

# Magnetic Resonance Imaging, Ultrasonography, and Conventional Radiography in the Assessment of Bone Erosions in Juvenile Idiopathic Arthritis

CLARA MALATTIA,<sup>1</sup> MARIA BEATRICE DAMASIO,<sup>1</sup> FRANCESCA MAGNAGUAGNO,<sup>1</sup>  
ANGELA PISTORIO,<sup>1</sup> MAURA VALLE,<sup>1</sup> CARLO MARTINOLI,<sup>2</sup> STEFANIA VIOLA,<sup>1</sup>  
ANTONELLA BUONCOMPAGNI,<sup>1</sup> ANNA LOY,<sup>1</sup> ANGELO RAVELLI,<sup>3</sup> PAOLO TOMÀ,<sup>1</sup>  
AND ALBERTO MARTINI<sup>3</sup>

**Objective.** To compare magnetic resonance imaging (MRI), conventional radiography, and ultrasonography in identifying bone erosions in patients with juvenile idiopathic arthritis (JIA), and to determine the validity and reliability of an MRI scale in detecting and grading joint damage.

**Methods.** In 26 JIA patients, the clinically more affected wrist was studied with MRI, radiography, and ultrasonography, coupled with standard clinical assessment and biochemical analysis. MR images were assessed independently by 2 readers according to an apposite devised scoring system.

**Results.** Of 26 patients, 25 (96.1%) had 1 or more erosions as detected by MRI, whereas conventional radiography and ultrasonography revealed erosions in 13 (50%) of 26 and 12 (50%) of 24 patients, respectively. The ability of MRI to detect erosive changes was significantly higher with respect to conventional radiography ( $P = 0.002$  with Bonferroni correction [ $P_B$ ]) and ultrasonography ( $P_B = 0.0002$ ) in the group of patients with <3 years' disease duration. Ultrasonography and conventional radiography were of equivalent value for the detection of destructive changes. Wrist MRI score correlated highly with radiographic erosion score ( $r_s = 0.82$ ) and with wrist limited range of motion score ( $r_s = 0.69$ ). The interreader intraclass correlation coefficient (ICC) for MRI score was excellent (0.97); intrareader ICCs were good for both investigators (0.97 and 0.79).

**Conclusion.** MRI seems to be a powerful tool to detect early structural damage in JIA. The proposed MRI scale for bone erosions appears promising in terms of reliability and construct validity. The pathophysiologic meaning and the prognostic value of bone erosions revealed only by MRI remain to be established in longitudinal studies.

## INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic childhood rheumatic disease and represents one of the leading causes of pediatric acquired disability (1).

It is a heterogeneous condition in which the outcome is variable and difficult to predict. Studies assessing long-term outcome of JIA have shown that a relevant proportion of patients may develop progressive joint destruction and serious physical disability (2). The development of erosions early in the disease course has been associated with a higher risk of progressive disease and has been included among the poor prognostic indicators of long-term outcome (3,4). Patients with wrist involvement are at high risk of experiencing radiographic progression, and the wrist has been shown to be the most informative joint to detect bone erosion with conventional radiography (4).

The increasing evidence that earlier therapeutic intervention improves long-term outcome and the development of new highly effective treatments for JIA (1) have highlighted the need for sensitive and specific imaging tools capable of disclosing early erosive changes, in order to identify patients who are at greater risk of poor functional outcome and who need aggressive treatment.

Supported by a grant from the European Union, Health-Child Integrated Project (IST-2004-027749).

<sup>1</sup>Clara Malattia, MD, Maria Beatrice Damasio, MD, Francesca Magnaguagno, MD, Angela Pistorio, MD, PhD, Maura Valle, MD, Stefania Viola, MD, Antonella Buoncompagni, MD, Anna Loy, MD, Paolo Tomà, MD: Istituto G. Gaslini, Genoa, Italy; <sup>2</sup>Carlo Martinoli, MD: Università di Genova, Genoa, Italy; <sup>3</sup>Angelo Ravelli, MD, Alberto Martini, MD: Istituto G. Gaslini and Università di Genova, Genoa, Italy.

Address correspondence to Clara Malattia, MD, Pediatria II, IRCCS G. Gaslini, Largo G. Gaslini 5, 16147 Genoa, Italy. E-mail: claramalattia@ospedale-gaslini.ge.it.

Submitted for publication April 29, 2008; accepted in revised form August 11, 2008.

Conventional radiography, which is the current standard for the assessment of joint damage in JIA, is quite insensitive as it usually reveals late and often irreversible signs of erosive disease (5–7). An increasing number of studies have described improved sensitivity of magnetic resonance imaging (MRI), compared with conventional radiography, in the detection of erosive changes in rheumatoid arthritis (RA) (8–14). Ultrasonography is well established in the assessment of synovitis, and there is increasing evidence of its potential role in the detection of osseous changes (15–17).

The aim of the present study was to compare the value of MRI, ultrasonography, and conventional radiography in the detection and grading of bone erosions in children with JIA. To our knowledge, no similar studies have been performed in JIA.

## PATIENTS AND METHODS

The present cross-sectional study included patients with JIA, diagnosed according to the International League of Associations for Rheumatology revised criteria (18), and wrist involvement, who were seen between June 2006 and March 2007 at the study center. The clinically more affected wrist was investigated with conventional radiography, MRI, and ultrasonography. Patients with severe wrist deformity, contraindication to MRI, and those requiring sedation to perform radiologic investigations were not included in the study. Institutional review board approval was obtained for this study.

**Clinical assessment.** The following clinical and laboratory parameters were recorded: number of joints with swelling, pain on motion/tenderness, restricted motion, physician's global assessment of overall disease activity, assessment of functional ability using the Childhood Health Assessment Questionnaire (C-HAQ) (19,20), Westergren erythrocyte sedimentation rate, and C-reactive protein level. In addition, the imaged wrist was scored as follows: swelling and tenderness were graded 0–3, and limitation of motion was graded 0–4 (21). All clinical measures were assessed by the same observer (SV) blinded to the results of imaging investigations. Clinical evaluations and imaging procedures were performed on the same day.

