One-year Followup Study on Clinical Findings and Changes in Magnetic Resonance Imaging-based Disease Activity Scores in Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To evaluate whether clinical disease activity findings during 1-year followup of patients with juvenile idiopathic arthritis (JIA) is associated with changes of magnetic resonance imaging (MRI)-based disease activity scores.

Methods. Patients with JIA who had active knee involvement were studied using an open-bore MRI. After followup of a median of 1.3 years, patients were re-evaluated and classified as improved or unimproved according to the American College of Rheumatology Pediatric-50 (ACR-Ped50) criteria. Baseline and followup MRI features were scored by 2 readers using the Juvenile Arthritis MRI Scoring (JAMRIS) system, comprising validated scores for synovial hypertrophy, bone marrow changes, cartilage lesions, and bone erosions.

Results. Data of 40 patients were analyzed (62.5% female, mean age 12.2 yrs). After followup, 27 patients (67.5%) were classified as clinically improved, whereas 13 patients (32.5%) showed no clinical improvement. The clinically improved patients showed a significant reduction in synovial hypertrophy scores during followup ($p < 0.001$), with substantial effects (standardized response mean –0.70). No such changes were observed for any of the other MRI features. Significant differences were detected regarding a change in synovial hypertrophy scores comparing clinically improved and unimproved patients ($p = 0.004$), without statistically significant differences for changes in scores for bone marrow changes ($p = 0.079$), cartilage lesions ($p = 0.165$), and bone erosions ($p = 0.078$).

Conclusion. This is one of the first studies to provide evidence for MRI-based improvement upon followup in JIA patients with knee involvement. There is a strong association with clinical improvement according to the ACR-Ped50 criteria and changes in MRI-based synovial hypertrophy scores, supporting the role of MRI as a responsive outcome measure to evaluate disease activity with antiinflammatory treatment strategies. (First Release Dec 1 2013; J Rheumatol 2014;41:119–27; doi:10.3899/jrheum.130235)

Key Indexing Terms:
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Juvenile idiopathic arthritis (JIA) is characterized by prolonged synovial inflammation that can lead to destruction of joints, pain, and loss of function[1]. Early disease control improves longterm outcome. Therefore, sensitive measures to assess individual response to therapy and general efficacy of treatment in JIA are warranted[2,3]. Physical examination only has limited reliability[4,5], and conventional radiography is insensitive in detecting soft

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tissue changes or the earliest stages of persistent erosive changes[6]. Hence, more sensitive and reliable measures should be used in the evaluation of early inflammatory and destructive changes in JIA.

Currently, evidence is fairly strong that magnetic resonance imaging (MRI) is an accurate diagnostic method to visualize synovial inflammation as well as early destructive modifications of cartilage and bone in JIA[7,8]. Moreover, MRI is the only imaging tool able to detect bone marrow edema. Nonetheless, MRI is still underused in clinical practice and research settings. One of the reasons for the underuse of MRI in the assessment of disease status in JIA relates to the lack of evidence in the literature of its ability to detect changes over time. The ability to detect changes (responsiveness) refers to the possibility of change in inflammatory disease status over time. Because the clinical manifestations of disease in children with JIA can change rapidly, imaging criteria should also be capable of detecting those changes.

Before the value of MRI as an outcome measure in daily practice, research, or clinical trials can be assessed, its sensitivity to detect clinical responsiveness to treatment over time has to be determined. In the current study we assessed whether clinical disease activity findings during 1-year followup of patients with JIA is associated with changes of MRI-based disease activity scores of the most commonly affected joint in JIA (i.e., the knee).

MATERIALS AND METHODS

Patients. Consecutive patients visited one of the outpatient clinics of 2 tertiary pediatric rheumatology centers. At the time of presentation, all children underwent clinical and laboratory assessment followed by MRI. Inclusion criteria for the current study were a followup period of at least 1 year, and clinically active disease with knee involvement at baseline. The patients were therefore either newly diagnosed with JIA or had clinically active arthritis owing to relapsing or unremitting disease. All patients fulfilled the International League of Associations for Rheumatology criteria for JIA, defined as an arthritis of unknown etiology that begins before the age of 16 and persists for at least 6 weeks[9]. Exclusion criteria were a history of intraarticular corticosteroid injection within the last 6 months, the need for anesthesia during the MRI examination, and general contraindications for MRI. Our study was performed in accordance with the Declaration of Helsinki and the local medical ethical regulations. Written informed consent was obtained from at least 1 parent of each child.

Clinical assessment. Physical examination was performed by the same experienced pediatric rheumatologists (MvV, JMvdB, KMD, MAJvR) during the research period. Clinical assessment included a 67-joint count defining the presence of swelling, pain on motion/tenderness, and limited range of motion (LOM). A physician's global assessment (PGA) of overall disease activity, a patient's global assessment of overall well being, and an assessment of patient's pain were all measured on a 100-mm visual analog scale. Functional ability was evaluated using the Dutch version of the Childhood Health Assessment Questionnaire[10,11]. Laboratory tests included the erythrocyte sedimentation rate (ESR) and the C-reactive protein level. After a followup period of at least 1 year, patients with JIA were re-evaluated and classified as improved or unimproved according to the American College of Rheumatology (ACR) Pediatric-50 (ACR-Ped50) criteria[12]. The ACR-Ped50 criteria were defined as an improvement of at least 50% in 3 of the 6 core set variables, with no more than 1 of the remaining variables worsening by more than 30%[12].

