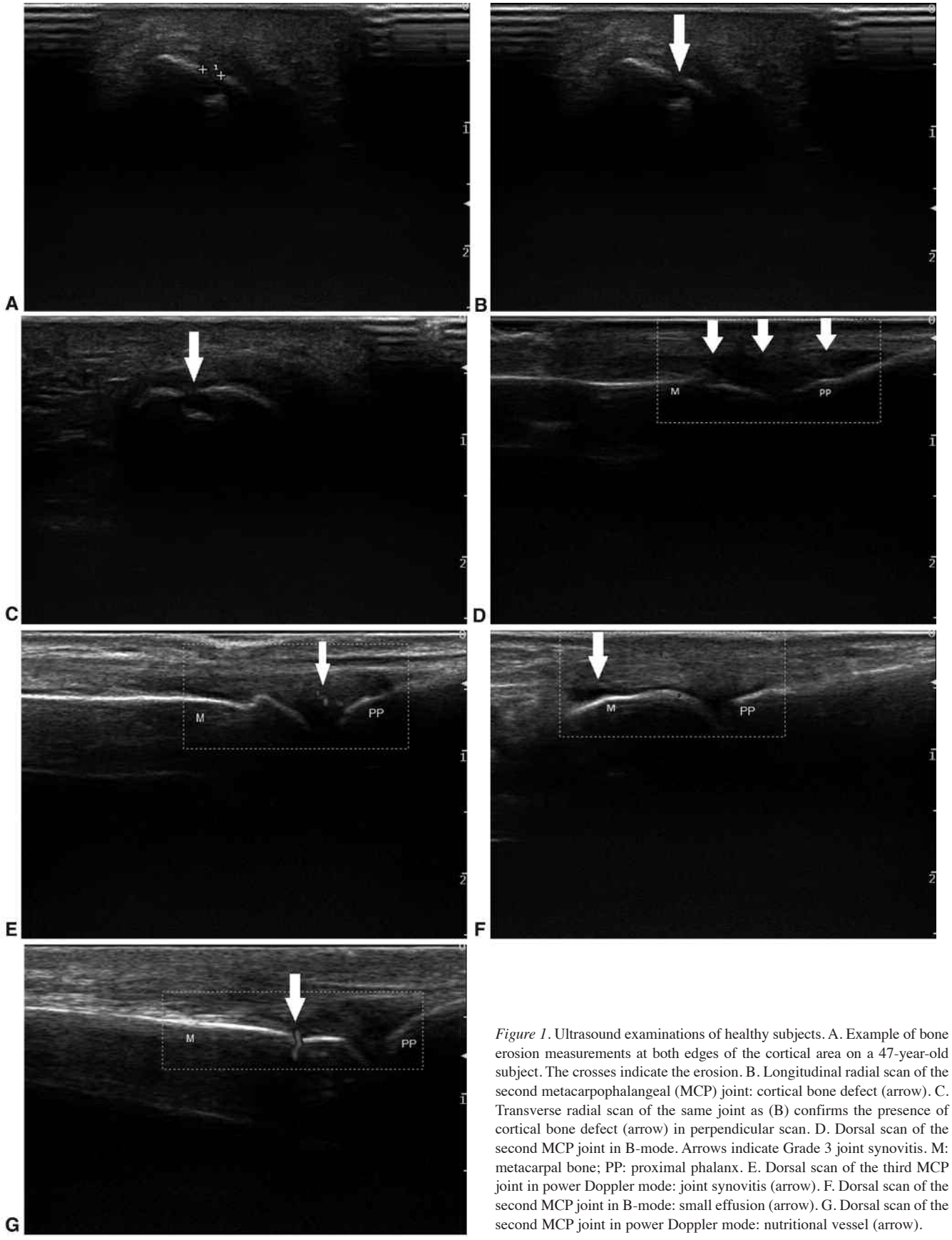

Figure 1. Ultrasound examinations of healthy subjects. A. Example of bone erosion measurements at both edges of the cortical area on a 47-year-old subject. The crosses indicate the erosion. B. Longitudinal radial scan of the second metacarpophalangeal (MCP) joint: cortical bone defect (arrow). C. Transverse radial scan of the same joint as (B) confirms the presence of cortical bone defect (arrow) in perpendicular scan. D. Dorsal scan of the second MCP joint in B-mode. Arrows indicate Grade 3 joint synovitis. M: metacarpal bone; PP: proximal phalanx. E. Dorsal scan of the third MCP joint in power Doppler mode: joint synovitis (arrow). F. Dorsal scan of the second MCP joint in B-mode: small effusion (arrow). G. Dorsal scan of the second MCP joint in power Doppler mode: nutritional vessel (arrow).