**Imaging assessment.** MRI was performed with a 1.5T MR scanner (Achieva Intera; Philips Medical Systems, Best, The Netherlands) using a Sense Flex small coil (Philips Medical Systems) with a field of view covering from the distal radioulnar joint to the metacarpal bases. The protocol included a T1-weighted 3-dimensional gradient echo sequence (GRE; repetition time [TR] 20 msec, echo time [TE] 5.5 msec, flip angle 25°, acquisition voxel size  $1 \times 1 \times 1$  mm), a turbo spin echo T2 with fat saturation (TR 2,715 msec, TE 70 msec, slice thickness 3 mm, interslice gap 0.3 mm), and a 3-dimensional GRE with fat saturation sequences (TR 40 msec, TE 7 msec, flip angle 25°, acquisition voxel  $1 \times 1 \times 1$  mm) after intravenous injection of a contrast agent (gadolinium diethylenetriaminepentaacetic

acid [Schering, Berlin, Germany] 0.2 ml/kg). All sequences were acquired in a coronal plane, with multiplanar reconstruction (Figure 1).

Because of the small size of carpal bones, owing to their incomplete ossification, a simplified version of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) MRI scoring system for erosions (22) was devised for use in pediatric patients. Erosions were defined, as suggested by the OMERACT group, as sharply marginated bone lesions with correct iuxta-articular localization and low signal intensity in T1-weighted images in at least 2 planes, with a cortical break seen in at least 1 plane (22). MRI images were scored at 15 sites within the carpus (each carpal bone as well as the metacarpal bases and the distal radius and ulna) using a 0–4 scale based on the proportion of the eroded bone compared with the total assessed bone volume (0 = no erosion, 1 = 1–25% of the bone eroded, 2 = 26–50% of the bone eroded, 3 = 51–75% of the bone eroded, and 4 = 76–100% of the bone eroded). In long bones, the assessed bone volume was measured from the articular surface to a depth of 1 cm. A total MRI score ranging from 0 to 60 was derived from the sum of erosion scores at all 15 sites. MRI score was assigned independently by a pediatric radiologist (MBD) and a pediatric rheumatologist (CM) after a training session with 2 radiologists with ~20 years of experience in musculoskeletal MRI (PT and CM).

The training of the 2 readers included review of wrist anatomy and observation of MRI bone abnormalities in JIA using MRI examples from 10 patients performed before June 2006.

Subsequently, in the calibration session, the 2 readers reviewed 4 additional MRI studies providing a score for erosions using the proposed MRI score. The results were then reviewed together with the trainers and a consensus was reached.

Ultrasonography was performed with an HDI 5000 ultrasonography system (Advanced Technologies Laboratories, Bothell, WA) using a 12.5-MHz linear array. The dorsal aspect of the wrist was scanned in the longitudinal and transversal planes. Bone erosions, defined as a cortical break of the bone surface seen in both planes (23), were scored according to a purposely devised score at 14 sites (first metacarpal base was not investigated) using a 0–2 scale (0 = regular bone surface with smooth echogenic interface, 1 = irregularities of the bone surface, 2 = formation of a well-defined rounded or oval defect seen in 2 planes) as shown in Figure 2. A total score was assigned after a consensus agreement between 2 radiologists with expertise in real-time musculoskeletal ultrasonography images (MV and PT).

Plain radiographs of both wrists were obtained in the posteroanterior projection using a computed radiography system (CR850-Carestream Health; Kodak Industrex Digital System, Rochester, NY) with  $18 \times 24$ -cm general purpose plates ( $1,792 \times 2,392$  matrix size, 0.1-mm pixel pitches) and the following setting: 100 mA, 45–48 kV, 32 msec, and film-focus distance 110 cm. Radiographs were assessed from the same areas as MRI score according to the erosive score domain of the Sharp/van der Heijde score recently adapted for use in JIA with the inclusion of new



**Figure 1.** A, Coronal gradient echo sequence 3-dimensional T1-weighted magnetic resonance image of the carpus in a patient with juvenile idiopathic arthritis. B, The bone erosion visible in the lunate in the coronal plane is confirmed on both axial and sagittal planes in the multiplanar reconstruction.

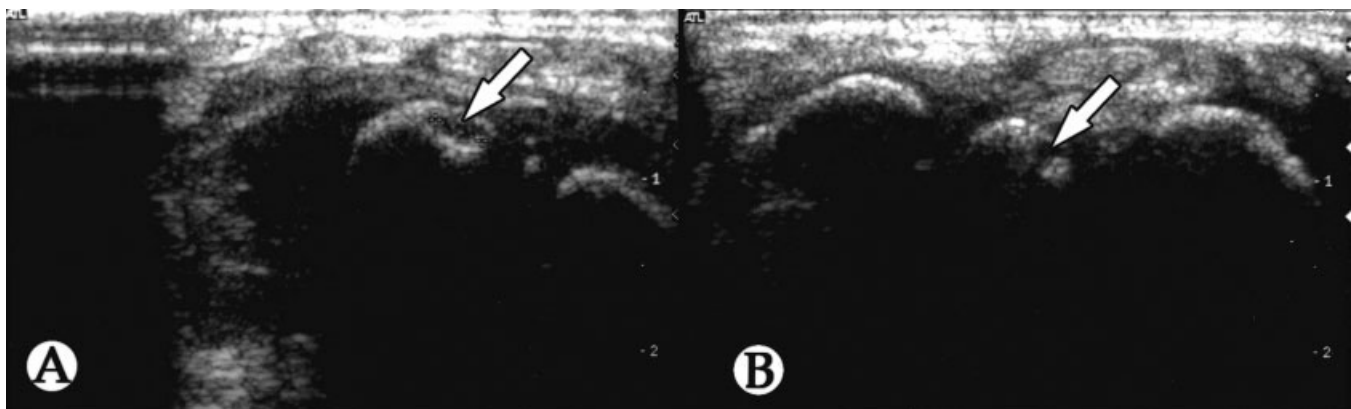
areas (24). The severity of bone damage was graded on a 0–5 scale (24). All radiographs were scored independently by 2 investigators, a musculoskeletal radiologist (FM) and a pediatric rheumatologist (AR) with familiarity with radiographic scoring.