MRI protocol. To increase feasibility, MR images were obtained using an open-bore 1.0-T magnet (Panorama HFO, Philips Medical Systems)[13]. The unsedated children were placed in the supine position with the knee joint centrally in the magnetic field in a dedicated knee coil. Contrast-enhanced MRI of the clinically most involved knee (target joint) was performed. If there were no differences in clinical disease activity between knees, the right knee was considered the target joint.

MRI sequences included sagittal T2-weighted fat-saturated images (TR 2800–4500 ms, TE 50 ms, slice thickness 4 mm, field of view 150 × 150 mm, matrix 300 × 242), coronal T2-weighted fat-saturated images (TR 2800–4500 ms, TE 50 ms, slice thickness 4 mm, field of view 150 × 150 mm, matrix 300 × 247), axial T2-weighted fat-saturated images (TR 2800–4500 ms, TE 50 ms, slice thickness 4 mm, field of view 150 × 150 mm, matrix 300 × 270), sagittal T1-weighted fat-suppressed images obtained before and after intravenous (IV) contrast injection (TR 450–650 ms, TE 10 ms, slice thickness 4 mm, field of view 150 × 150 mm, matrix 300 × 248), and axial T1-weighted fat-saturated images obtained after IV contrast injection (TR 400–750 ms, TE 10 ms, slice thickness 4 mm; field of view 150 × 150 mm, matrix 272 × 192). Postcontrast images were obtained in the early phase (< 5 min) after IV injection of a gadolinium-containing contrast agent (0.1 mg/kg of body weight, gadobutrol, Schering).

Image analysis. The image sets were scored independently by a musculoskeletal radiologist (MM, 17 yrs of experience in musculoskeletal radiology) and a radiology trainee (RH, 4 yrs of experience in musculoskeletal radiology). For the purpose of our study, MRI datasets were anonymized, therefore both readers were blinded to clinical history. Following the reading, MRI scores of cases with any discrepancy between readers were re-evaluated to reach consensus. The MR images were scored in accordance with the objective and standardized semiquantitative Juvenile Arthritis MRI Scoring (JAMRIS) system. Both readers were experienced with the JAMRIS system[14,15], and have trained together previously. The reliability of JAMRIS and definitions according to the JAMRIS system are described elsewhere in detail[15]. Briefly, synovial hypertrophy was scored semiquantitatively based on the maximal thickness in any slice (grade 0, < 2 mm; grade 1, 2–4 mm; grade 2, > 4 mm) at 6 sites of the knee joint (patellofemoral, suprapatellar recesses, infrapatellar fat pad, adjacent to the cruciate ligaments, and adjacent to the medial condylar and lateral posterior condylar). The inflamed synovial membrane is thickened, irregular, and can have wavy outlines. The signal intensity of this hypertrophic synovial membrane is low to intermediate on T1-weighted images and high on T2-weighted images. Enhancement (signal intensity increase) was judged by comparison between T1-weighted images obtained before and after IV gadolinium contrast medium administration[15]. Bone marrow changes suggestive of bone marrow edema, cartilage lesions, and bone erosions were scored in 8 anatomical regions (medial and lateral patella, medial and lateral femur condylar, medial and lateral weight-bearing femur, and medial and lateral tibia plateau) based on the percentage of the surface area/bone volume involved at each site (grade 0, none; grade 1, < 10% of surface area/bone volume; grade 2, 10% to 25% of surface area/bone volume; grade 3, > 25% of surface area/bone volume). Bone marrow changes were defined as lesions within the trabecular bone, with ill-defined margins and high signal intensity on T2-weighted fat-saturated images and low signal intensity on T1-weighted images[15]. The cartilage was scored for the presence of lesions (superficial loss and/or thinning, or deep loss to the subchondral bone)[15]. A bone erosion was defined as a sharply marginated bone lesion with correct juxtaarticular localization and typical signal characteristics, and visible in 2 planes with a cortical break in at least 1 plane[15].

Statistics. Descriptive statistics were reported in terms of percentages, means, medians, ranges, interquartile ranges (IQR), and SD. The Mann-Whitney U test and the Fisher's exact test were used to analyze

differences between groups/scores. The Wilcoxon signed-rank test was used to analyze differences within groups. All tests assumed a 2-tailed probability, and a p value of < 0.05 indicated a significant difference. Correlations were assessed using the Spearman's rank correlation coefficient (R_s) and classified as follows: $R_s < 0.40$ poor, ≥ 0.40–0.60 moderate, > 0.60–0.80 substantial, and > 0.80 good. The single measure intraclass correlation coefficient (ICC) was used to analyze interreader reliability and classified as follows: ICC < 0.40 poor, ≥ 0.40–0.60 moderate, > 0.60–0.80 substantial, and > 0.80 good. To assess the responsiveness of the JAMRIS system, the differences between the 2 timepoints were used for calculating the standardized response mean (SRM = mean change of the score/SD change of the score), and classified as follows: SRM < 0.40 poor, ≥ 0.40–0.60 moderate, > 0.60–0.80 substantial, and > 0.80 good[16]. All data were analyzed using SPSS version 18.0.