Table 1. Patient characteristics.

Characteristics	Patients with Early-onset Arthritis, n = 127	Controls, n = 127
Men, %	22	22
Women, %	78	78
Age, yrs, mean	50.3	50.0
DAS28, mean	5	NA
Radiographic bone erosion, %	26	NA
Anti-CCP positivity, %	35.7	NA
IgM RF positivity, %	42.9	NA

DAS28: 28-joint count Disease Activity Score; NA: not assessable; CCP: cyclic citrullinated peptide; RF: rheumatoid factor.

and 56.1 years (± 12.3) for healthy subjects with synovitis. This difference was not statistically significant (p = 0.066). Median age (minimum-maximum) for subjects with synovitis was 58 years (24.2–72.9).

Twenty-four joints with effusions were found in 21 out of 127 healthy subjects (17%; Figure 1F). Such effusions were small to moderate.

Case-control study. Each patient in the ESPOIR cohort was age-matched and sex-matched to a healthy subject in the control group.

The reliability among the 4 examiners of the ESPOIR cohort was excellent, with very good agreement on the interclass correlation coefficient (0.82 for synovitis in B-mode and 0.92 for synovitis in PD mode). Between the sono-

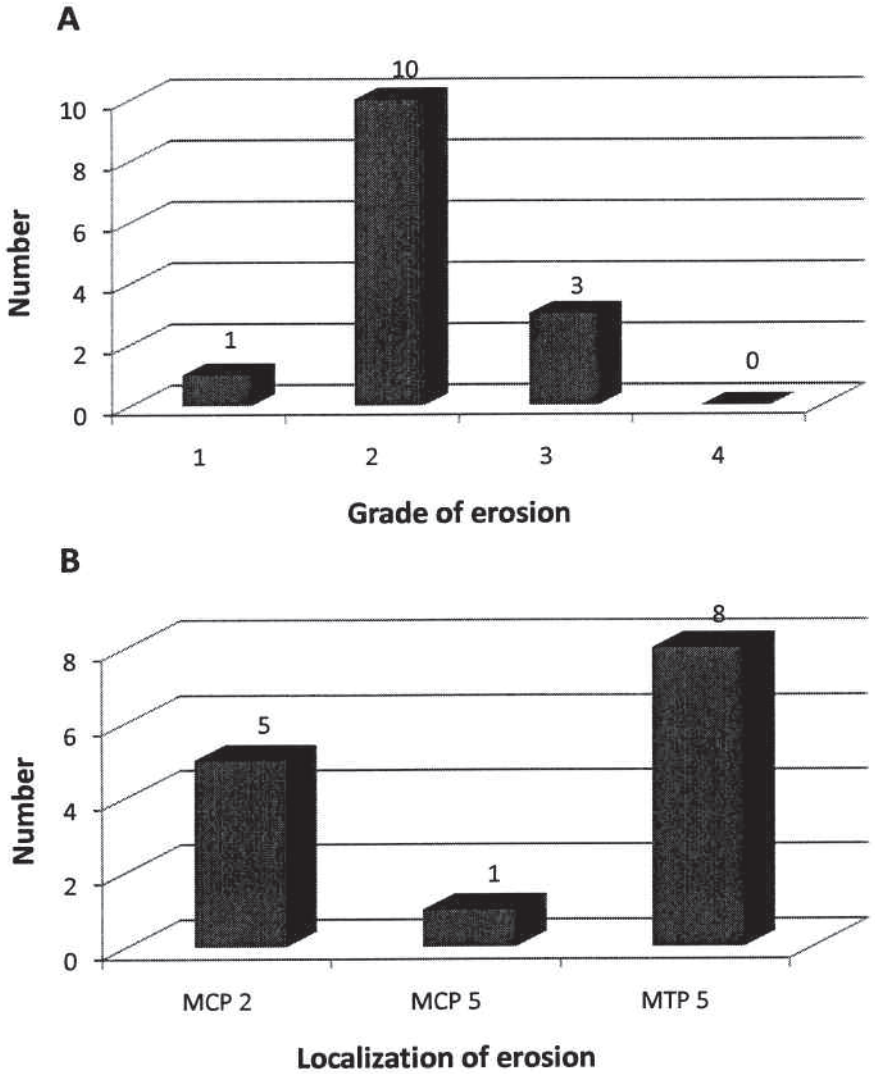

Figure 2 (A, B). Bone erosion and synovitis in healthy subjects. A. Number of cases of bone erosion of each grade. Eleven out of 14 of the cases of bone erosion (78%) were scored grade 1 or 2 (< 2 mm). B. Number of cases of bone erosion in each metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joint examined. Five cases of bone erosion were located on the second MCP and 8 on the fifth MTP.