All imaging modalities were evaluated with investigators blinded to clinical information and to the results of other imaging techniques.

**Statistical analysis.** Qualitative data were compared by chi-square test or by Fisher's exact test. In case of multiple comparisons, Bonferroni correction was applied ( $P_B$ ). Quantitative variables among different groups of observa-

tions were compared by means of the Kruskal-Wallis test; the Mann-Whitney U test with Bonferroni correction was used as a posterior test ( $P_B$ ). All tests were 2-sided and a  $P$  value less than 0.05 was considered statistically significant.

Concordance between imaging procedures was evaluated by Cohen's kappa coefficient (25) with the cutoffs proposed by Landis and Koch (26). The reliability and construct validity of MRI score were analyzed to provide a preliminary validation of the scoring method. Interobserver reliability was assessed for all of the images read by the 2 observers. Intraobserver reliability was based on a subset of 10 randomly selected patients whose MRI scans were



**Figure 2.** Ultrasonographic scan of the dorsal wrist of a patient with juvenile idiopathic arthritis. Grade 2 bone erosion (arrow) on the dorsal side of the lunate bone is visualized on both A, longitudinal and B, transverse planes.

read a second time in a blinded manner by the 2 observers, 6 weeks after the previous review. Inter- and intraobserver agreement were analyzed by computing the intraclass correlation coefficient (ICC) (27) and agreement was classified as follows: ICC <0.4 = poor,  $\geq 0.4$ –0.80 = moderate, and >0.80 = good agreement (28).

The independent scores of the 2 observers were then averaged, and this average was used for the analyses. Correlation between quantitative parameters was investigated by Spearman's rank order correlation coefficient ( $r_s$ ). For the purpose of this analysis, correlations >0.7 were considered high, correlations ranging from 0.4 to 0.7 were considered moderate, and correlations <0.4 were considered low (29). Statistical analysis was performed with Statistica software (StatSoft, Tulsa, OK).

## RESULTS

Patients' characteristics and the results of the clinical and laboratory assessments are summarized in Table 1. Of 26 patients, 25 (96.1%) had 1 or more erosions at 1 or more bony sites of the wrist detected by MRI; by comparison, conventional radiography revealed erosions in only 13 of 26 patients (50%;  $P_B = 0.0005$ ). Ultrasonography, performed in 24 of 26 patients, visualized erosive changes in 12 of 24 patients (50%;  $P_B = 0.0004$ ). Ten of these 24 patients were concordant for erosive changes on radiography and ultrasonography, 10 were concordantly negative, and only 4 were discordant, resulting in a concordance kappa coefficient of 0.7 (95% confidence interval [95% CI] 0.3–1). Patients were then categorized into groups of disease duration (<3 years, 3–5.5 years, and  $\geq 5.6$  years) according to 33.3rd and 66.7th percentiles, and the results of the 3 imaging modalities were compared.

As shown in Figure 3, MRI revealed erosive changes in 100% of patients with shorter disease duration (mean MRI total score 3.6), while radiography and ultrasonography visualized erosions in 22.2% ( $P_B = 0.002$ ) and 11.1% ( $P_B = 0.0002$ ) of patients, respectively. In patients with disease duration  $\geq 3$  years, although MRI remained the most sensitive technique to detect erosions, differences with respect to radiography and ultrasonography were much less evident. Indeed, the percentage of patients with erosions revealed by radiography and ultrasonography increased to 77.8% and 85.7%, respectively, in patients with  $\geq 5.6$  years' disease duration (mean MRI total score 8.6).

MRI was the most sensitive imaging modality in disclosing bone lesions in each carpal bone as well as in metacarpal bases, distal radius, and ulna, as depicted in Figure 4. Interestingly, erosions revealed by MRI were mainly located in areas such as the capitate, hamate, and some metacarpal bases that are not included in the RA radiographic scores but that have been recently integrated in a version of the Sharp/van der Heijde score adapted for use in JIA (24). MRI identified erosions in 149 (38%) of 390 bones. The mean total MRI erosion score was 8.6 (total MRI score ranging from 0 to 53). Most carpal bones showed a grade 1 bone erosion and only

