Magnetic resonance imaging in juvenile idiopathic arthritis diagnosis and follow-up, beyond imagination
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Chapter 7

One-year follow-up study on clinical findings and changes in MRI-based disease activity scores in juvenile idiopathic arthritis

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Abstract

Objectives
To evaluate whether clinical disease activity findings during 1-year follow-up in juvenile idiopathic arthritis (JIA) patients is associated with changes of MRI-based disease activity scores.

Methods
JIA patients with active knee involvement were studied using an open-bore MRI. After follow-up of a median of 1.3 years, patients were re-evaluated and classified as improved or not improved according to the ACR Pediatric-50 criteria. Baseline and follow-up MRI features were scored by two readers using the 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). After follow-up, 27 (67.5%) patients were classified as clinically improved, whereas 13 (32.5%) patients showed no clinical improvement. The clinically improved patients showed a significant reduction in synovial hypertrophy scores during follow-up ($P < 0.001$), with substantial effects (standardized response mean [SRM], -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 non-improved 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 ($P = 0.078$).

Conclusions
This is the first study providing evidence for MRI-based improvement upon follow-up in JIA patients with knee involvement. There is a strong association with clinical improvement according to the ACR Pediatric-50 criteria and changes in MRI-based synovial hypertrophy scores, supporting the role of MRI as a responsive outcome measure to evaluate disease activity to anti-inflammatory treatment strategies.
Introduction

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 long-term outcome. Therefore, sensitive measures to assess individual response to therapy and general efficacy of treatment in JIA are warranted (2, 3). Physical examination has only limited reliability (4, 5), and conventional radiography is insensitive in detecting soft-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, there is fair strength of evidence 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 oedema. Nonetheless, MRI is still under-utilized both in clinical practice and research settings. One of the reasons for the under-utilization of MRI in the assessment of disease status in JIA relates to the lack of evidence in the literature on its ability to detect changes over time. The ability to detect changes (responsiveness) refers to the possibility of subjects to change inflammatory disease status over time. As the clinical manifestations of disease in children with JIA can change rapidly, imaging criteria should also be capable to detect these 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 follow-up in JIA patients 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 two tertiary paediatric rheumatology centres. At the time of presentation, all children underwent clinical and laboratory assessment followed by MRI. Inclusion criteria for the current study were a follow-up period of at least one year, and clinical active disease with knee involvement at baseline. The patients comprised therefore newly diagnosed JIA patients and patients with a clinically active arthritis owing to
relapsing or unremitting disease. All patients fulfilled the International League of Associations for Rheumatology (ILAR) criteria for JIA, defined as an arthritis of unknown aetiology that begins before the age of 16 and persists for at least 6 weeks (9). Exclusion criteria were: a history of intra-articular corticosteroid injection within the last six months, the need for anaesthesia during the MRI examination, and general contraindications for MRI. This study was performed in accordance with the declaration of Helsinki and the local medical ethical regulations. Written informed consent was obtained from at least one parent of each child.

Clinical assessment
Physical examination was performed by the same experienced paediatric 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. A physician’s global assessment 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-analogue scale. Functional ability was evaluated using the Dutch version of the childhood health assessment questionnaire (CHAQ) (10, 11). Laboratory tests included the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level. After a follow-up period of at least 1 year, JIA patients were re-evaluated and classified as improved or not improved 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 three of the six core set variables, with no more than one of the 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, Best, the Netherlands) (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 clinical most involved knee (target joint) was performed. If there were no differences in clinical disease activity between knees, the right knee was considered to be the target joint.

MRI sequences included sagittal T2-weighted fat saturated images (TR 2800-4500ms; TE 50ms; slice thickness 4mm; field of view 150 x 150mm; matrix 300 x 242), coronal T2-weighted fat-saturated images (TR 2800-4500ms; TE 50ms; slice thickness 4mm; field of view 150 x 150mm; matrix 300 x 247), axial T2-weighted fat-saturated images (TR 2800-4500ms; TE 50ms; slice thickness 4mm; field of view 150 x 150mm; matrix 300 x 270), sagittal T1-weighted images
obtained before and after intravenous contrast injection (TR 450-650ms; TE 10ms; slice thickness 4mm; field of view 150 × 150mm; matrix 300 × 248), and axial T1-weighted fat-saturated images obtained after intravenous contrast injection (TR 400-750ms; TE 10ms; slice thickness 4mm; field of view 150 × 150mm; matrix 272 × 192). Post-contrast images were obtained in the early phase (<5 min) after intravenous injection of Gd (0.1 mmol per kilogram of body weight, gadobutrol, Bayer healthcare, Berlin, Germany).

