Magnetic resonance imaging in juvenile idiopathic arthritis diagnosis and follow-up, beyond imagination
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Chapter 4

Reliability and responsiveness of the Juvenile Arthritis MRI Scoring (JAMRIS) system for the knee

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Abstract

Objective
To assess the reliability and responsiveness of a new Juvenile Arthritis MRI Scoring (JAMRIS) system for evaluating disease activity of the knee.

Methods
Twenty-five juvenile idiopathic arthritis (JIA) patients with clinical knee involvement were studied using open-bore 1-T MRI. MRI features of synovial hypertrophy, bone marrow changes, cartilage lesions and bone erosions were independently scored by five readers using the JAMRIS system. In addition, the JAMRIS system was determined to be a follow-up parameter by two readers to evaluate the response to therapy in 15 consecutive JIA patients.

Results
Inter-reader (ICCs 0.86–0.95) and intra-reader reliability (ICCs 0.92–1.00) for the scoring of JAMRIS features was good. Reliability of the actual scores and changes in scores over time was good for all items: ICCs 0.89–1.00, 0.87–1.00, respectively. Concerning therapy response, the mean synovial hypertrophy scores decreased significantly (mean 1.1 point; P < 0.001, SRM −0.65). No change was observed with respect to bone marrow change, cartilage lesion and bone erosion scores.

Conclusions
The JAMRIS proved to be a simple and highly reliable assessment score in the evaluation of JIA disease activity of the knee. The JAMRIS system may serve as an objective and accurate outcome measure in future research and clinical trials.
Introduction

Juvenile idiopathic arthritis (JIA) is the most common auto-inflammatory musculoskeletal disease in childhood, with a prevalence that varies between 16 and 150 per 100,000 (1). JIA is not a single disease, but a term that encompasses all forms of arthritis of unknown etiology and pathophysiology that begins before the age of 16 years and persists for more than 6 weeks (2). It is characterized by prolonged synovial inflammation that can lead to the destruction of joints, pain and loss of function (1).

As early therapeutic intervention improves long-term outcome, objective and accurate measures in the assessment of disease activity are needed for the evaluation of individual response to therapy and general efficacy of treatment in JIA (3, 4). Physical examination, even by an experienced observer, has only limited reliability (5, 6). Conventional radiography is insensitive in detecting soft tissue changes, such as synovitis which is one of the most critical hallmarks of disease activity in JIA, as well as in detecting the earliest stages of persistent erosive changes (7). Within the past 10 years, the use of magnetic resonance imaging (MRI) and advances in MRI techniques have substantially improved the evaluation of joint abnormalities in JIA patients (8, 9). Currently, MRI is considered to be the most suitable imaging technique in this respect. Although MRI has been evaluated for the standardized evaluation of wrist involvement in both JIA and rheumatoid arthritis patients (10-12), standardized measures for data acquisition and interpretation are currently not available regarding the evaluation of disease status of the knee, as the most commonly affected joint in JIA (9). Hence, this technique is under-utilized in research and clinical trials. Part of the reason for the under-utilization of MRI as an outcome measure in clinical trials in JIA relates to the lack of standardization of protocols and scales for data acquisition and interpretation, respectively, in the literature. In addition, standardized knowledge of the normal joint of interest is required as the developmental growth process of joints in pediatric patients should be taken into account and not be mistaken for a joint abnormality (9, 13). The development of an MRI outcome measure for the assessment of disease status in JIA is important and, therefore, of specific interest in the outcome measures in the rheumatology (OMERACT) group.

The utility of MRI in the assessment of JIA joint abnormalities is limited by the fact that there is no generally accepted, easy-to-use MRI scoring system for the assessment of the disease status in JIA. We set out to design a new scoring system. Because the evaluation and the weighing of certain pathological MRI features are lacking, we realized that the initial score should be broadly inclusive (14). During the current study special attention was given to the refinement of the
initial system in order to develop an easy-to-use scoring system with good inter- and intra-reader reliability. The aim of our study, therefore, is to assess the reliability and responsiveness of the newly developed Juvenile Arthritis MRI Scoring (JAMRIS) system for evaluating disease activity of the most commonly affected joint in JIA (i.e. the knee).