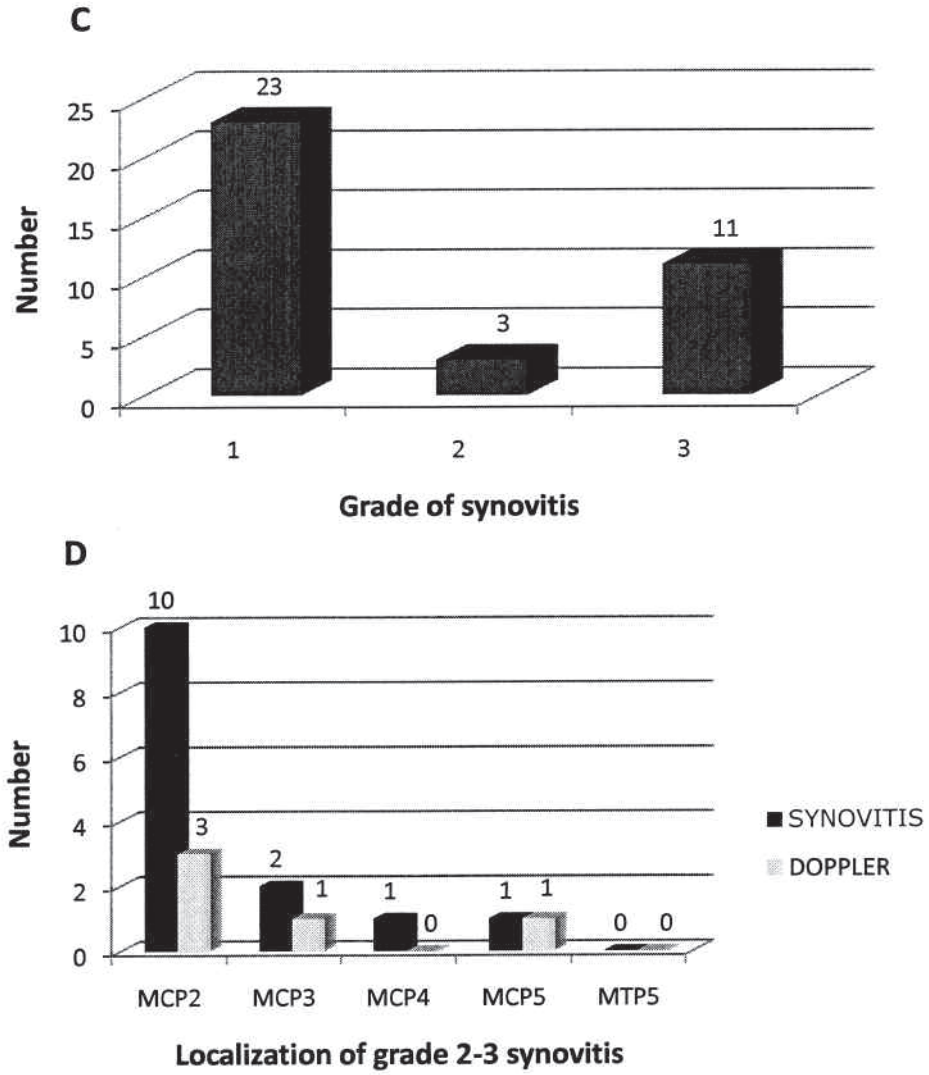

Figure 2 (C, D). C. Number of cases of synovitis of each grade. Fourteen cases of synovitis were found in 12 subjects, considering grade 2–3 synovitis as pathological. D. Number of cases of grade 2–3 synovitis in B-mode and cases of synovitis with power Doppler signal in each joint. Ten cases of synovitis were located on the second MCP. No expression of synovitis was detected in the fifth MTP.

grapher who performed the US examinations on healthy subjects and one of the operators who performed the ESPOIR cohort US, the interobserver κ value for agreement analysis of reproducibility for the detection of cortical bone erosion was 0.86, and for synovitis, 0.88.