RESULTS

Patients. We prospectively collected data from 40 patients with JIA (62.5% female) with a mean age of 12.2 years (SD 2.8), between January 2009 and January 2011. Patients included 13 (32.5%) newly diagnosed with JIA and 27 (67.5%) with relapsing or unremitting disease. Table 1 shows the baseline characteristics. Clinical JIA subtypes were represented: 11 (27.5%) persistent oligoarthritis, 8 (20.0%) extended oligoarthritis, 17 (42.5%) rheumatoid factor (RF)-negative polyarthritis, 1 (2.5%) RF-positive polyarthritis, 1 (2.5%) enthesitis-related arthritis, and 2 (5.0%) undifferentiated JIA.

After a median followup period of 1.3 years (IQR 1.1–1.5), all patients were re-evaluated. Improvement was observed in 27 patients (67.5%) with JIA according to the ACR-Ped50 criteria, and 13 patients (32.5%) showed no improvement. No significant differences were observed at baseline in age, sex, clinical measures, or JAMRIS scores between the acute and relapsing/unremitting patients.

Table 1. Characteristics at study entry of 40 patients with clinically active JIA. Except where otherwise indicated, values are median (interquartile range).

	All Patients, n = 40
Clinical characteristics	
No. (%) female	25 (62.5)
Age at study visit, yrs, mean (SD)	12.2 (2.8)
Disease duration at study visit, yrs	2.3 (0.7–5.0)
PGA of overall disease activity[a]	31 (20–48)
Patient's global assessment of overall well being[a]	17 (1–48)
Patient's pain assessment[a]	26 (3–67)
CHAQ score[b]	0.625 (0.125–1.124)
No. active joints	2 (1–3)
No. joints with limited range of motion	1 (0–2)
ESR, mm/h[c]	5 (2–8)
CRP, mg/dl[d]	1 (1–1)
JAMRIS scores, mean (min–max)	
Synovial hypertrophy, 0–12	2.03 (0–12)
Bone marrow changes, 0–24	0.85 (0–7)
Cartilage lesions, 0–24	0.08 (0–2)
Bone erosions, 0–24	0.05 (0–1)

[a] Measured on a 0–100 mm visual analog scale (0 = best, 100 = worst). [b] Units; 0 = best, 3 = worst. [c] Normal < 15 mm/h. [d] Normal < 0.6 mg/dl. PGA: physician's global assessment; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; JIA: juvenile idiopathic arthritis; CHAQ: Childhood Health Assessment Questionnaire; JAMRIS: Juvenile Arthritis Magnetic Resonance Imaging Scoring system.

No differences were detected in clinical improvement between patients newly diagnosed with JIA and patients with relapsing or unremitting disease regarding sex, clinical variable, or JAMRIS scores at baseline. Further, the number of patients showing improvement according to the ACR-Ped50 criteria was comparable between patients newly diagnosed with JIA and patients with relapsing or unremitting disease [76.9% (10/13) vs 63.0% (17/27), p = 0.484, respectively].

Medication. Diagnosis of early *de novo* JIA was followed by the initiation of treatment [disease-modifying antirheumatic drug (DMARD) in 69.2% (9/13) and biologicals in 30.8% (4/13) of the patients with JIA)]. The treatment strategies chosen in the relapsing/unremitting disease group consisted of a change or intensification of treatment after the first MRI in 60.4% (19/27) of the patients [i.e., start or increase in dosing of methotrexate (MTX) in almost 50% (13/27), start a biological in 18.5% (5/27), change in dosing of both MTX and the biological in 3.7% (1/27), or no change in medication in 22.2% (6/27)] under continuation of DMARD. The motivation for not changing treatment strategy was a "spontaneous" clinical improvement in 4 patients in the first weeks following MRI or insufficient signs of disease activity on MRI in 2 patients with JIA.

A change or intensification of treatment after the first MRI was observed in 85.2% (23/27) of the clinically improved patients (ACR-Ped50). No change in treatment strategy was observed in 14.8% (4/27) of the clinically improved patients, because sufficient clinical improvement was gained with the continuation of the initial therapy. In 69.2% (9/13) of the clinically unimproved patients with JIA, a change or intensification of treatment was adopted without success, whereas in 30.8% (4/13) of the clinically unimproved patients it had been decided not to change treatment.