**Table 1. Demographic features and results of the clinical and laboratory assessment of the 26 patients enrolled\***

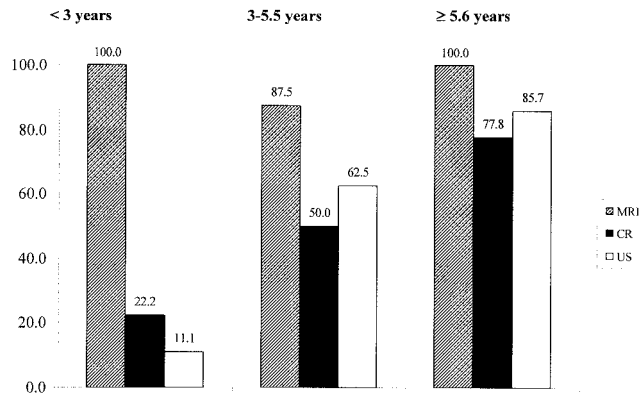
Characteristic	Value
Sex	
Male	4 (15.4)
Female	22 (84.6)
Systemic arthritis	11 (42.3)
RF-negative polyarthritis	4 (15.4)
RF-positive polyarthritis	1 (3.8)
Oligoarthritis	
Extended	9 (34.6)
Persistent	1 (3.8)
Age at study visit, years	10 (5.6–18.5)
Disease duration, years	4.2 (0.2–12.5)
No. of active joints	9.5 (1–42)
No. of joints with limited range of motion	8 (0–42)
VAS physician, cm	8.2 (3–10)
Score pain	2 (0–3.0)
Score swelling	1 (0–3.0)
Limited range of motion score	2 (0–4.0)
C-HAQ score	0.3 (0–2.7)
VAS pain, cm	2.5 (0–10)
Global VAS patient, cm	3.1 (0–9.9)
CRP level, mg/dl	3.5 (0.3–20.2)
ESR, mm/hour	45 (5–93)
Second-line drug therapy	
Methotrexate	16 (61.5)
Cyclosporine	2 (7.7)
Biologic therapy	
Etanercept	5 (19.2)
Anakinra	2 (7.7)
Systemic corticosteroid therapy	7 (26.9)

\* Values are the number (percentage) or median (range). RF = rheumatoid factor; VAS = visual analog scale; C-HAQ = Childhood Health Assessment Questionnaire; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

1 patient had a severe grade 4 erosion of the scaphoid. Conventional radiography identified erosions in 47 (12%) of 390 bones and ultrasonography in 35 (9.6%) of 364 bones.

Ultrasonography was superior to conventional radiography in the detection of erosive changes in the capitate, lunate, and distal radius and ulna. All but 1 of the sonographic lesions, not seen on radiography, corresponded exactly to MRI erosions in a site-specific analysis.

Twelve (46.1%) of 26 patients showed bone lesions on MRI that were not detected by radiography; these patients had a significantly lower total MRI score (mean  $\pm$  SD 3.2  $\pm$  1.7) compared with patients whose MRI and radiography scores were both positive (mean  $\pm$  SD 9.4  $\pm$  6.1;  $P_B = 0.001$ ) (Figure 5). Moreover, patients with a positive MRI and a negative radiographic erosion score had a statistically significant shorter disease duration (mean  $\pm$  SD 3.2  $\pm$  2.9 years) compared with patients with a positive score in both MRI and radiographs (mean  $\pm$  SD 6.1  $\pm$  3.4 years;  $P = 0.03$ ).



**Figure 3.** Percentage of juvenile idiopathic arthritis patients with bone erosions as revealed by the 3 imaging modalities (magnetic resonance imaging [MRI], conventional radiography [CR], and ultrasonography [US]). Patients are grouped according to disease duration (<3 years, 3–5.5 years, and ≥5.6 years).

Twelve (52.2%) of 23 patients had a positive MRI score and a negative ultrasonography score. The mean ± SD total MRI score in these patients was significantly lower ( $3.9 \pm 2.0$ ) compared with that of patients with a positive

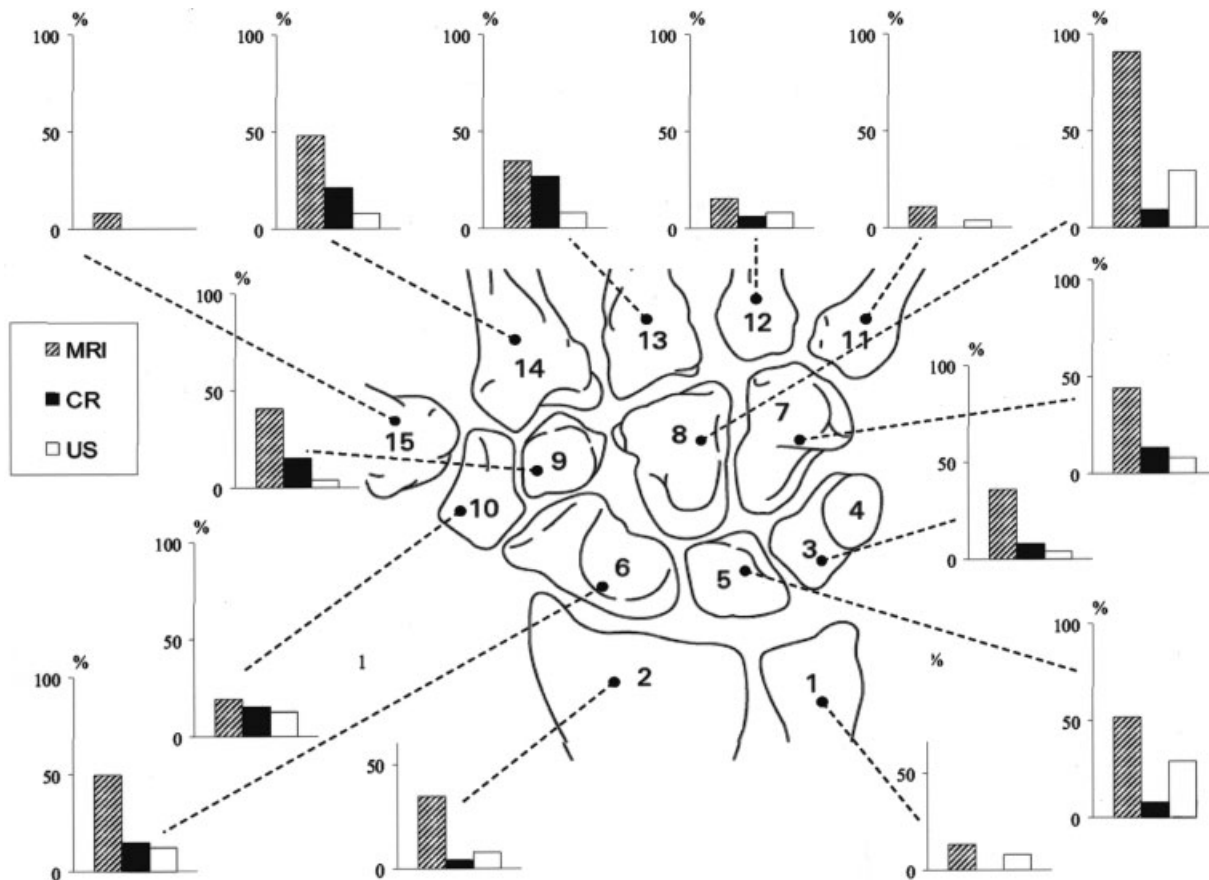
score in both imaging techniques ( $7.8 \pm 3.4$ ;  $P_B = 0.022$ ) (Figure 5).