A significantly higher expression of bone erosion and synovitis was discovered in the ESPOIR cohort patients compared to healthy subjects. Bone erosion was discovered in 11% of the control group versus 36% of the patients in the ESPOIR cohort ($p < 0.001$), and grade 2–3 synovial thickening in B-mode was found in 9% of the control group versus 75% of the patients in the ESPOIR cohort ($p < 0.001$). Meanwhile, there was no significant difference between the number of erosions of grade 3 and 4 (Table 2).

Diagnostic value of US. To confirm the ability of US to discriminate between patients with early arthritis and healthy subjects, ROC curves were performed (Figure 3). ROC curves revealed good discrimination (area under the curve = 0.85 for joint synovitis and 0.65 for bone erosion) and allowed a cutoff at 1 grade 2–3 synovial thickening in B-mode, with a sensitivity of 74.8% and a specificity of 90.5%.

However, to confirm diagnosis of early arthritis with higher specificity, cutoff set at 2 joints with grade 2–3 synovial thickening in B-mode or 2 cases of bone erosion gave optimal results, with a specificity of 98.4% and 100%, respectively, and a sensitivity of 59.8% and 17%.

A combination of neither PD signal plus bone erosion nor bone erosion plus synovial thickening on the same joint nor synovial vascularity in PD plus erosion was seen in healthy subjects.

Table 2. Comparison between patients with early-onset arthritis and healthy subjects in relation to the number of cases of bone erosion and joint synovitis.

	Patients, n = 127, Mean ± SD	Healthy Subjects, n = 127 Mean ± SD	p
No. subjects with synovial joint thickening in B-mode	0.75 ± 0.436 N = 95	0.09 ± 0.294 N = 12	< 0.001
No. subjects with synovial joint vascularity in power Doppler	0.50 ± 0.502 N = 64	0.04 ± 0.195 N = 5	< 0.001
No. subjects with bone erosion	0.36 ± 0.483 N = 46	0.11 ± 0.314 N = 14	< 0.001
No. grade 1 bone erosions	0.3 ± 0.903 N = 38	0.01 ± 0.089 N = 1	< 0.001
No. grade 2 bone erosions	0.32 ± 0.711 N = 41	0.08 ± 0.270 N = 10	< 0.001
No. grade 3 bone erosions	0.09 ± 0.334 N = 11	0.02 ± 0.152 N = 3	< 0.059*
No. grade 4 bone erosions	0.02 ± 0.125 N = 2	0 N = 0	0.158*

N: absolute number. * Not significant.

DISCUSSION

Our study is the first to directly compare over 100 patients with early arthritis to age-matched and sex-matched healthy individuals. Moreover, unlike the majority of existing studies, our main objective was to examine bone erosion and joint synovitis in healthy subjects.

Our study confirms the presence of bone erosion and synovial thickening in B-mode with a high frequency in healthy subjects. Prior MRI studies have demonstrated the presence of bone erosion in healthy people. Using MRI, Szkudlarek and colleagues found 1 case of bone erosion in the fifth MTP joints[7] and 9 cases in the MCP joints in 20 members of a control group[3]. Ejbjerg and colleagues[11] found 5 cases of bone erosion in MCP in 28 participants of a control group, and Tan and colleagues[12] found 14 cases of bone erosion in MCP in 28 healthy subjects.

However, US studies disagree regarding the detection of bone erosion in healthy subjects. Wakefield, *et al*[4] found 1 case of erosion in the MCP, which they explained by the presence of a trauma. In our study, only 1 healthy subject out of the 14 members who presented with bone erosion in the control group had a traumatic history. In US, Wiell, *et al*[6], Dohn, *et al*[5], and Szkudlarek, *et al*[7] also found bone erosion in healthy subjects. Szkudlarek found 1 case of bone erosion in the fifth MTP joints[7] and none in the MCP joint[3], while Dohn[5] found 6 cases of bone erosion in 16 MCP and Wiell found 1 case of bone erosion in MCP and 3 in MTP 1 in 5 healthy subjects. However, other studies[3,13,14,15,16], including Schmidt, *et al*, with 102 healthy subjects[13], did not find any bone erosion. Schmidt and colleagues did a circumferential scan of the second MCP joints in 102 control subjects and reported no erosive changes. Several hypotheses can explain these discrepancies. First, the majority of these studies included a very small number of healthy subjects, except the Schmidt study[13]. But in that study, only the second MCP was studied, with a 10 MHz probe. The huge improvement of resolution of US images thanks to the use of higher frequencies allows detection of smaller abnormal features than in the past.

