# Juvenile idiopathic arthritis and the temporomandibular joint: a case–control study of magnetic resonance imaging findings in relation to clinical and psychosocial factors

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## Abstract

**Aim** In juvenile idiopathic arthritis (JIA), the temporomandibular joint (TMJ) is a particularly challenging joint to assess both clinically and with imaging. The aim of this article is to investigate TMJ magnetic resonance imaging (MRI) findings in relation to clinical and psychosocial factors in patients with JIA and healthy individuals related to TMJ arthritis in JIA.

**Material and methods** In total, 45 patients (6–16 years) with JIA and 16 healthy age- and sex-matched controls were examined according to the diagnostic criteria for temporomandibular disorders (DC/TMD). The subjects answered questionnaires about psychosocial factors (pain intensity, pain-related disability, depression, stress, catastrophising, pain locations, and jaw function) and underwent bilateral MRI of the TMJ.

**Results** There were no significant differences between JIA patients and healthy individuals in any of the TMJ MRI findings. Moderate/severe changes among JIA patients were found only for effusion, synovial thickening, condylar flattening, and erosion, with no moderate/severe changes in healthy individuals. In JIA patients, orofacial pain intensity was related to TMJ bone marrow oedema, and pain in jaw muscles during jaw function was related to TMJ bone marrow oedema and erosion. There were no significant correlations between psychosocial aspects and MRI findings.

**Conclusions** This study indicates a substantial overlap of TMJ MRI findings in both the inflammatory domain and the damage domain between JIA patients and healthy individuals. In JIA patients, the inflammatory MRI sign of bone marrow oedema seems to influence orofacial pain intensity.

KEYWORDS Juvenile idiopathic arthritis; Magnetic resonance imaging; Orofacial pain; Psychosocial factors; Temporomandibular joint.

## Introduction

Juvenile idiopathic arthritis (JIA) is characterised by joint and systemic inflammation with an onset before 16 years of age [Petty et al., 2004]. In a recent population-based study in Sweden, the incidence rate of JIA was estimated to be 12.8/100,000 in children under the age of 16 years [Berthold et al., 2019]. Between 40% and 96% of children with JIA develop temporomandibular joint (TMJ) arthritis [Cannizzaro et al., 2011; Stoll et al., 2018b]. TMJ arthritis is often pain-free in JIA and difficult to diagnose clinically. Crepitus, stiffness, and restricted mouth opening are associated with TMJ arthritis. TMJ inflammation can lead to cartilage and articular bone destruction resulting in mandibular growth disturbances and facial asymmetry [Stoustrup et al., 2019]. However, only weak relations have been found between clinical signs and symptoms versus radiological findings in general [Kristensen et al., 2016]. In a magnetic resonance imaging (MRI) study of 50 JIA patients, TMJ damage was associated with reduced function but not with TMJ pain [Rongo et al., 2019].

Psychosocial factors such as coping with pain, anxiety and depression may also influence pain, course of the disease (seen in rheumatoid arthritis patients), and outcome of therapy [Nerurkar et al., 2019; Kuijper et al., 2018]. Depression and anxiety in JIA children are often similar to what reported for other chronic childhood diseases, although at higher rates than in healthy children [Fair et al., 2019]. JIA has been found to be associated with psychological distress, jaw dysfunction, and loss of daily living activities. Systemic inflammatory activity appears to be an important contributor to orofacial pain in JIA [Dimitrijevic Carlsson et al., 2019].

Therefore, the aims of this study were to: 1) compare TMJ MRI findings in JIA patients and age- and sex-matched healthy control individuals, and 2) investigate the correlations between MRI findings in JIA patients and the clinical and psychosocial factors as determined through standardised diagnostic criteria for temporomandibular disorders. We hypothesised that there would be significant differences between the JIA patients and the controls in MRI findings in the TMJs and that there would

| | | PATIENTS | | | | | HEALTHY INDIVIDUALS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Percentiles | | | | | Percentiles | | | | |
| | | Median | 25th | 75th | %pos | n | Median | 25th | 75th | % pos | n |
| Individuals | | | | | | | | | | | |
| Age | years | 12 | 10 | 15 | | 45 | 13 | 10 | 13 | | 16 |
| Gender | male/female | | | | | 12/33 | | | | | 5/11 |
| Age at diagnosis | years | 9 | 5 | 12 | | 45 | n.a. | | | | |
| Disease duration | years | 4 | 3 | 7 | | 45 | n.a. | | | | |
| Disease activity | | | | | | | | | | | |
| JADAS71 | 0-101 | 6.0 | 2.8 | 9.8 | | 45 | n.a. | | | | |
| Erythrocyte sedimentation rate* | mm | 6 | 3 | 10 | | 45 | 0 | 0 | 0 | | 16 |
| C-reactive protein* | mg/L | 0 | 0 | 0 | 9 | 45 | 0 | 0 | 0 | 0 | 16 |
| Rheumatoid factor | IU/mL | 0 | 0 | 0 | 9 | 45 | 0 | 0 | 0 | 0 | 16 |
| Anti-citrullinated antibodies | U/mL | 0 | 0 | 0 | 9 | 43 | 0 | 0 | 0 | | 16 |
| DC/TMD diagnoses | | | | | | | | | | | |
| Myalgia | n | | | | | 10 | | | | | 1 |
| Myofascial pain with referral | n | | | | | 2 | | | | | 0 |
| Arthalgia | n (joints) | | | | | 8 | | | | | 0 |
| Headache attributed to TMD | n | | | | | 3 | | | | | 0 |
| Combinations from above | | | | | | | | | | | 0 |
| Myalgia and arthralgia | n | | | | | 2 | | | | | 0 |
| Myalgia, arthralgia and headache | n | | | | | 2 | | | | | 0 |