The interreader agreement for scoring erosions, as assessed by the ICC, was excellent (0.97, 95% CI 0.93–0.99). The intrareader ICCs were good for both investigators (rheumatologist ICC 0.97, 95% CI 0.85–0.99; radiologist ICC 0.79, 95% CI 0.21–0.95).

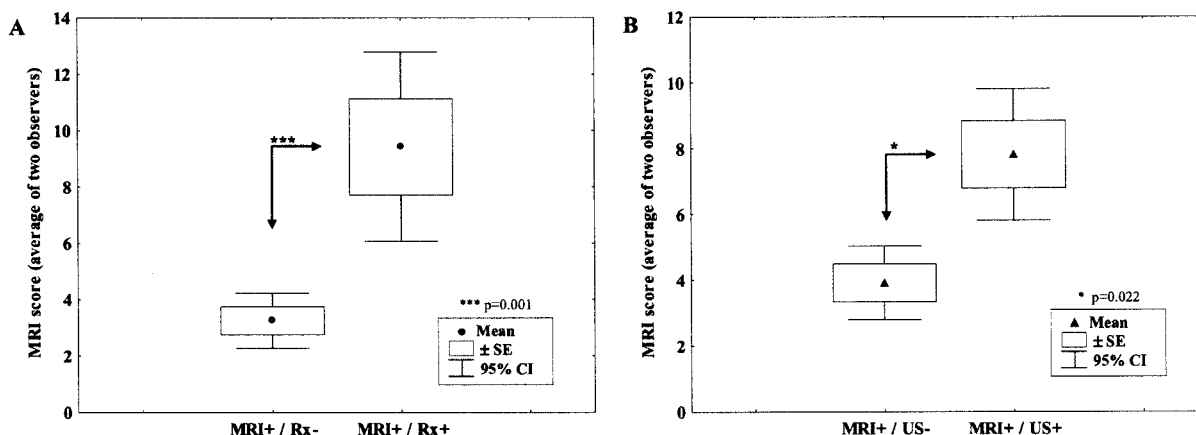
There was strong positive correlation between MRI score and radiographic score ( $r_s = 0.82$ ,  $P < 0.0001$ ). MRI score and radiographic score were highly correlated with wrist limitation of motion ( $r_s = 0.69$ ,  $P = 0.0001$  and  $r_s = 0.77$ ,  $P < 0.0001$ , respectively), a clinical indicator of disease damage, but poorly correlated with active disease parameters. No significant correlation was demonstrated between the functional ability assessed by the C-HAQ and MRI score.

**DISCUSSION**

With the advent of new disease-modifying therapy for JIA, early detection of damage and aggressive control of the disease can decrease the chance of further disability. Imaging techniques are playing an increasingly important



**Figure 4.** Distribution of erosive changes, as revealed by the 3 different imaging modalities (magnetic resonance imaging [MRI], conventional radiography [CR], and ultrasonography [US]). MRI was the most sensitive imaging modality in disclosing bone lesions in each carpal bone as well as in metacarpal bases, distal radius, and ulna. 1 = distal ulna; 2 = distal radius; 3 = triquetrum; 4 = pisiform; 5 = lunate; 6 = scaphoid; 7 = hamate; 8 = capitate; 9 = trapezoid; 10 = trapezium; 11 = 5th metacarpal base; 12 = 4th metacarpal base; 13 = 3rd metacarpal base; 14 = 2nd metacarpal base; 15 = 1st metacarpal base.



**Figure 5.** A, Comparison of magnetic resonance imaging (MRI) semiquantitative erosion scores between patients with an MRI positive erosion score and a negative radiographic erosion score (MRI+/Rx-) and patients with a concordant positive erosion score (MRI+/Rx+). A statistically significant lower MRI score was observed for MRI+/Rx- patients compared with MRI+/Rx+ patients. B, Comparison of MRI erosion scores between patients with an MRI positive score and a negative ultrasonography (US) erosion score (MRI+/US-) and patients with a concordant positive erosion score (MRI+/US+). A statistically significant lower MRI score was observed for MRI+/US- patients compared with MRI+/US+ patients. Rx = conventional radiography; 95% CI = 95% confidence interval.

role in the assessment of disease progression and response to treatment in adult RA (30). The OMERACT group developed an internationally accepted scoring system for MRI of the wrist and metacarpophalangeal (MCP) joints of RA patients (22).

In contrast to the many studies performed in adults, to our knowledge, no studies comparing MRI with other imaging techniques in JIA have been reported in the literature, nor has a pediatric-targeted MRI scoring system been published. The aim of our study was to assess which imaging technique is most suitable for the early identification of bone erosions in JIA. Although the knee is the most commonly affected joint in patients with JIA, the wrist was selected because it is the site most vulnerable to changes seen on radiographs, and for the prognostic value of its involvement (31–33).