Given the lack of comparison with computed tomography (CT) or MRI, it is not possible to conclude whether the erosions seen on the US examinations in our study are real bone erosions. Very good correlations between US, MRI, and CT for the detection of bone erosion in patients with RA have already been demonstrated[5].

However, the US erosions in the Dohn, Wiell, and Szkudlarek studies[5,6,7] were not confirmed by MRI (excepting 1 case of bone erosion on MTP1 in the Szkudlarek study, which was correlated by MRI and by ultrasound). These findings may be explained by a high US sensitivity, and physiologic bone notches may be mistaken for erosions.

For synovitis, all MRI studies involving at least 5 healthy subjects found synovitis[3,7,11]. However, US studies are discordant between each other for the detection of synovitis. Szkudlarek, Wiell, and Keen[3,6,7,17] found synovial thickening in B-mode at frequencies similar to those in our study. Szkudlarek found 23 synovial thickenings in B-mode in the MTP joints[7] and 3 in the MCP joints on 20 controls[3]. However, several other US studies did not find synovial thickening in B-mode in healthy subjects, such as Terslev, *et al*[18] in 27 healthy subjects and Hau, *et al*[19] in 15. The high frequency of synovial thickening in our healthy subjects may be caused by asymptomatic osteoarthritis, given that exclusion criteria were clinical and that no radiography was performed.

There is no report in the literature describing foramen at MCP joints. Foramen corresponds to the presence of nutritional vessels and is defined as a linear discontinuity of cortical bone with parallel edges and Doppler signal due to the presence of nutritional vessels. Therefore, an MRI was performed on a healthy subject with a vascular foramen in US (data not shown). This MRI was not contained in the initial study protocol but it seemed interesting to confirm that the images displayed by US corresponded well to MRI foramen. The MRI confirmed it. The lack of a description of foramen in these joints can be explained by the probe used, since a very sensitive Doppler is necessary.

As expected, there was a significant difference between the number of bone erosions and synovitis in patients and in controls. However, no significant difference in the number of erosions of grade 3 and 4 was found. But large bone erosions (> 2 mm) are uncommon in very early arthritis, and we cannot exclude that the number of subjects was too small to highlight such a difference.

It has been shown that US is more sensitive than standard radiography in detection of bone erosions, but its specificity