Materials and methods

Patients and MRI protocol

A collaborative program between two tertiary pediatric rheumatology centers was established in 2007, incorporating pediatric rheumatologists and radiologists who were experienced in the research field of imaging in JIA. Patients visited one of the outpatient clinics of these two centers. All patients fulfilled the International League of Associations for Rheumatology (ILAR) criteria for JIA (2). The indication for MRI was evaluation of disease activity before initiation or a proposed change in treatment. Exclusion criteria were: a history of intra-articular corticosteroid injection within the last 6 months, the need for anesthesia during the MRI examination, and general contraindications for MRI. The institutional review board waived informed consent for the current study, because the cases were derived from an existing MRI in the JIA study database, in which written informed consent was obtained from at least one parent of each child.

Prospectively collected MRI datasets from two substudies were integrated in this report. In substudy 1 the inter- and intra-observer reliability were assessed. MR images for the assessment of reliability were randomly selected from MRIs of clinically active knees performed between December 2008 and February 2011. In substudy 2 we evaluated the responsiveness of the JAMRIS system. MR image sets for both substudies were obtained using an open-bore 1.0-T magnet (Panorama HFO, Philips Medical Systems, Best, the Netherlands). No sedation was used and the children were placed in the supine position with the knee joint centrally in the magnetic field using a dedicated knee coil. MRI in paediatric JIA patients proved to be feasible using an open-bore system (14), and by using a dedicated knee coil an adequate signal-to-noise ratio was obtained. Contrast-enhanced MRI of the clinically most involved knee (target joint) was performed. If there were no differences in clinical activity between the knees, the right knee was considered to be the target joint. To provide an optimal discrimination between enhancing synovium and joint effusion, post contrast images were obtained in the early phase (<5 min) after intravenous injection of Gd (0.1 mg per kilogram of body weight, gadopentetate dimeglumine, Schering, Berlin, Germany) (15). See Table 1 for the acquired sequences.
Reliability and responsiveness of the JAMRIS system

Substudy 1; reliability. To evaluate the inter-observer reliability image sets of 25 JIA patients (68% female, mean age 13.7 years [SD 2.8, range 8.2–16.9 years]) were scored independently by five readers, including one reader who was not affiliated with either of the two centers. Patients had a median disease duration of 3.2 years (IQR 1.1–7.2 years). Frequency of JIA subtypes was as follows: 7 (28%) persistent oligoarthritis, 4 (16%) extended oligoarthritis, 10 (40%) polyarthritis, 2 (8%) psoriatic arthritis, and 2 (8%) enthesitis-related arthritis. Readers comprising two musculoskeletal radiologists (17, and 10 years of experience), one pediatric radiologist (4 years of experience), one radiology musculoskeletal fellow (4 years of experience), and a radiology trainee (4 years of experience). All readers were blinded to clinical history, including the duration, extent and severity of the symptoms. MR images were scored in accordance with the scoring systems as described below (JAMRIS). To analyze the intra-reader reliability, datasets of these 25 patients were evaluated twice within an interval of 6 months by two readers. To assess the feasibility of JAMRIS the duration of the scoring sessions was timed.

Substudy 2; responsiveness. To evaluate the JAMRIS system as a follow-up parameter, two readers independently evaluated the MR images of 15 consecutive JIA patients (53% female, mean age 12.4 years [SD 3.2, range 8.4–15.3 years]) with clinically active disease at baseline, and who showed clinical improvement according to the American College of Rheumatology (ACR) pediatric 50 criteria during follow-up (16). The JIA patients selected for substudy 2 had a median disease duration of 1.9 years (IQR 0.5–5.0 years). Frequency of JIA subtypes was as follows: 3 (20%) persistent oligoarthritis, 2 (13%) extended oligoarthritis, 7 (47%) polyarthritis, 1 (7%) psoriatic arthritis, 1 (7%) enthesitis-related arthritis, and 1 (7%) undifferentiated JIA. For this longitudinal exercise, images were read blinded to chronological order.