Change in clinical variables within the clinically improved patient group. During followup, significant reductions in these measures were observed among the clinically improved patients: median PGA of overall disease activity (36 vs 5, $p < 0.001$), patient global assessment of overall well being (13 vs 0, p = 0.021), patient pain assessment (26 vs 3, p = 0.009), patient functional ability (0.500 vs 0.125, p = 0.005), and number of actively inflamed joints (2 vs 0, $p < 0.001$).

Differences in clinical variable between clinically improved versus unimproved JIA patient groups. Statistically significant differences were found between clinically improved versus unimproved patients with JIA regarding changes in

variables during followup in the PGA of overall disease activity ($p < 0.001$), patient's pain assessment ($p = 0.026$), patient's global assessment of overall well being ($p = 0.016$), the number of actively inflamed joints ($p < 0.001$), and the erythrocyte sedimentation rate (ESR; $p = 0.025$). Median changes and differences between groups regarding clinical variables from baseline to followup are summarized in Table 2.

Responsiveness of imaging scores. Clinically improved patients showed a significant reduction in synovial hypertrophy scores during followup; from a mean synovial hypertrophy score of 2.63 at baseline to a mean score of 0.81 after followup ($p < 0.001$). The responsiveness of the JAMRIS system concerning the improved patients showed substantial effect regarding change in synovial hypertrophy scores (SRM –0.70, 95% CI –0.33 to –1.08). No significant changes were observed in bone marrow change, cartilage lesion, or bone erosion scores. Changes in MRI scores from baseline to followup are summarized in Table 2. In the current study, destructive changes of cartilage and bone were seen in 10% (4/40) and 7.5% (3/40) of the patients, respectively.

Differences in imaging scores between clinically improved and unimproved patients with JIA. Clinically improved patients with JIA showed statistically significant changes in synovial hypertrophy scores as compared with the clinically unimproved patients (–1.52 vs 1.67, respectively; $p = 0.004$), as shown in Figure 1A. No statistically significant differences were observed regarding changes in bone marrow, cartilage lesion, and bone erosion scores between clinically improved and unimproved patients (Figure 1B-D).

Among clinically improved patients, 7.4% (2/27, deriving from the relapsing group) showed an increase in synovial hypertrophy scores, 29.6% (8/27) showed no change, and 63.0% (17/27) showed a decrease in synovial hypertrophy scores (Figure 2). Of the 10 patients who were improved clinically but showed either no change or worsening of synovitis on imaging, 4 had subclinical synovitis and 6 had no signs of MRI-based knee synovitis at baseline or followup. Concerning clinically unimproved patients, 46.2% (6/13) showed an increase (Figure 3), 38.5% (5/13) showed no change, and 15.3% (2/13) showed a decrease in synovial hypertrophy scores.

Change in MRI findings in relation to clinical responsiveness on the basis of joints. The change in MRI-based synovial hypertrophy scores in relation to the change in swelling, pain/tenderness, and LOM of the target knees is depicted in Table 3. Changes during followup in synovial hypertrophy scores correlated substantially with changes observed in the presence of swelling ($R_s = 0.79$, $p < 0.001$) and LOM ($R_s = 0.65$, $p < 0.001$) of the target knee. No relevant correlation was found between the change in presence of pain/tenderness and changes in synovial hypertrophy scores.

Relationship between change in clinical measures and MRI scores. Changes during followup in synovial hypertrophy scores correlated moderately with changes observed in the PGA of overall disease activity score ($R_s = 0.45$, $p = 0.002$). No relevant correlations were found between the other MRI scores and clinical variables.

Interobserver variability. About the interreader reliability of the baseline scores and followup scores, the single-measure ICC were good for all items: 0.89–1.00 and 0.87–1.00,

Table 2. Summary of changes from baseline to followup in clinically improved (ACR-Ped50) and unimproved patients with JIA. Except where otherwise indicated, values are median (interquartile range), and Mann-Whitney U test was used to analyze differences between groups.

	ACR-Ped50, n = 27	No Improvement, n = 13	p
Change in clinical variables			
PGA of overall disease activity[b]	–30 (–37– –17)	6 (–9–17)	< 0.001
Patient's global assessment of overall well being[b]	–9 (–20–0)	1 (–3–35)	0.016
Patient's pain assessment[b]	–9 (–26–0)	0 (–5–36)	0.026
CHAQ csore[c]	–1.250 (–0.625–0.000)	0.000 (–0.125–0.125)	0.250
No. active joints	–2 (–4– –1)	0 (0–1)	< 0.001
No. joints with limited range of motion	0 (–1–0)	0 (–2–2)	0.644
ESR, mm/h	0 (–4–0)	0 (–2–3)	0.025
CRP level, mg/dl	–1 (–1–0)	–1 (–1–0)	0.545
Change in JAMRIS scores, mean (min–max)			
Synovial hypertrophy	–1.52 (–8–2)	1.67 (–4–8)	0.004
Bone marrow changes	–0.11 (–7–2)	1.25 (0–6)	0.079
Cartilage lesions	–0.04 (–1–0)	0.42 (0–4)	0.165[a]
Bone erosions	–0.04 (–1–0)	0.17 (0–1)	0.078[a]

[a] Chi-square test. [b] Measured on a 0–100 mm visual analog scale (0 = best, 100 = worst). [c] Units; 0 = best, 3 = worst. PGA: physician's global assessment; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ACR-Ped50: American College of Rheumatology Pediatric-50 criteria; JIA: juvenile idiopathic arthritis; CHAQ: Childhood Health Assessment Questionnaire; JAMRIS: Juvenile Arthritis Magnetic Resonance Imaging Scoring systemic.