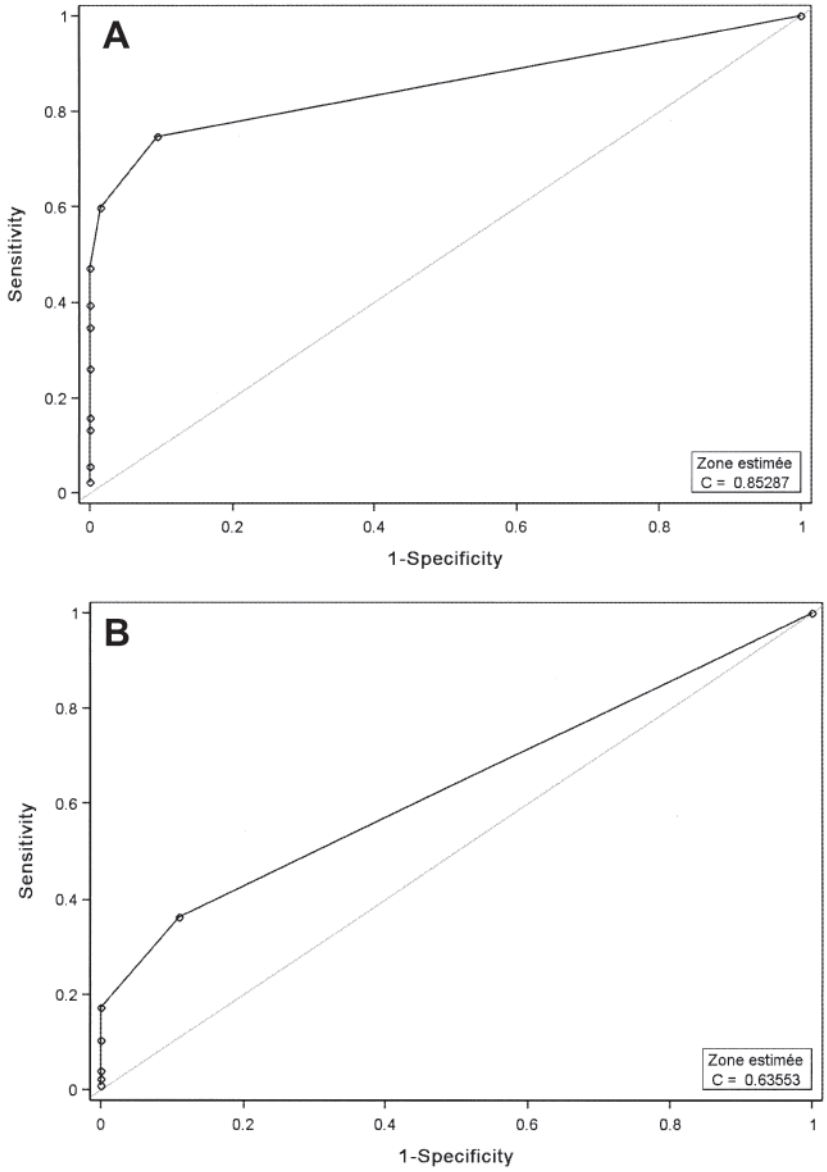

Figure 3. Receiver-operation characteristic (ROC) curves for synovitis (A) and bone erosion (B) in discriminating between healthy subjects and patients with early-onset arthritis. Cutoff was set at 1 case of synovitis, with a good sensitivity of 74.8% (95% CI 67.2%–82.3%) and a high specificity of 90.5% (95% CI 85.4%–95.6%). If higher specificity is required, cutoffs at 2 cases of synovitis or 2 cases of bone erosion resulted in specificity of 98.4% (95% CI 96.2%–100%) and 100%, respectively, and lower sensitivity of 59.8% (95% CI 51.2%–68.3%) and 17% (95% CI 10.5%–23.5%), respectively (area under the curve = 0.85 for synovitis and 0.63 for bone erosion).

has not yet been established. To increase its specificity, several approaches can be proposed. In our study, the presence of isolated bone erosion or a grade 2 and 3 synovial thickening in B-mode were associated with 11% and 9.5% of false positives, respectively. To consider the diagnosis of early arthritis, a cutoff at 1 joint with grade 2–3 synovial thickening in B-mode makes it possible to discriminate between patients with early arthritis and healthy subjects with a good sensitivity of 74.8% and a high specificity of 90.5%. Yet, if higher specificity is required to confirm the diagnosis of early arthritis, cutoffs at 2 joints with grade 2–3 synovial thickening [specificity of 98.4%, sensitivity of 59.8%, area under the curve (AUC) = 0.85] or 2 cases of bone erosion (specificity 100%, sensitivity 17%, AUC = 0.63) were optimal. These associations allow us to consider the US as pathological, but these signs are not specific to rheumatic disorders.

Currently there is no study of the diagnostic value of US in RA. A similar type of case study would be required to evaluate the specificity of US for diagnosis of RA, includ-

ing patients with osteoarthritis, rheumatological disease due to crystal deposits, and other inflammatory rheumatism.

The presence of isolated synovial thickening in B-mode or isolated bone erosion in US is not sufficient to confirm the diagnosis of early inflammatory arthritis, since these abnormalities may be present in healthy subjects. However, to discriminate between patients with early arthritis and healthy subjects, 1 joint with grade 2–3 synovial thickening (sensitivity 74.8%, specificity 90.5%) in B-mode was optimal. But to confirm diagnosis of early arthritis with higher specificity, a cutoff at 2 joints with synovial thickening or 2 cases of bone erosion gave an optimal result, with specificity of 98.4% and 100%, respectively. So, the presence of > 1 case of joint synovitis or bone erosion is a strong argument for the diagnosis of early inflammatory arthritis. The combination of neither PD signal plus bone erosion nor bone erosion plus synovial thickening on the same joint was seen in healthy subjects.

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APPENDIX

Study collaborators. Investigators of the French Early Arthritis Cohort ESPOIR: F. Berenbaum, Paris-Saint Antoine; M.C. Boissier, Paris-Bobigny; A. Cantagrel, Toulouse; B. Combe, Montpellier; M. Dougados, Paris-Cochin; P. Boumier, Amiens; R.M. Flipo, Lille; P. Goupille, Tours; F. Liote, Paris-Lariboisière; X. Le Loet and O. Vittecoq, Rouen; X. Mariette, Paris Bicetre; O. Meyer, Paris Bichat; T. Schaeverbeke, Bordeaux; J. Sibilia, Strasbourg.

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