Consistent with the results of previous studies in patients with RA (8,9,11,34), in our cohort of JIA patients, MRI was the best method for the identification of erosions, revealing more than twice as many erosions as radiography and ultrasonography. The better accuracy of MRI in detecting erosive changes was much more evident in the group of patients with shorter disease duration (<3 years). These findings are consistent with the results of an established RA followup study demonstrating that erosions on MRI preceded detectable radiographic erosions by a median of 2 years (35). The lag time for MRI erosion to become visible on radiographs is likely to be related to size or volume, as suggested by Ejbjerg et al, who demonstrated that MRI erosions  $\leq 30\%$  of the bone volume were most often not detected on conventional radiography (36). Indeed, in our study the mean total MRI score observed in patients with erosions detected only by MRI was significantly lower than that observed in patients whose erosions were also visualized by radiographs and ultrasonography.

Furthermore, patients with lower MRI scores had also a significantly shorter disease duration, suggesting that MRI is better suited for detection of the earliest stages of erosive changes. The greater sensitivity of MRI to incipient destructive changes could be leveraged to identify patients at higher risk for progression and therefore in need of aggressive therapy. In addition, its capability to detect minimal erosive changes could make MRI a more useful tool than radiographs in the evaluation of the disease-modifying potential of antirheumatic drugs.

In our study, all patients with a disease duration <3 years showed minor erosive changes at 1 or more bony sites on MRI. Multiple factors may contribute to this unexpected result. First, it is well established that patients with polyarticular arthritis and wrist disease, as in our cohort, are at high risk of experiencing destructive joint damage (4,37). Second, the use of 3-dimensional image acquisition with multiplanar reconstructions of 1-mm MRI slices, as in the present study, is considered optimal for identifying the smallest erosive changes. The higher sensitivity for erosive changes of the 3-dimensional T1-weighted gradient echo images compared with standard 2-dimensional spin echo sequences has been recently demonstrated by other authors (38). One concern, however, is that this increased sensitivity may be at the cost of reduced specificity, and that some of these lesions may not progress to true erosions as seen on radiographs. McQueen et al, in a previous study, reported that in patients with RA, only 1 of 4 erosions detected on MRI progressed to become radiographic erosions over 2 years (39), raising the question of the significance of erosions detected exclusively by MRI (40). This question has been addressed through adequately comparative studies between MRI findings and reliable references such as histopathology (41), miniarthroscopy (42), and computerized tomography (43,44)

that demonstrated that MRI erosions in RA represent real bone pathology. Because there is no available gold standard in JIA for the determination of bone damage to which to relate MRI score, its construct validity was preliminarily investigated. MRI findings were set against other measures that evaluate the same phenomenon. Overall, the high levels of concordance between MRI and standardized measurement of radiographic damage, and the reasonable agreement with clinical indicators of joint damage, such as limited joint motion, gave supportive, preliminary evidence for the construct validity of our MRI scales. The observed poor correlation with the C-HAQ score might be due to the fact that this measure was found to reflect both disease activity and damage (45); furthermore, we should take into account that MRI visualized minor erosive changes not able to impact functional ability assessed by the C-HAQ. Finally, the susceptibility of the MRI scale to false-positive results for erosions was also considered. Erosions revealed by MRI were mainly located on the capitate and lunate, which are considered difficult areas with an intrinsically higher risk of being scored as false-positive due to their anatomic peculiarities. The wide spectrum of bone lesions that might be confused with erosions has been recently fully described by McQueen et al (46). Furthermore, Ejbjerg et al have demonstrated that small erosion-like changes are occasionally found by MRI in the wrist of healthy subjects, most often occurring in the capitate and lunate bones (47).

Only longitudinal followup of our patients with repeat MRI scans and radiographs will allow us to identify false-positives and to address the following critical questions: 1) how accurately our MRI measures reflect eroding processes within carpal bones, and 2) if minimal erosive changes, revealed on MRI in this pilot study, reflect an increased risk for development of a progressive eroding disease, and should therefore be considered a marker of prognostic significance.

The high interobserver and intraobserver ICCs provide preliminary evidence that our MRI score is a reliable instrument for assessing bone damage in JIA, which is a prerequisite feature for any scoring method to be considered of clinical value and a critical concern if wider application of the scoring is considered. In keeping with previous works, conventional radiography and ultrasonography appear to be of limited value for the detection of the earliest stages of erosive changes compared with MRI. The rate of detection of MRI erosive changes by radiography and ultrasonography increased, as discussed above, with the extent of bone damage, as defined by MRI grading. Of course, the performance differences are also explained by physical principles of the examinations (projection versus sectional imaging techniques) and by technical aspects such as the accessibility of ultrasound examination. Furthermore, to make ultrasound evaluation feasible and to increase opportunities for standardized, reproducible scanning methodology for image acquisition, we chose to assess only the dorsal view of the wrist, resulting, by default, in a lower performance of ultrasound. The choice to explore only the dorsal aspect of the wrist is questionable. A study aimed at establishing if there is a significant

difference in the percentage of patients with erosion identified when looking at all joint surfaces accessible by ultrasound examination, in order to avoid losing information on the extent of bone damage, is ongoing. Finally, in our study, only 1 radiographic view was obtained, which may have resulted in underestimating the value of radiography.

The sensitivity of ultrasonography has been reported to be greater than that of conventional radiography for visualizing erosions in RA finger joints, and to be comparable with that of MRI in some studies (15,16) but not in others (9,34). As mentioned above, this disparity probably relates to the fact that ultrasonography sensitivity in the detection of bone lesions is greatly site dependent and related to the accessibility of the joint. When compared with MRI, ultrasound performance is very good for easily accessible joints such as the second and fifth MCP joints and the interphalangeal joints, but is poor for anatomically complicated and less accessible joints such as the wrist (16).

In our study, ultrasonography and conventional radiography were of equivalent value to detect destructive changes. We found ultrasound to be superior to conventional radiography in the detection of bone lesions in only a few carpal bones, which are somewhat more accessible for ultrasound evaluation. Even if the pathologic specificity of these sonographic lesions was confirmed through a site-by-site comparison with MRI, further validation studies are warranted to establish the potential value of ultrasound in the assessment of bone damage.