**Image analysis**

The image sets were scored independently by a musculoskeletal radiologist (MM, 17 years of experience in musculoskeletal radiology) and a radiology trainee (RH, 4 years of experience in musculoskeletal radiology). For the purpose of this study, MRI datasets were anonymized, therefore both readers were blinded to clinical history. The MR images were scored in accordance with the objective and standardized semi-quantitative Juvenile Arthritis MRI Scoring (JAMRIS) system. Both readers were experienced with using 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 semi-quantitatively based on the maximal thickness in any slice (grade 0, <2mm; grade 1, 2–4mm; grade 2, >4mm) at six sites of the knee joint (patellofemoral, suprapatellar recesses, infrapatellar fat pad, adjacent to the cruciate ligaments, and adjacent to the medial- 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 intravenous gadolinium contrast medium administration (15). Bone marrow changes suggestive of bone marrow oedema, cartilage lesions and bone erosions were scored in eight 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, 10–25% 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 juxta-articular localisation, typical signal characteristics and visible in two planes with a cortical break in at least one plane (15).
Statistics

Descriptive statistics were reported in terms of percentages, means, medians, ranges, interquartile ranges and standard deviations. The Mann-Whitney U test and the Fisher's exact test were used to analyze differences between groups/scores. The Wilcoxon signed ranks test was used to analyze differences within groups. All tests assumed a 2-tailed probability and a P value of less than 0.05 indicated a significant difference. Correlations were assessed using the Spearman's rank correlation coefficient ($R_s$), and was classified as follows: $R_s < 0.40 = \text{poor}$, $0.40-0.60 = \text{moderate}$, $0.60-0.80 = \text{substantial}$ and $>0.80 = \text{good}$ correlation. The single measure intraclass correlation coefficient (ICC) was used to analyze inter-reader reliability, and was classified as follows: ICC $<0.40 = \text{poor}$, $0.40-0.60 = \text{moderate}$, $0.60-0.80 = \text{substantial}$, and $>0.80 = \text{good}$ reliability. To assess the responsiveness of the JAMRIS system, the differences between the two timepoints were used for calculating the standardized response mean (SRM = mean change of the score / SD change of the score), and was classified as follows: SRM $<0.40 = \text{poor}$, $0.40-0.60 = \text{moderate}$, $0.60-0.80 = \text{substantial}$ and $>0.80 = \text{good}$ effect (16). All data were analyzed by using SPSS version 18.0 (SPSS, Chicago, ILL, USA).

Results

Patients

We prospectively collected data of 40 JIA patients (62.5% female patients) with a mean age of 12.2 years (SD 2.8), between January 2009 and January 2011. Patients included 13 (32.5%) newly diagnosed JIA patients and 27 (67.5%) patients 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-negative polyarthritis, 1 (2.5%) rheumatoid factor-positive polyarthritis, 1 (2.5%) enthesitis-related arthritis, and 2 (5.0%) undifferentiated JIA.

After a median follow-up period of 1.3 years (IQR 1.1-1.5) all patients were re-evaluated. Improvement was observed in 27 (67.5%) JIA patients according to the ACR-Ped50 criteria and 13 (32.5%) patients showed no improvement. No significant differences were observed at baseline in age, gender, clinical parameters, or JAMRIS scores between the acute and relapsing/unremitting patients.
With respect to clinical improvement, no differences were detected between newly diagnosed JIA patient and patients with relapsing or unremitting disease regarding gender, clinical parameters, or JAMRIS scores at baseline. Furthermore, the number of patients showing improvement according to the ACR-Ped50 criteria was comparable between newly diagnosed JIA patients and patients with relapsing or unremitting disease; 76.9% (10/13) vs. 63.0% (17/27), \( P = 0.484 \), respectively.