Table 1. MRI acquisitions

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Plane</th>
<th>FS</th>
<th>Gd</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>ST (mm)</th>
<th>Gap (mm)</th>
<th>FOV (mm)</th>
<th>Matrix</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 SPIR</td>
<td>Sag</td>
<td>+</td>
<td>-</td>
<td>2800–4500</td>
<td>50</td>
<td>4</td>
<td>0.4</td>
<td>150 × 150</td>
<td>300 × 242</td>
<td>3:27.6</td>
</tr>
<tr>
<td>T2 SPIR</td>
<td>Cor</td>
<td>+</td>
<td>-</td>
<td>2800–4500</td>
<td>50</td>
<td>4</td>
<td>0.4</td>
<td>150 × 150</td>
<td>300 × 247</td>
<td>5:24.8</td>
</tr>
<tr>
<td>T2 SPIR</td>
<td>Ax</td>
<td>+</td>
<td>-</td>
<td>2800–4500</td>
<td>50</td>
<td>4</td>
<td>0.4</td>
<td>150 × 150</td>
<td>300 × 270</td>
<td>5:08.0</td>
</tr>
<tr>
<td>T1 TSE</td>
<td>Sag</td>
<td>-</td>
<td>-</td>
<td>450–650</td>
<td>10</td>
<td>4</td>
<td>0.4</td>
<td>150 × 150</td>
<td>300 × 248</td>
<td>3:07.1</td>
</tr>
<tr>
<td>T1 TSE</td>
<td>Sag</td>
<td>-</td>
<td>+</td>
<td>450–650</td>
<td>10</td>
<td>4</td>
<td>0.4</td>
<td>150 × 150</td>
<td>300 × 248</td>
<td>3:07.1</td>
</tr>
<tr>
<td>T1 SPIR</td>
<td>Ax</td>
<td>+</td>
<td>+</td>
<td>400–750</td>
<td>10</td>
<td>4</td>
<td>0.4</td>
<td>150 × 150</td>
<td>272 × 192</td>
<td>2:38.3</td>
</tr>
</tbody>
</table>

SPIR: spectral presaturation inversion recovery; TSE: turbo spin echo; Sag: sagittal; Cor: coronal; Ax: axial; FS: fat saturation (+: yes; – no); Gd: IV injection of an intravenous gadolinium contrast agent (+: sequence obtained before Gd injection; –: sequence obtained after Gd injection [0.1 mmol per kilogram of body weight, gadobutrol, Bayer healthcare, Berlin, Germany]); TR: repetition time; TE: echo time; ST: slice thickness; FOV: field of view

SPIR: spectral presaturation inversion recovery; TSE: turbo spin echo; Sag: sagittal; Cor: coronal; Ax: axial; FS: fat saturation (+: yes; – no); Gd: IV injection of an intravenous gadolinium contrast agent (+: sequence obtained before Gd injection; –: sequence obtained after Gd injection [0.1 mmol per kilogram of body weight, gadobutrol, Bayer healthcare, Berlin, Germany])); TR: repetition time; TE: echo time; ST: slice thickness; FOV: field of view
Juvenile Arthritis MRI Scoring system for the knee

The Juvenile Arthritis MRI Scoring (JAMRIS) system for the knee comprises four MRI features; one soft-tissue item (synovial hypertrophy), two bone items (bone marrow changes, bone erosions) and one cartilage item (cartilage lesions). The JAMRIS system includes, therefore, two features assessing early inflammatory changes (synovial hypertrophy, bone marrow changes) and two features focusing on late destructive changes (cartilage lesions, bone erosions). An extensive overview of the JAMRIS system is depicted in Figure 1.

<table>
<thead>
<tr>
<th>Synovial hypertrophy score (maximal synovial thickness)</th>
<th>Bone marrow change score (involvement of bone volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>0-2mm</td>
</tr>
<tr>
<td>Patellofemoral</td>
<td></td>
</tr>
<tr>
<td>Suprapatellar recesses</td>
<td></td>
</tr>
<tr>
<td>Infrapatellar fat pad</td>
<td></td>
</tr>
<tr>
<td>Cruciate ligaments</td>
<td></td>
</tr>
<tr>
<td>Medial posterior condyle</td>
<td></td>
</tr>
<tr>
<td>Lateral posterior condyle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cartilage lesion score (involvement of cartilage surface area)</th>
<th>Bone erosion score (involvement of bone volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>None</td>
</tr>
<tr>
<td>Patella, medial</td>
<td></td>
</tr>
<tr>
<td>Patella, lateral</td>
<td></td>
</tr>
<tr>
<td>Femur, medial condyle</td>
<td></td>
</tr>
<tr>
<td>Femur, lateral condyle</td>
<td></td>
</tr>
<tr>
<td>Femur, medial weight-bearing region</td>
<td></td>
</tr>
<tr>
<td>Femur, lateral weight-bearing region</td>
<td></td>
</tr>
<tr>
<td>Tibia, medial tibia plateau</td>
<td></td>
</tr>
<tr>
<td>Tibia, lateral tibia plateau</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Juvenile Arthritis MRI Scoring (JAMRIS) system score form for the knee, comprising synovial hypertrophy, bone marrow changes, cartilage lesions and bone erosions

Synovial hypertrophy.