TABLE 1 Demographic data, disease activity and temporomandibular disorder diagnoses for 45 patients with juvenile idiopathic arthritis and 16 age-and sex-matched healthy individuals
n = number of observations; n.a. = not applicable. JADAS71 = 71-joint Juvenile Arthritis Disease Activity Score; DC/TMD = diagnostic criteria for temporomandibular disorders. *Normal values for ESR (<30 mm/h) and CRP (<5 mg/L) were counted as 0.

be significant correlations between MRI findings and clinical and psychological factors in JIA patients.

## Materials and methods

### Subjects

The JIA patients included in this study were consecutively referred from four paediatric departments in southeast Sweden (Linköping University Hospital, Vrinnevi Hospital/Norrköping, Motala Hospital, and Västervik Hospital) to the Center of Oral Rehabilitation in Linköping between 2015 and 2018 (Table 1). The study included 45 JIA patients (33 girls and 12 boys). Sixteen healthy age- and sex-matched children were recruited among recall patients at the Public Dental Health Clinics in Linköping to serve as controls.

This study was approved by the Regional Ethics Review Board in Linköping, Sweden (2014/461-31). All subjects and parents received verbal and written information about the study and signed an informed consent form before enrollment.

Inclusion criteria were age between 6 and 16 years and a JIA diagnosis according to the 2004 ILAR classification criteria [Petty et al., 2004]. Exclusion criteria for all individuals were diabetes mellitus, inflammatory bowel disease, chronic pain conditions other than JIA, and psychiatric diseases (other than depression and/or anxiety).

The JIA diagnoses included 19 patients (43%) with oligoarthritis, 15 (33%) with polyarthritis, and 11 (24%) with other subtypes of JIA (systemic arthritis, psoriatic arthritis, enthesitis-related arthritis, or undifferentiated arthritis). Sixteen (36%) of JIA patients were positive for antinuclear antibodies (ANA). The patient sample was representative of JIA patients in Scandinavia [Berntson et al., 2003]. Five patients were HLA-B27-positive. At inclusion, 41 patients had ongoing pharmacological therapy for their JIA, 27 of whom had treatment with disease-modifying anti-rheumatic drugs; 5 had methotrexate only, 7 methotrexate in combination with biologics (adalimumab or etanercept), and 3 biologics alone; 31 patients had been prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and six were on oral corticosteroid therapy (prednisolone).

### MR imaging of the TMJ

All individuals underwent MRI of the TMJs at a median of 68 days (25th/75th percentiles: 46/106, maximum value: 266 days) after the clinical examination. MR imaging was performed at Linköping University Hospital using a 1.5T Achieva dStream unit (Philips Medical Systems, Best, the Netherlands) with flexible coils centred over the TMJ. An axial T1-weighted localiser was used to orient the long axis of the condyle in the closed-mouth position. Sagittal proton- and T2-weighted images were obtained perpendicular to the long axis of the condyle in the closed-mouth position. Proton-weighted sagittal images were also obtained in the open-mouth position. Coronal images were obtained parallel to the long axis with proton-weighted, T2-weighted, and short tau inversion recovery (STIR) sequences.

In the present study, contrast-enhanced MRI was not used due to several reasons like anxiety, stress as well as the potential risks related to invasive procedures on healthy controls. Moreover, our ethical permission did not allow contrast-enhanced MRI in healthy individuals. This is in line with a recent study evaluating the association between MRI findings and TMJ pain [Eriksen et al., 2020]. The JIA patients received three MRI examinations over two years. Moreover, the toxic contrasting agents used in gadolinium-enhanced