Some limitations of our study should be considered. Our findings are of value only for patients with wrist disease, who are nevertheless at higher risk of developing severe erosive disease (4). The lack of MR images of age-matched healthy controls is a potential weakness of this explorative study. In fact, growing joints change anatomically over time, making it very difficult to establish if differences in the appearance of bone surface are pathologic or part of the normal development of these joints. This study also suffers from a lack of an established gold standard for bone erosion to compare MRI; as a consequence, the true discriminative power of MRI for erosions cannot be definitely determined. Finally, the validation analysis of our MRI score was cross-sectional, and therefore issues of predictive validity over time and responsiveness to clinically meaningful change remain to be examined; this is crucial before the MRI score can be used to guide therapeutic decisions or as an end point in clinical trials.

In summary, MRI shows remarkable promise as a tool for disclosing bone damage in JIA patients with shorter disease duration, when radiography and ultrasound yield negative results. The greater sensitivity of MRI to disclose incipient destructive changes could be leveraged to select patients for more aggressive therapy and to monitor treatment response. Nevertheless, the pathophysiologic meaning of bone lesions revealed only by MRI and their prognostic value remains to be established. Preliminary results in terms of reliability and construct validity of our MRI score appear promising; however, its suitability for both clinical and research contexts is yet to be tested in large-scale longitudinal studies.

## ACKNOWLEDGMENT

We wish to acknowledge the technical staff of the Radiology Department of the G. Gaslini Institute for their supervision of the MRI scans.

## AUTHOR CONTRIBUTIONS

Dr. Malattia had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study design.** Malattia, Damasio, Pistorio, Tomà, Martini.

**Acquisition of data.** Malattia, Damasio, Magnaguagno, Valle, Viola, Buoncompagni, Loy, Ravelli, Tomà.

**Analysis and interpretation of data.** Malattia, Damasio, Pistorio, Martinoli, Ravelli, Tomà, Martini.

**Manuscript preparation.** Malattia, Damasio, Martini.

**Statistical analysis.** Pistorio.

## REFERENCES

- Ravelli A, Martini A. Juvenile idiopathic arthritis [review]. *Lancet* 2007;369:767–78.
- Levinson JE, Wallace CA. Dismantling the pyramid. *J Rheumatol Suppl* 1992;33:6–10.
- Ravelli A, Martini A. Early predictors of outcome in juvenile idiopathic arthritis [review]. *Clin Exp Rheumatol* 2003;21 (5 Suppl 31):S89–93.
- Magni-Manzoni S, Rossi F, Pistorio A, Temporini F, Viola S, Beluffi G, et al. Prognostic factors for radiographic progression, radiographic damage, and disability in juvenile idiopathic arthritis. *Arthritis Rheum* 2003;48:3509–17.
- Brower AC. Use of the radiograph to measure the course of rheumatoid arthritis: the gold standard versus fool's gold. *Arthritis Rheum* 1990;33:316–24.
- Doria AS, Babyn PS, Feldman B. A critical appraisal of radiographic scoring systems for assessment of juvenile idiopathic arthritis [review]. *Pediatr Radiol* 2006;36:759–72.
- Babyn P, Doria AS. Radiologic investigation of rheumatic diseases. *Rheum Dis Clin North Am* 2007;33:403–40.
- Gilkeson G, Polisson R, Sinclair H, Vogler J, Rice J, Caldwell D, et al. Early detection of carpal erosions in patients with rheumatoid arthritis: a pilot study of magnetic resonance imaging. *J Rheumatol* 1988;15:1361–6.
- Backhaus M, Kamradt T, Sandrock D, Loreck D, Fritz J, Wolf KJ, et al. Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. *Arthritis Rheum* 1999;42:1232–45.
- McQueen FM. Magnetic resonance imaging in early inflammatory arthritis: what is its role? *Rheumatology (Oxford)* 2000;39:700–6.
- McQueen FM, Stewart N, Crabbe J, Robinson E, Yeoman S, Tan PL, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. *Ann Rheum Dis* 1998;57:350–6.
- Ostergaard M, Gideon P, Sorensen K, Hansen M, Stoltenberg M, Henriksen O, et al. Scoring of synovial membrane hypertrophy and bone erosions by MR imaging in clinically active and inactive rheumatoid arthritis of the wrist. *Scand J Rheumatol* 1995;24:212–8.
- Jorgensen C, Cyteval C, Anaya JM, Baron MP, Lamarque JL, Sany J. Sensitivity of magnetic resonance imaging of the wrist in very early rheumatoid arthritis. *Clin Exp Rheumatol* 1993;11:163–8.
- Foley-Nolan D, Stack JP, Ryan M, Redmond U, Barry C, Ennis J, et al. Magnetic resonance imaging in the assessment of rheumatoid arthritis: a comparison with plain film radiographs. *Br J Rheumatol* 1991;30:101–6.
- Szkudlarek M, Klarlund M, Narvestad E, Court-Payen M, Strandberg C, Jensen KE, 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.
- Wakefield RJ, Gibbon WW, Conaghan PG, O'Connor P, McGonagle D, Pease C, 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.
- Ostergaard M, Szkudlarek M. Ultrasonography: a valid method for assessing rheumatoid arthritis? [editorial]. *Arthritis Rheum* 2005;52:681–6.
- Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton 2001. *J Rheumatol* 2004;31:390–2.
- Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. *Arthritis Rheum* 1994;37:1761–9.
- Ruperto N, Ravelli A, Pistorio A, Malattia C, Viola S, Cavuto S, et al. The Italian version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). *Clin Exp Rheumatol* 2001;19(4 Suppl 23):S91–5.
- Ravelli A, Viola S, Ruperto N, Corsi B, Ballardini G, Martini A. Correlation between conventional disease activity measures in juvenile chronic arthritis. *Ann Rheum Dis* 1997;56:197–200.
- Ostergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejlberg B, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies: core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. *J Rheumatol* 2003;30:1385–6.
- Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005;32:2485–7.
- Ravelli A, Ioseliani M, Norambuena X, Sato J, Pistorio A, Rossi F, et al. Adapted versions of the Sharp/van der Heijde score are reliable and valid for assessment of radiographic progression in juvenile idiopathic arthritis. *Arthritis Rheum* 2007;56:3087–95.
- Cohen J. Statistical power analysis for the behavioral sciences. New York: Academic Press; 1977.
- Landis JR, Koch GC. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74.
- Deyo RA, Diehr P, Patrick DL. Reproducibility and responsiveness of health status measures: statistics and strategies for evaluation. *Control Clin Trials* 1991;12 Suppl 4:142–58S.
- Fleiss JL. The design and analysis of clinical experiments. New York: Wiley; 1986.
- Huber AM, Feldman BM, Rennebohm RM, Hicks JE, Lindsley CB, Perez MD, et al, for the Juvenile Dermatomyositis Disease Activity Collaborative Study Group. Validation and clinical significance of the Childhood Myositis Assessment Scale for assessment of muscle function in the juvenile inflammatory myopathies. *Arthritis Rheum* 2004;50:1595–603.
- McQueen FM, Ostergaard M. Established rheumatoid arthritis: new imaging modalities. *Best Pract Res Clin Rheumatol* 2007;21:841–56.
- Oen K. Long-term outcomes and predictors of outcomes for patients with juvenile idiopathic arthritis. *Best Pract Res Clin Rheumatol* 2002;16:347–60.
- Lang BA, Schneider R, Reilly BJ, Silverman ED, Laxer RM. Radiologic features of systemic onset juvenile rheumatoid arthritis. *J Rheumatol* 1995;22:168–73.
- Scott DL, Coulton BL, Popert AJ. Long term progression of joint damage in rheumatoid arthritis. *Ann Rheum Dis* 1986;45:373–8.
- Hoving JL, Buchbinder R, Hall S, Lawler G, Coombs P, McNealy S, et al. A comparison of magnetic resonance imaging, sonography, and radiography of the hand in patients with early rheumatoid arthritis. *J Rheumatol* 2004;31:663–75.
- Ostergaard M, Hansen M, Stoltenberg M, Jensen KE, Szkud-