### Table 1. Patient characteristics at study entry of 40 JIA patients with clinically active disease activity

<table>
<thead>
<tr>
<th>A. Clinical characteristics</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. (%) female</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Age at study visit, mean years (SD)</td>
<td>12.2 (2.8)</td>
</tr>
<tr>
<td>Disease duration at study visit, years</td>
<td>2.3 (0.7 – 5.0)</td>
</tr>
<tr>
<td>Physician's global assessment of overall disease activity( ^a )</td>
<td>31 (20 – 48)</td>
</tr>
<tr>
<td>Patient's global assessment of overall well-being( ^b )</td>
<td>17 (1 – 48)</td>
</tr>
<tr>
<td>Patient's pain assessment( ^b )</td>
<td>26 (3 – 67)</td>
</tr>
<tr>
<td>C-HAQ score( ^c )</td>
<td>0.625 (0.125 – 1.124)</td>
</tr>
<tr>
<td>No. of active joints</td>
<td>2 (1 – 3)</td>
</tr>
<tr>
<td>No. of joints with limited range of motion</td>
<td>1 (0 – 2)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/hour( ^d )</td>
<td>5 (2 – 8)</td>
</tr>
<tr>
<td>C-reactive protein level, mg/l( ^e )</td>
<td>1 (1 – 1)</td>
</tr>
<tr>
<td>B. JAMRIS scores( ^f )</td>
<td></td>
</tr>
<tr>
<td>Synovial hypertrophy, mean (min-max), (0-12)</td>
<td>2.03 (0 – 12)</td>
</tr>
<tr>
<td>Bone marrow changes, mean (min-max), (0-24)</td>
<td>0.85 (0 – 7)</td>
</tr>
<tr>
<td>Cartilage lesions, mean (min-max), (0-24)</td>
<td>0.08 (0 – 2)</td>
</tr>
<tr>
<td>Bone erosions, mean (min-max), (0-24)</td>
<td>0.05 (0 – 1)</td>
</tr>
</tbody>
</table>

\( ^a \) Except where otherwise indicated, values are median (inter-quartile range)

\( ^b \) Measured on a 0-100 mm visual analogue scale (0 = best, 100 = worst)

\( ^c \) Units; 0 = best, 3 = worst

\( ^d \) Normal < 15mm/h

\( ^e \) Normal < 0.6 mg/l

\( ^f \) Values are means of values for observer 1 and observer 2

### Medication

Diagnosis of early de-novo JIA was followed by the initiation of treatment (DMARDs in 69.2% (9/13) and biologicals in 30.8% (4/13) of the JIA patients). 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 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) of the children), or no change in medication in 22.2% (6/27) under continuation.
of DMARDs. 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 JIA patients.

A change or intensification of treatment after the first MRI was observed in 85.2% (23/27) of the clinically improved JIA 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 non-improved JIA patients a change or intensification of treatment was adopted without success whereas in 30.8% (4/13) of the clinically non-improved patients it had been decided not to change treatment.

Change in clinical parameters within the clinically improved patient group
With respect to the clinically improved patients a significant reduction in the median physicians’ global assessment of overall disease activity (36 vs. 5, \( P < 0.001 \)), patient’s global assessment of overall well-being (13 vs. 0, \( P = 0.021 \)), patient’s pain assessment (26 vs. 3, \( P = 0.009 \)), patient’s functional ability (0.500 vs. 0.125, \( P = 0.005 \)), and number of actively inflamed joints (2 vs. 0, \( P < 0.001 \)) was observed during follow-up.

Differences in clinical parameters between clinically improved versus non-improved JIA patient groups
Statistical significant differences were found between clinically improved versus non-improved JIA patients regarding changes in parameters during follow-up in the physicians’ global assessment of overall disease activity \( (P < 0.001) \), patient’s pain assessment \( (P = 0.016) \), patient’s global assessment of overall well-being \( (P = 0.026) \), the number of actively inflamed joints \( (P < 0.001) \), and the erythrocyte sedimentation rate \( (P = 0.025) \). Median changes and differences between groups regarding clinical parameters from baseline to follow-up are summarized in Table 2A.