Synovial hypertrophy was defined as enhancing thickened synovium (>2 mm). 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 (adapted from Østergaard et al (11)).
The presence of synovial hypertrophy was evaluated at six sites of the knee joint: patellofemoral, suprapatellar recesses, infrapatellar fat pad, adjacent to the cruciate ligaments (ACL and PCL), and adjacent to the medial and lateral posterior condyle. Synovial thickness was scored semi-quantitatively based on the maximal thickness of any slice at each site as follows: grade 0 if <2 mm, grade 1 if ≥2–4 mm and grade 2 if >4 mm, resulting in a minimum score of 0 and a maximum score of 12 (Figure 2) (Adapted from Guermazi et al (17)).

**Figure 2.** Patellofemoral synovial hypertrophy. Axial fat-saturated contrast-enhanced T1-weighted images obtained in (a) a 13-year-old girl with a maximal synovial thickness of 0.9 mm resulting in a synovial hypertrophy score of 0 (<2 mm), (b) an 11-year-old boy with a maximal synovial thickness of 2.8 mm resulting in a synovial hypertrophy score of 1 (2–4 mm), and (c) a 17-year-old girl with a maximal synovial thickness of 6.6 mm resulting in a synovial hypertrophy score of 2 (>4 mm).

**Bone marrow changes suggestive of bone marrow edema.**

Bone marrow changes suggestive of bone marrow edema 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 (adapted from Østergaard et al (11)). The presence of bone marrow changes was scored in eight anatomical regions. The patella was divided into two regions, the medial and lateral patella on the axial view. The femur was divided into four anatomical regions; the medial and lateral condyle, and the medial and lateral weight-bearing femur. The tibia was divided into two regions: the medial and lateral tibial plateau. Bone marrow changes, suggestive of bone marrow edema, were scored semi-quantitatively based on the subjectively estimated percentage of involved bone volume at each site as follows: grade 0, none; grade 1, <10% of the whole bone volume; grade 2, ≥10–25% of the whole bone volume; grade 3, >25% of the whole bone volume, resulting in a minimum score of 0 and a maximum score of 24 (Figure 3) (adapted from Hunter et al (18)).
Figure 3. Bone marrow changes suggestive of bone marrow edema in the lateral condyle of the femur. Coronal fat-saturated T2-weighted images obtained in (a) a 15-year old girl with no bone marrow changes resulting in a bone marrow change score of 0, (b) a 12-year-old girl with bone marrow changes scored as grade 1 (<10% of whole bone volume), (c) an 11-year-old boy with bone marrow changes suggestive of bone marrow edema scored as grade 2 (10–25% of the whole bone volume), and (d) a 14-year-old boy with bone marrow changes scored as grade 3 (>25% of whole bone volume).

**Cartilage lesions.**

The cartilage was scored for the presence of lesions (superficial loss and/or thinning, or deep loss to the subchondral bone, adapted from Gyllys-Morin et al (19)) in the previously mentioned eight anatomical regions: the medial and lateral patella, the medial and lateral condyles, the medial and lateral weight-bearing femur, and the medial and lateral tibial plateau. The cartilage lesions were scored semi-quantitatively based on the subjectively estimated percentage of involved surface area at each site as follows: grade 0, none; grade 1, <10% of region of cartilage surface area; grade 2, ≥10–25% of the region of cartilage surface area; grade 3, >25% of the region of the cartilage surface area, resulting in a minimum score of 0 and a maximum score of 24 (adapted from Hunter et al (18)).

**Bone erosions.**

A bone erosion was defined as a sharply marginated bone lesion, with correct juxta-articular localization, typical signal characteristics, and visible in two planes with a cortical break in at least one plane (11). On T1-weighted images there is a loss of the normal low signal intensity of cortical bone and loss of the normal high signal intensity of trabecular bone (adapted from Østergaard et al (11)).