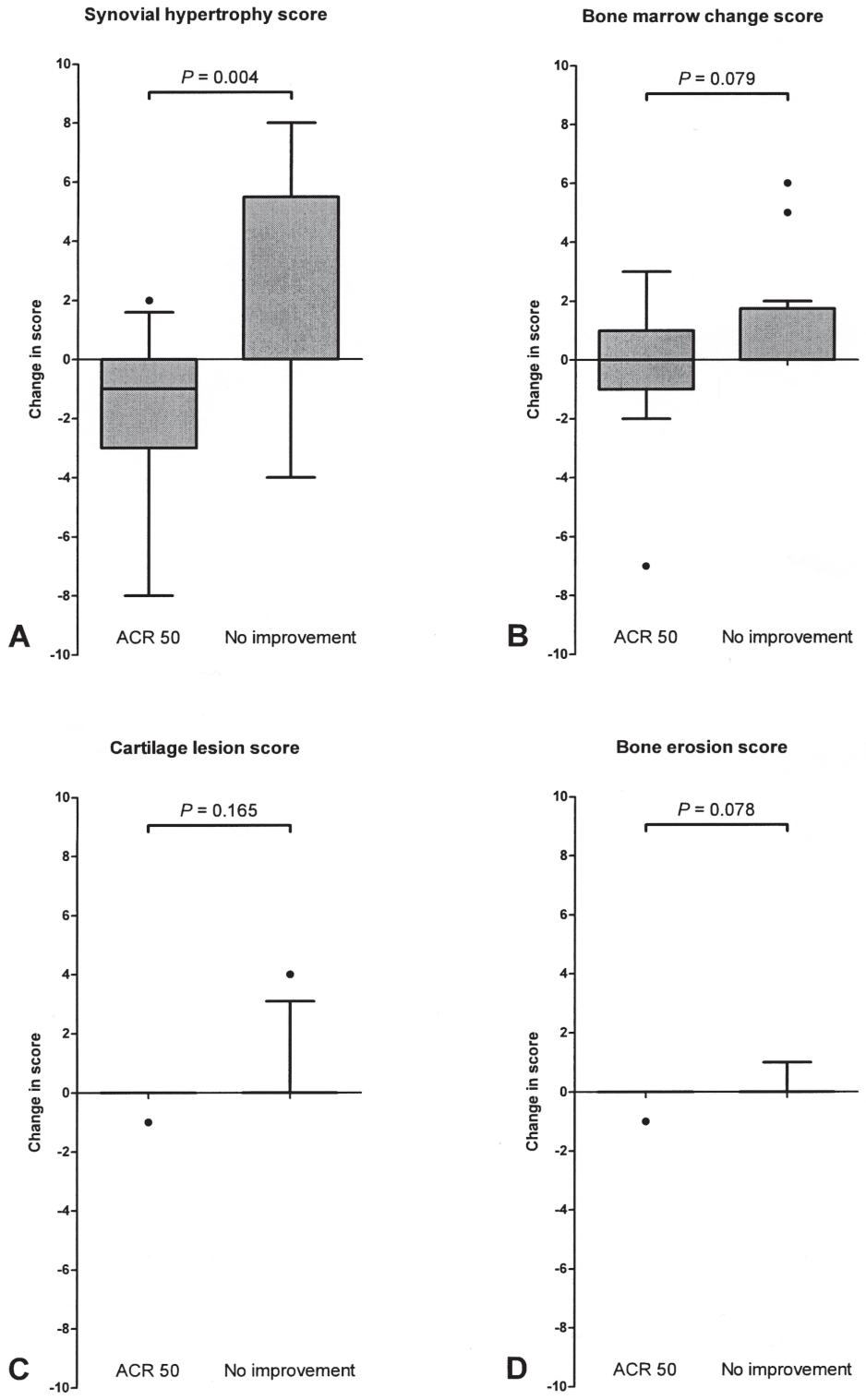

Figure 1. Differences in changes of JAMRIS scores in JIA patients during followup between clinically improved (ACR50) and unimproved (No improvement) scores. A. Synovial hypertrophy. B. Bone marrow changes. C. Cartilage lesions. D. Bone erosions. JIA: juvenile idiopathic arthritis; JAMRIS: Juvenile Arthritis Magnetic Resonance Imaging Scoring system; ACR50: American College of Rheumatology 50 criteria.