Responsiveness of imaging scores
Clinically improved patients showed a significant reduction in synovial hypertrophy scores during follow-up; from a mean synovial hypertrophy score of 2.63 at baseline to a mean score of 0.81 after follow-up \( (P < 0.001) \). 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 – -1.08)). No significant changes were observed in bone marrow change, cartilage lesion, and bone erosion scores. Changes in MRI scores from baseline to follow-up are summarized in Table 2B. In the current study, destructive changes of cartilage and bone was seen in 10% (4/40), and 7.5% (3/40) of the patients, respectively.
Table 2. Summary of changes from baseline to follow-up in clinically improved (ACR-Ped50) and non-improved (no improvement) JIA patients

<table>
<thead>
<tr>
<th>A. Change in clinical parameters</th>
<th>ACR-Ped50 n = 27</th>
<th>No improvement n = 13</th>
<th>P valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician’s global assessment of overall disease activityd</td>
<td>-30 (-37 - -17)</td>
<td>6 (-9 - 17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient’s global assessment of overall well-beingd</td>
<td>-9 (-20 - 0)</td>
<td>1 (-3 - 35)</td>
<td>0.016</td>
</tr>
<tr>
<td>Patient’s pain assessmentd</td>
<td>-9 (-26 - 0)</td>
<td>0 (-5 - 36)</td>
<td>0.026</td>
</tr>
<tr>
<td>C-HAQ scoree</td>
<td>-1.250 (-0.625 – 0.000)</td>
<td>0.000 (-0.125 – 0.125)</td>
<td>0.250</td>
</tr>
<tr>
<td>No. of active joints</td>
<td>-2 (-4 - -1)</td>
<td>0 (0 – 1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of joints with limited range of motion</td>
<td>0 (-1 – 0)</td>
<td>0 (-2 – 2)</td>
<td>0.644</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/hour</td>
<td>0 (-4 – 0)</td>
<td>0 (-2 – 3)</td>
<td>0.025</td>
</tr>
<tr>
<td>C-reactive protein level, mg/l</td>
<td>-1 (-1 – 0)</td>
<td>-1 (-1 – 0)</td>
<td>0.545</td>
</tr>
<tr>
<td>B. Change in JAMRIS scoresf</td>
<td>Synovial hypertrophy, mean (min-max)</td>
<td>-1.52 (-8 – 2)</td>
<td>1.67 (-4 – 8)</td>
</tr>
<tr>
<td>Bone marrow changes, mean (min-max)</td>
<td>-0.11 (-7 – 2)</td>
<td>1.25 (0 – 6)</td>
<td>0.079</td>
</tr>
<tr>
<td>Cartilage lesions, mean (min-max)</td>
<td>-0.04 (-1 – 0)</td>
<td>0.42 (0 – 4)</td>
<td>0.165c</td>
</tr>
<tr>
<td>Bone erosions, mean (min-max)</td>
<td>-0.04 (-1 – 0)</td>
<td>0.17 (0 – 1)</td>
<td>0.078c</td>
</tr>
</tbody>
</table>

a Except where otherwise indicated, values are median (inter-quartile range)  
b Except where otherwise indicated, Mann-Whitney U test was used to analyze differences between groups.  
c Chi-square test  
d Measured on a 0-100 mm visual analogue scale (0 = best, 100 = worst)  
e Units; 0 = best, 3 = worst  
f Values are means of values for observer 1 and observer 2

Differences in imaging scores between clinically improved and non-improved JIA patients

Clinically improved JIA patients showed statistically significant changes with respect to synovial hypertrophy scores as compared with the clinically non-improved patients (-1.52 vs. 1.67, respectively; P = 0.004), as shown in Figure 1A. No statistical significant differences were observed regarding changes in bone marrow change, cartilage lesion and bone erosion scores between clinically improved and non-improved patients (Figure 1B-D).

With respect to 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) patients showed a decrease in synovial hypertrophy scores (Figure 2). Of these 10 patients who were improved clinically but showed either no change or worsening of synovitis on imaging, 4 had subclinical synovitis, and 6 patients had no signs of MRI-based knee synovitis at baseline nor at follow-up. Concerning clinically non-improved patients, 46.2% (6/13) showed an increase (Figure 3), 38.5% (5/13) showed no change, and 15.3% (2/13) patients showed a decrease in synovial hypertrophy scores.
Figure 1. Differences in changes of JAMRIS scores in JIA patients during follow-up between clinically improved (ACR 50) and non-improved (No improvement), with respect to (a) synovial hypertrophy, (b) bone marrow changes, (c) cartilage lesions, and (d) bone erosions.
Changes in MRI-based disease activity scores in JIA

Figure 2. Decrease in synovial hypertrophy score after follow-up in a clinically improved JIA patient. Axial fat-saturated contrast-enhanced T1-weighted images obtained in a 9-year old girl with (a) a patellofemoral synovial hypertrophy score of 2 (>4mm) at baseline, (b) and a decrease in synovial hypertrophy resulting in a patellofemoral synovial hypertrophy score of 0 (<2mm) after follow-up.