The presence of bone erosions was scored in the eight anatomical regions: medial and lateral patella, medial and lateral condyles, medial and lateral weight-bearing femur, and the medial and lateral tibial plateau. The bone erosions were scored semi-quantitatively based on the subjectively estimated percentage of involved bone volume at each site as follows: grade 0, none; grade 1, <10% of the whole bone volume; grade 2, ≥10–25% of the whole bone volume; grade 3, >25% of the whole bone volume, resulting in a minimum score of 0 and a maximum score of 24 (adapted from Hunter et al (18)).
Statistics
Descriptive statistics were reported in terms of percentages, means, ranges and standard deviations (SD). The Kruskal–Wallis test was used to analyze differences between groups/scores. The Wilcoxon signed ranks test was used to analyze differences within groups. Both tests assumed a two-tailed probability and a $P$ value of less than 0.05 indicated a significant difference. Because the sum of scores were considered to be continuous data, the single measure intraclass correlation coefficient (ICC) was used to analyze inter- and intra-reader reliability, and was classified as follows: ICC $<0.40 =$ poor, $0.40–0.60 =$ moderate, $0.60–0.80 =$ substantial and $>0.80 =$ good reliability. To assess the responsiveness of the JAMRIS system, the differences between time point A and time point B 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 $<0.40 =$ poor, $0.40–0.60 =$ moderate, $0.60–0.80 =$ substantial and $>0.80 =$ good effect (20). All data were analyzed by using SPSS version 16.0 (SPSS, Chicago, ILL, USA). Statistical analyses were performed in close collaboration with a clinical epidemiologist.

Results
Inter-reader reliability
When the scores of the five readers were compared, there were no significant differences for synovial hypertrophy ($P = 0.930$), bone marrow changes suggestive of bone marrow edema ($P = 0.782$), cartilage lesion ($P = 0.937$) or bone erosion scores ($P = 0.943$) (Table 2). Consequently, inter-reader reliability was good for all features (ICC 0.86–0.95) (Table 2). ICCs for synovial hypertrophy 0.95 (95% CI 0.91–0.97), bone marrow changes 0.86 (95% CI 0.77–0.93), cartilage lesions 0.91 (95% CI 0.85–0.96) and bone erosions 0.88 (95% CI 0.80–0.94) were good.
Table 2. Reliability of synovial hypertrophy, bone marrow changes, cartilage lesion and bone erosion scores from 25 juvenile idiopathic arthritis (JIA) patients with MRI of the knee

<table>
<thead>
<tr>
<th></th>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Reader 3</th>
<th>Reader 4</th>
<th>Reader 5</th>
<th>P valueb</th>
<th>ICCc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial hypertrophy (0–12)</td>
<td>3.68 (0–12)</td>
<td>4.28 (0–12)</td>
<td>4.52 (0–12)</td>
<td>3.68 (0–12)</td>
<td>4.00 (0–11)</td>
<td>0.930</td>
<td>0.95 (95% CI 0.91–0.97)</td>
</tr>
<tr>
<td>Bone marrow changes (0–24)</td>
<td>1.20 (0–7)</td>
<td>1.28 (0–6)</td>
<td>1.80 (0–9)</td>
<td>1.52 (0–7)</td>
<td>1.16 (0–7)</td>
<td>0.782</td>
<td>0.86 (95% CI 0.77–0.93)</td>
</tr>
<tr>
<td>Cartilage lesions (0–24)</td>
<td>0.48 (0–5)</td>
<td>0.52 (0–6)</td>
<td>0.60 (0–6)</td>
<td>0.52 (0–5)</td>
<td>0.56 (0–3)</td>
<td>0.937</td>
<td>0.91 (95% CI 0.85–0.96)</td>
</tr>
<tr>
<td>Bone erosions (0–24)</td>
<td>0.16 (0–1)</td>
<td>0.24 (0–2)</td>
<td>0.20 (0–2)</td>
<td>0.24 (0–2)</td>
<td>0.16 (0–2)</td>
<td>0.943</td>
<td>0.88 (95% CI 0.80–0.95)</td>
</tr>
</tbody>
</table>

a Values are means (min–max)
b P values indicate differences between readers (Kruskal–Wallis test)
c Single measure intraclass correlation coefficient
Intra-reader reliability

Intra-reader reliability was good for all scored items. Single measure ICCs for both readers were as follows: synovial hypertrophy 0.99 (95% CI 0.98–1.00) and 1.00 (95% CI 0.99–1.00), bone marrow changes 0.96 (95% CI 0.93–0.98) and 0.97 (95% CI 0.93–0.99), cartilage lesions 0.99 (95% CI 0.97–0.99) and 0.98 (95% CI 0.96–0.99), bone erosions 0.92 (95% CI 0.83–0.96) and 1.00 (95% CI 1.00–1.00), respectively.