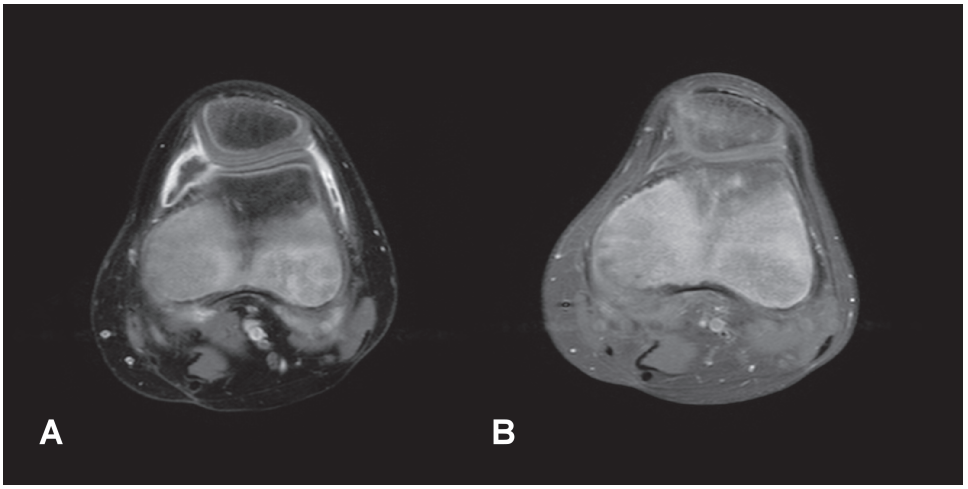

Figure 2. Decrease in synovial hypertrophy score after followup in a clinically improved patient with JIA. Axial fat-saturated contrast-enhanced T1-weighted images obtained from a 9-year-old girl with A. a patellofemoral synovial hypertrophy score of 2 (> 4 mm) at baseline; and B. a decrease in synovial hypertrophy resulting in a patellofemoral synovial hypertrophy score of 0 (< 2 mm) after followup. JIA: juvenile idiopathic arthritis.

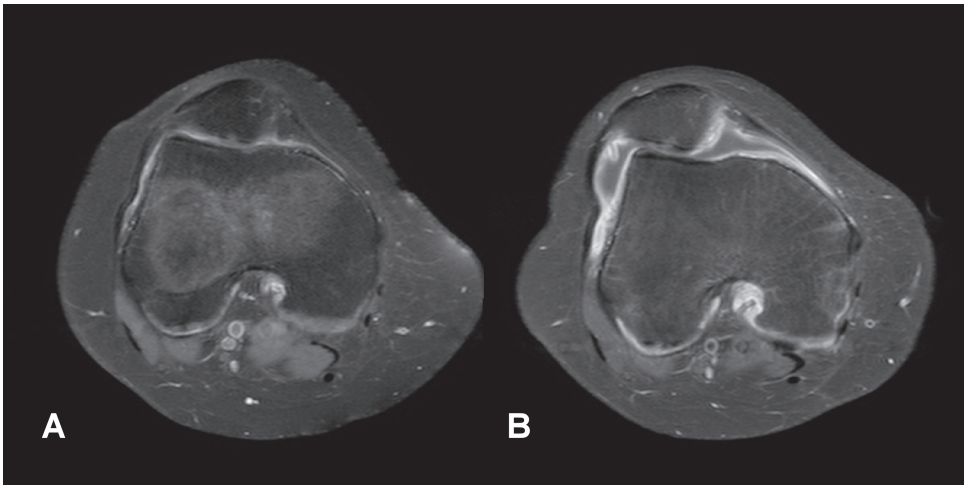

Figure 3. Increase in synovial hypertrophy scores during followup in a clinically unimproved patient with JIA. Axial fat-saturated contrast-enhanced T1-weighted images obtained from a 16-year-old girl with A. no JAMRIS synovial hypertrophy score at baseline; and B. an increase in synovial hypertrophy resulting in a patellofemoral synovial hypertrophy score of 2 (> 4 mm) after followup. JIA: juvenile idiopathic arthritis; JAMRIS: Juvenile Arthritis Magnetic Resonance Imaging Scoring system.

respectively. Single-measure ICC for the baseline scores and followup scores were as follows: synovial hypertrophy 0.94 (95% CI 0.90–0.98) and 0.92 (95% CI 0.84–0.97), bone marrow changes 0.89 (95% CI 0.74–0.95) and 0.87 (95% CI 0.77–0.95), cartilage lesions 1.00 (95% CI 1.00–1.00) and 1.00 (95% CI 1.00–1.00), bone erosions 1.00 (95% CI 1.00–1.00) and 1.00 (95% CI 1.00–1.00), respectively. Additionally, the Bland-Altman plots showed a good agreement regarding the baseline scores (Figure 4A-B) and followup scores (Figure 4C-D) of synovial hypertrophy and bone marrow changes between the 2 readers.