- lerek M, Pedersen-Zbinden B, et al. New radiographic bone erosions in the wrists of patients with rheumatoid arthritis are detectable with magnetic resonance imaging a median of two years earlier. *Arthritis Rheum* 2003;48:2128–31.
36. Ejlberg BJ, Vestergaard A, Jacobsen S, Thomsen H, Ostergaard M. Conventional radiography requires a MRI-estimated bone volume loss of 20% to 30% to allow certain detection of bone erosions in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther* 2006;8:R59.
37. Cassone R, Falcone A, Rossi F, Magni-Manzoni S, Felici E, Buoncompagni A, et al. Unilateral destructive wrist synovitis in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2004;22:637–42.
38. Ejlberg BJ, Narvestad E, Jacobsen S, Thomsen HS, Ostergaard M. Optimised, low cost, low field dedicated extremity MRI is highly specific and sensitive for synovitis and bone erosions in rheumatoid arthritis wrist and finger joints: comparison with conventional high field MRI and radiography. *Ann Rheum Dis* 2005;64:1280–7.
39. McQueen FM, Benton N, Crabbe J, Robinson E, Yeoman S, McLean L, et al. What is the fate of erosions in early rheumatoid arthritis? Tracking individual lesions using x rays and magnetic resonance imaging over the first two years of disease. *Ann Rheum Dis* 2001;60:859–68.
40. Goldbach-Mansky R, Woodburn J, Yao L, Lipsky PE. Magnetic resonance imaging in the evaluation of bone damage in rheumatoid arthritis: a more precise image or just a more expensive one? [editorial]. *Arthritis Rheum* 2003;48:585–9.
41. McGonagle D, Gibbon W, O'Connor P, Blythe D, Wakefield R, Green M, et al. A preliminary study of ultrasound aspiration of bone erosion in early rheumatoid arthritis. *Rheumatology (Oxford)* 1999;38:329–31.
42. Ostendorf B, Peters R, Dann P, Becker A, Scherer A, Wedekind F, et al. Magnetic resonance imaging and miniarthroscopy of metacarpophalangeal joints: sensitive detection of morphologic changes in rheumatoid arthritis. *Arthritis Rheum* 2001;44:2492–502.
43. Dohn UM, Ejlberg BJ, Court-Payen M, Hasselquist M, Narvestad E, Szkudlarek M, et al. Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with conventional tomography in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther* 2006;8:R110.
44. Perry D, Stewart N, Benton N, Robinson E, Yeoman S, Crabbe J, et al. Detection of erosions in the rheumatoid hand: a comparative study of multidetector computerized tomography versus magnetic resonance scanning. *J Rheumatol* 2005;32:256–67.
45. Palmisani E, Solari N, Magni-Manzoni S, Pistorio A, Labo E, Panigada S, et al. Correlation between juvenile idiopathic arthritis activity and damage measures in early, advanced, and longstanding disease. *Arthritis Rheum* 2006;55:843–9.
46. McQueen F, Ostergaard M, Peterfy C, Lassere M, Ejlberg B, Bird P, et al. Pitfalls in scoring MR images of rheumatoid arthritis wrist and metacarpophalangeal joints. *Ann Rheum Dis* 2005;64 Suppl 1:48–55.
47. Ejlberg B, Narvestad E, Rostrup E, Szkudlarek M, Jacobsen S, Thomsen HS, et al. Magnetic resonance imaging of wrist and finger joints in healthy subjects occasionally shows changes resembling erosions and synovitis as seen in rheumatoid arthritis. *Arthritis Rheum* 2004;50:1097–106.