Feasibility

The scoring took an acceptable median of 6.6 (SD 1.5) minutes per patient, indicating good feasibility of the JAMRIS system. The scoring duration ranged from 4.8 minutes per patient for reader 2 to 8.4 minutes per patients for reader 3.

Responsiveness

All JIA patients were treated for 12 months or longer with a disease-modifying anti-rheumatic drug (DMARD) and/or a TNF-α blocker. Actual scores were obtained at time point A and again at time point B after a median follow-up time of 1.4 years (IQR 1.2–1.7) (Table 3). A statistically significant decrease concerning synovial hypertrophy scores (mean 1.1) was observed between time points (P < 0.001). The responsiveness of the JAMRIS system showed a substantial effect regarding change in synovial hypertrophy scores (SRM = -0.65). No change was seen in bone marrow change (SRM = -0.15), cartilage lesion and bone erosion scores. Regarding the inter-reader reliability of the status scores (time points A and B) the ICCs were good for all items: 0.89–1.00 and 0.87–1.00, respectively. ICCs for the status scores (time points A and B) were as follows: synovial hypertrophy 0.96 (95% CI 0.90–0.99), 0.92 (95% CI 0.76–0.97); bone marrow changes 0.89 (95% CI 0.66–0.96), 0.87 (95% CI 0.60–0.96); cartilage lesions 1.00 (95% CI 1.00–1.00), 1.00 (95% CI 1.00–1.00); bone erosions 1.00 (95% CI 1.00–1.00), 1.00 (95% CI 1.00–1.00), respectively.
Table 3. Mean (range) status scores of 15 JIA MRIs at time point A and the change scores for each reader

<table>
<thead>
<tr>
<th>Reader No.</th>
<th>1</th>
<th>2</th>
<th>Mean of Readers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Synovial hypertrophy (0-12)</td>
<td>1.7 (0–9)</td>
<td>1.5 (0–7)</td>
</tr>
<tr>
<td></td>
<td>Bone marrow changes (0–24)</td>
<td>0.5 (0–3)</td>
<td>0.5 (0–4)</td>
</tr>
<tr>
<td></td>
<td>Cartilage lesions (0–24)</td>
<td>0.0 (0–0)</td>
<td>0.0 (0–0)</td>
</tr>
<tr>
<td></td>
<td>Bone erosions (0–24)</td>
<td>0.0 (0–0)</td>
<td>0.0 (0–0)</td>
</tr>
<tr>
<td>Change scores</td>
<td>Synovial hypertrophy</td>
<td>-1.2 (-7–1)</td>
<td>-0.9 (-5–1)</td>
</tr>
<tr>
<td></td>
<td>Bone marrow changes</td>
<td>-0.2 (-2–2)</td>
<td>-0.2 (-3–2)</td>
</tr>
<tr>
<td></td>
<td>Cartilage lesions</td>
<td>0.0 (0–0)</td>
<td>0.0 (0–0)</td>
</tr>
<tr>
<td></td>
<td>Bone erosions</td>
<td>0.0 (0–0)</td>
<td>0.0 (0–0)</td>
</tr>
</tbody>
</table>

Discussion

This paper describes the developmental process and the reliability of a standardized Juvenile Arthritis MRI Scoring (JAMRIS) system for the knee. Our study shows good reliability in terms of ICC for the different items scored, which supports the applicability of JAMRIS as an objective, simple and accurate outcome measure in future research and clinical trials in the evaluation of JIA disease status of the knee.