DISCUSSION

In our study, improvement of JIA disease activity according to the ACR-Ped50 criteria appeared to be associated with a significant decrease in MRI-based synovial hypertrophy scores. Whereas a substantial effect regarding the change in synovial hypertrophy scores upon treatment of active disease was observed during a 1-year followup period, no significant changes were found in bone marrow changes, cartilage lesions, and bone erosions. Moreover, changes during followup in synovial hypertrophy scores correlated substantially with changes observed in the presence of

Table 3. Change in MRI-based synovial hypertrophy scores in relation to the change of presence of swelling, pain/tenderness, and LOM of the target knee in clinically improved patients with JIA. MRI score refers to JAMRIS synovial hypertrophy score.

	Decrease	No Change	Increase	Total
Presence of swelling				
Decrease	15	2	0	17
No change	1	7	0	8
Increase	0	1	1	2
Total	16	10	1	27
Presence of pain/tenderness				
Decrease	9	7	1	17
No change	2	5	1	8
Increase	0	1	1	2
Total	11	13	3	27
Presence of LOM				
Decrease	11	6	0	17
No change	2	6	0	8
Increase	0	0	2	2
Total	13	12	2	27

MRI: magnetic resonance imaging; LOM: limited range of motion; JIA: juvenile idiopathic arthritis; JAMRIS: Juvenile Arthritis Magnetic Resonance Imaging Scoring system.

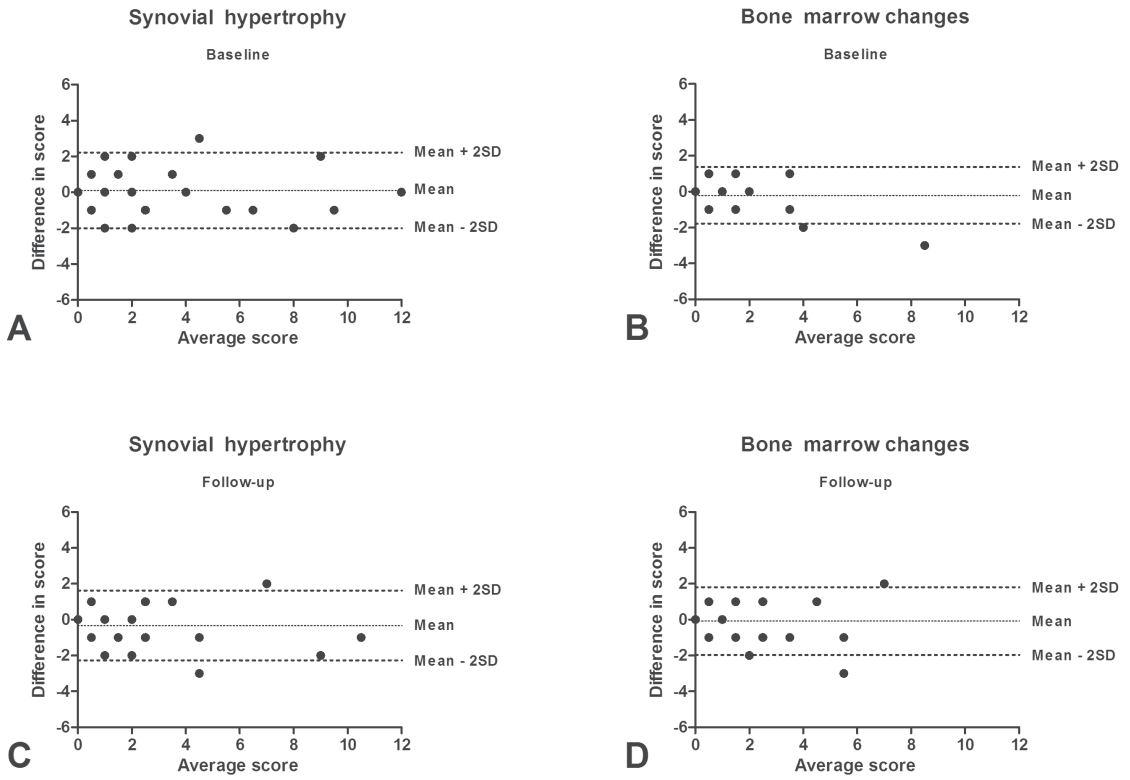

Figure 4. Bland-Altman plots of the difference against mean score of both readers concerning A. baseline synovial hypertrophy scores; B. baseline bone marrow change scores; C. followup synovial hypertrophy scores; and D. followup bone marrow change scores.

swelling and LOM of the target knee. This is one of the first studies providing evidence for MRI-based improvement during followup in JIA patients with knee involvement upon start or adjustment of antiinflammatory treatment[17].

The JAMRIS synovial hypertrophy score for the knee proved to be informative, enabling a clear discrimination between clinically improved and unimproved patients with JIA. The ability to detect changes over time is an important and critical quality of any outcome measure. These results support its application to assess early arthritis in an objective way — thus avoiding variability in clinical scores. Moreover, the use of objective measures could improve patient care by tailoring the exposure time to antirheumatic drugs, either in daily practice, cohort studies, or clinical trials. Our results are in line with a recent study by Malattia, *et al*, who showed good responsiveness of MRI-based synovial hypertrophy scores in the wrist joints of patients with JIA[18]. These results, in combination with the results of our current study, support the use of MRI as a reliable outcome measure in clinical practice in various joints.