Figure 3. Increase in synovial hypertrophy scores during follow-up in a clinically non-improved JIA patient. Axial fat-saturated contrast-enhanced T1-weighted images obtained in a 16-year old girl with (a) no JAMRIS synovial hypertrophy score at baseline, (b) and an increase in synovial hypertrophy resulting in a patellofemoral synovial hypertrophy score of 2 (>4mm) after follow-up.

Relationship between change in clinical parameters and MRI scores
Changes during follow-up in synovial hypertrophy scores correlated moderately with changes observed in the physicians’ global assessment 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.

Inter-observer variability
With respect to the inter-reader reliability of the baseline scores and follow-up scores, the single measure ICC’s were good for all items: 0.89–1.00 and 0.87–1.00, respectively. Single measure ICC’s for the baseline scores and follow-up 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 (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 follow-up scores (Figure 4C-D) of synovial hypertrophy and bone marrow changes between the two readers.

![Bland-Altman plots](image)

**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) follow-up synovial hypertrophy scores (d) follow-up bone marrow change scores.

### Discussion

In this 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 one-year follow-up period, no significant changes were found with respect to bone marrow changes, cartilage lesions and bone erosions. This is the first study providing evidence for MRI-based improvement upon follow-up in JIA patients with knee involvement upon start or adjustment of anti-inflammatory treatment.
Changes in MRI-based disease activity scores in JIA

The JAMRIS synovial hypertrophy score for the knee proved to be informative, enabling a clear discrimination between clinically improved and non-improved JIA patients. The ability to detect changes over time is an important and critical quality of any outcome measure. These results support its application in order 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 anti-rheumatic drugs, either in daily practice, cohort studies or clinical trials. Our results are in line with a recent study performed by Malattia et al. who showed good responsiveness of MRI-based synovial hypertrophy scores in the wrist joints of JIA patients (17). 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 towards early suppression of inflammation in order 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 non-invasive modality but the inter-reader reliability of ultrasound is dubious, and the detection of synovial thickening in the knee joint in all detail is limited (18). 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 oedema 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 intravenous 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, 19). 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 follow-up of JIA patients.

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 practical limitations in daily practice. These include the necessity for sedation in very young children, the need of an intravenous 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 of age (20).
The performance of an MRI examination for the assessment of more than one or two joints has practical limitations because of time constraints. This reduces feasibility of MRI in pediatric JIA patients. It is, therefore, important to focus on a clinically frequently involved joint, with respect to presence of arthritis. Thereby most of the JIA patients can be enclosed, and in that way increase 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 involvement of wrist. Therefore, we focused on JIA patients with knee involvement, as the most commonly affected joint in JIA.

No significant changes were observed with respect to bone marrow changes, cartilage lesions and bone erosions. The presence of bone marrow changes is an important predictor of early erosive joint damage in adult rheumatoid arthritis (22, 23), though its prognostic value in JIA has never been assessed. Some differences were found in changes of bone marrow oedema scores between clinically improved and non-improved JIA patients, but its responsiveness was very low. Therefore the clinical relevance of bone marrow oedema in paediatric JIA patients remains unclear and should be addressed in larger follow-up studies. The lack of absolute change in cartilage lesion and bone erosion scores between the timepoints can be the result of selection bias. Therefore, 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 JIA patients with a more severe course of the disease.

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 oedema in wrists and knees of healthy children is high (24, 25). Thus, the lack of MR images of age-matched healthy controls is a potential weakness of most imaging study in children – in particular in relation to bone marrow changes. Another limitation is the lack of blinding concerning the paediatric rheumatologist regarding the MRI results. In 2 out of 40 JIA patients the treatment strategy was not adjusted following the MRI findings.

In summary, we can conclude from our prospective cohort study in JIA 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 time points, 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 changes, making its clinical relevance as a disease activity parameter in children with JIA uncertain and should be addressed in larger long-term follow-up studies.
References