Since the development of highly effective therapies for rheumatic diseases, the main goal of treatment consists of complete suppression of joint inflammation to prevent destructive changes. Therefore, outcome measures in clinical trials should comprise sensitive and reliable measures of inflammation (9). Contrast-enhanced MRI is the most suitable imaging technique to date for serving this purpose by accurately detecting synovial hypertrophy, one of the most critical hallmarks of disease activity in JIA. Furthermore, it is the only technique able to visualize bone marrow changes suggestive of bone marrow edema (19). In rheumatoid arthritis it has been shown that both synovial hypertrophy and bone marrow edema are key predictors of early erosive joint damage. Currently, these are considered the most sensitive MRI features for monitoring disease activity (21-24). Prolonged disease activity may ultimately lead to cartilage and bone damage which are responsible for most disability in JIA (25, 26). Apart from synovial hypertrophy and bone marrow edema, cartilage lesions and bone erosions were also included in JAMRIS to monitor the presence and deterioration of damage to the knee.
The inter-reader reliability of the scored items was good for all MRI features (ICCs 0.86–0.95). This is a promising and strong characteristic of the JAMRIS system because of the fact that readers had variable levels of experience (from 4 to 17 years of experience in musculoskeletal radiology) in the evaluation of MR images of JIA patients, and the MRI datasets were scored completely separately. The reliability scores for the knee are comparable to values seen in reliability studies regarding JIA and rheumatoid arthritis MRI scores of the wrist (10, 27). In the development of the JAMRIS system, we primarily focused on early-stage JIA disease activity. The JAMRIS scale for bone marrow changes, cartilage lesions and bone erosions affecting < 25% of the surface area / bone volume is, therefore, more sensitive to change compared to the rough division used in current JIA and rheumatoid arthritis MRI scores of the wrist (10, 11). Our data regarding the JAMRIS system as a follow-up parameter suggest that the scoring system is able to measure change in articular disease activity in longitudinal settings. High reliability and sensitivity to change were observed for synovial hypertrophy (ICC = 0.92; SRM = -0.65). However, it should be noted that – contrary to synovial hypertrophy – there was no such absolute change in bone marrow, cartilage lesion and bone erosion scores between time points. The presence of bone marrow changes is an important predictor of early erosive joint damage in rheumatoid arthritis (21, 22), though its prognostic value in JIA has never been assessed. The clinical relevance of presence of bone marrow changes in pediatric JIA patients is therefore unclear and might be unrelated to JIA disease activity but part of the joint development or the patient's mobility (sports) instead.

There is a degree of histopathological variation of the synovial membrane in knees of patients with active arthritis (28). Further, it is common practice to evaluate not one but several regions of the joint in the most accepted scoring systems concerning the evaluation of joint abnormalities (11, 18, 29-31). The knee was divided accordingly into six or eight easy-to-use regions for the evaluation of inflammation and damage. Although synovial volume has greater sensitivity than maximal synovial thickness in the assessment of clinical synovitis, synovial thickness is more practical to use because it can be easily measured, requires no post-processing and correlates well with synovial volume (19). Therefore, the enhancing synovial membrane was scored semi-quantitatively based on the maximal thickness in millimeters in any slice at each site, to ensure that the JAMRIS system would be a sensitive yet reader-friendly measurement tool.

Several advanced MRI techniques are available for the evaluation of inflammatory and destructive changes in JIA, including dynamic contrast-enhanced MRI (DCE-MRI), T2-mapping, diffusion weighted MRI (DWI), and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) (32, 33).
Currently, these imaging techniques are used particularly in the context of research and to a lesser extent in daily practice. Moreover for the interpretation and post-processing of these images specialized knowledge is needed. At this moment, advanced imaging techniques are, therefore, not valuable for the use in an easy-to-use scoring method such as the JAMRIS system.

Radiography of bilateral joints is considered to be of great importance in the assessment of damage and growth disturbances in both JIA and RA (26, 30). MRI of both knees is feasible in pediatric JIA patients (14). Current limiting factors in the MRI examination of bilateral joints include the reduction of resolution when both joints undergo imaging together or an increase in imaging time when joints undergo imaging separately. Moreover, only one joint can undergo imaging with contrast enhancement. Despite practical limitations, the JAMRIS system could provide more complete information when both knees are scored. The additional value of MRI of bilateral knees in the evaluation of disease status in JIA patients is being addressed in an ongoing study.

A limitation of our study is the lack of MR images of age-matched healthy controls. Because growing joints mature, it may be difficult to establish whether differences in the appearance of the knee joint are pathological or part of normal maturation. For instance, the prevalence of bony depressions and signal changes suggestive of bone marrow edema in the wrists and knees of healthy children is high (13, 34).

In summary, the JAMRIS system was developed and validated for the evaluation of inflammatory and destructive changes in the knees of JIA patients. It proved to be an easy-to-use and reliable assessment score in the evaluation of JIA disease activity in terms of inflammation and damage, and may therefore be used as an objective outcome measure in future research and clinical trials. The use of JAMRIS as a follow-up parameter for synovial hypertrophy is promising. More follow-up data in JIA will be needed to assess the reliability concerning a change in bone marrow change, cartilage lesion and bone erosion scores over time.
References