The trend toward early suppression of inflammation to prevent cartilage lesions and bone erosions shifts the emphasis from conventional radiography for late radiological signs to early stage radiological manifestations by MRI. Ultrasound is an easy and noninvasive modality, but the interreader reliability of ultrasound is dubious, and the detection of synovial thickening in the knee joint in all detail is limited[19]. MRI plays an increasing role in the evaluation of disease status in JIA, being the more sensitive imaging modality for the detection of synovial inflammation, early destructive changes, and bone marrow edema in JIA[7,8]. However, in daily practice MRI is as yet not commonly used to objectively assess disease activity.

Our recent studies have indicated that MRI represents an accurate technique using a highly reproducible and reliable scoring system (JAMRIS)[15]. JAMRIS is based on the use of IV contrast, because imaging without contrast is inferior in detecting early synovial inflammation[14]. MRI has previously been shown to be more sensitive and reliable than physical examination by expert rheumatologists in the detection of joint inflammation[4,20]. We now add another piece of evidence to support the applicability of MRI in assessing disease activity as an objective and reliable outcome measure during monitoring and followup of patients with JIA.

Although MRI is the most sensitive imaging modality concerning the evaluation of early signs of inflammation and late destructive changes of cartilage and bone, it has some limitations in daily practice. These include the necessity for sedation in very young children, the need of an IV contrast agent for the detection of synovial disease, and the limited number of joints that can be evaluated during one imaging session because of time constraints[7,14]. Despite these practical limitations, the results of our current study imply that contrast-enhanced MRI can be used as a sensitive outcome measure in research and clinical trials. Moreover, MRI in children with JIA proved to be feasible in patients as young as 5 years[13].

These limitations make it important to focus on a clinically frequently involved joint regarding the presence of arthritis. In that way, most of the patients with JIA can be included, increasing the value of MRI as an outcome measure for research in JIA. Although JIA patients with principal wrist involvement have been reported to show poor therapy response and a destructive course of the disease[3,21], only a relatively small subgroup of the children with JIA presents with wrist involvement. Therefore, we focused on JIA patients with knee involvement, because it is the most commonly affected joint in JIA. However, the most frequently involved joint may vary according to the country where the population is assessed. This might hamper the generalizability of our study findings for the complete JIA population. Therefore, our results need external validation in an independent cohort to test the strength and applicability of our findings.

No significant changes were observed in bone marrow changes, cartilage lesions, or bone erosions. The presence of bone marrow changes is an important predictor of early erosive joint damage in adult rheumatoid arthritis[22,23], although its prognostic value in JIA has never been assessed. Some differences were found in changes of bone marrow edema scores between clinically improved and unimproved patients with JIA, but its responsiveness was very low. Therefore the clinical relevance of bone marrow edema in pediatric patients remains unclear and should be addressed in larger followup studies. The lack of absolute change in cartilage lesion and bone erosion scores between the timepoints can be the result of selection bias. Our results might indicate that the patients enrolled in the current study had only mild to moderate disease activity. Thus, our results need external validation in an independent cohort of patients with JIA who have a more severe course of the disease.

In the current study, 6 out of 27 clinically improved patients were found to have no signs of synovitis upon MRI at baseline or followup. The reliability of the clinical assessment is, therefore, questionable. Our results imply that it is difficult to assess whether, for example, a joint is swollen because of inflammatory disease activity or other factors, such as subcutaneous fat or soft tissue edema[24]. Further, pain and limited range of motion in a joint are apparently not always an expression of inflammatory activity.

In fact, some limitations of our study should be considered. First, the study cohort was relatively small. Moreover, as growing joints change anatomically, it is difficult to establish whether differences in the appearance of the knee joint are pathological or part of the normal developmental process upon MR imaging. For instance, the frequency of signal changes suggestive of bone marrow edema in wrists and knees of healthy children is high[25,26]. Thus, the lack of MR images of age-matched healthy controls is a potential weakness of most imaging studies in

children — in particular in relation to bone marrow changes. Another limitation is the lack of blinding concerning the pediatric rheumatologist regarding the MRI results. In 2 out of 40 patients with JIA, the treatment strategy was not adjusted following the MRI findings. Further, the heterogeneity of the studied patients with JIA (67.5% relapsed or unremitting disease, 32.5% newly diagnosed JIA) should be considered a limitation. It is unknown whether previous episodes of synovitis may have produced histopathological changes in the group of patients who presented with relapsed or unremitting disease that were not present in the group of patients with newly diagnosed disease.

We conclude that there is a strong association with improvement of clinical disease activity findings and changes in MRI-based synovial hypertrophy scores. A substantial effect regarding change in synovial hypertrophy scores was observed between timepoints, supporting the role of MRI as an objective, reliable, feasible, and responsive outcome measure in future research and clinical trials. No important changes were observed regarding bone marrow, making its clinical relevance as a disease activity measure in children with JIA uncertain. This aspect should be addressed in larger longterm followup studies.

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