| Domains | Definition | Grading |
|---|---|---|
| Inflammatory domain | | |
| Bone marrow oedema | Compared to the mandibular ramus, hyperintense marrow signaling within the condyle on fluid-sensitive images, and/or hypointense signaling on T1 weighted images without fat saturation. | Absent or present |
| Joint effusion | Increased joint fluid with isointense signaling of joint space compared to that of cerebrospinal fluid on fluid-sensitive images | Absent: ≤1mm fluid<br>Small: >1 and ≤2mm fluid or involving entire joint<br>Large: ≥2mm fluid |
| Synovial thickening | Thickened synovial lining of the TMJ with intermediate signal on fluid-sensitive images | Absent<br>Mild: >1mm and ≤2mm thickness<br>Moderate/severe: >2mm thickness |
| Damage domain | | |
| Condylar flattening | Loss of the round or slightly angular shape of the condylar head, viewed in the sagittal-oblique plane | Absent<br>Mild: flattening involves part of the surface<br>Moderate/severe: flattening involves entire surface or loss of height |
| Erosions | Any irregularity or break of the bony joint surface leading to the loss of the smooth continues outline of the bone | Absent<br>Mild: presence of irregularities involving part of the condylar surface<br>Moderate/severe: presence of deep breaks in the subchondral bone seen in two planes, or irregularities involving the entire articulating |
| Disc abnormalities | Any abnormality of the articulating disc, including flattening, displacement or destruction | Absent or present |

TABLE 2 Assessment protocol for evaluation of temporomandibular joint changes on magnetic resonance imaging.

MRI present a risk [Rozenfeld and Podberesky, 2018]. Clinical practice at the Center for Oral Rehabilitation avoids using intravenous contrast agents for MR imaging due to the reasons stated above.

We decided to include healthy individuals for the MRI examination in this study, mainly because there is little knowledge available about TMJ MRI findings in otherwise healthy people. Indeed, available knowledge points to the presence of MRI findings in the inflammatory and damage domains [Tolend et al., 2018] in healthy individuals, which makes it important to include these subjects to fulfil the aim of discovering significant differences between JIA and control findings. We obtained ethical approval to include healthy children in a single MRI examination.

Two observers, maxillofacial radiologists with more than 15 years of experience evaluating TMJ MR images, evaluated all 61 MRI examinations (122 TMJs). Before assessing the MR images the observers calibrated themselves to definitions of imaging characteristics and to the presence and severity of change by evaluating 10 TMJ MRI examinations in adolescents (20 TMJs) randomly selected from the Department of Radiology, Linköping (Sweden) which were not included in the study.

The 61 MRIs included in the study were then evaluated individually and formed the basis for calculations of interobserver reliability. When the observers' assessments differed, consensus was reached through discussion to produce the results used for statistical analysis.

After four months, the MR images were re-evaluated, which formed the basis for calculation of the intraobserver reliability. In all evaluations, the observers were blinded to any information regarding case history and clinical status.

The protocol for interpretation of the images, a modified image scoring system developed by Tolend et al. [2018], established a score for the three conditions in the inflammatory and damage domains, as listed in Table 2. In the inflammatory domain, all conditions were categorised as absent or present. Joint effusion was scored as small or large and synovial thickening was scored as mild or moderate/severe. The three conditions in the damage domain were also categorised as absent or present, with condylar flattening and erosion further classified as mild or moderate/severe. MR images of healthy individuals and the imaging protocol sequences are shown in Figure 1. MR images of JIA patients demonstrating findings and severity in the inflammatory and damage domains are shown in Fig. 2.

### Clinical examination

The diagnostic criteria (DC) for temporomandibular disorders (TMD) were used to diagnose the patients. The DC/TMD comprise two domains: Axis I for physical diagnoses and Axis II for several domains concerning pain and its consequences [Schiffman et al., 2014]. The applied clinical examination corresponds well to the consensus-based recommendations for clinical orofacial examination in JIA, except for examination of craniofacial deformations, which were not assessed in the present study [Stoustrup et al., 2017]. The clinical examination for Axis I diagnostics requires a pain history assessed on a questionnaire and a well-defined and structured clinical examination. Clinical assessments evaluate familiar pain localisations, jaw movement capacity (lateral, protruding, and mouth opening), familiar jaw movement pain, TMJ noises, and familiar pain upon palpation of the masticatory muscles and TMJ. The criteria for DC/TMD Axis I diagnoses are validated for patients aged 18 years and older, and they comprise TMJ arthralgia, masticatory muscle myalgia, headache attributed to TMD, degenerative joint disease, and TMJ disk displacements. Multiple diagnoses are allowed in DC/TMD.

DC/TMD Axis II is based on validated questionnaires and interpretation guidelines including instruments to assess the impact of the pain on general, work-related, and social activities, jaw function, and psychosocial functioning and distress. All JIA patients and healthy individuals were examined

by one dentist (ADC) calibrated in the clinical and research use of DC/TMD by the DC/TMD Training and Calibration Center at the Department of Orofacial Pain and Jaw Function, Faculty of Odontology, Malmö University, Sweden. All participants completed the questionnaires before the clinical examination. Participants who were 12 – 16 years of age answered all questions. Questions about stress and catastrophising were not answered by children younger than 12 years of age.

A detailed description and appropriate references to each instrument of the questionnaires used in this study are available in a publication by Dimitrijevic Carlsson et al. [2019]. In brief, pain intensity and pain-related disability

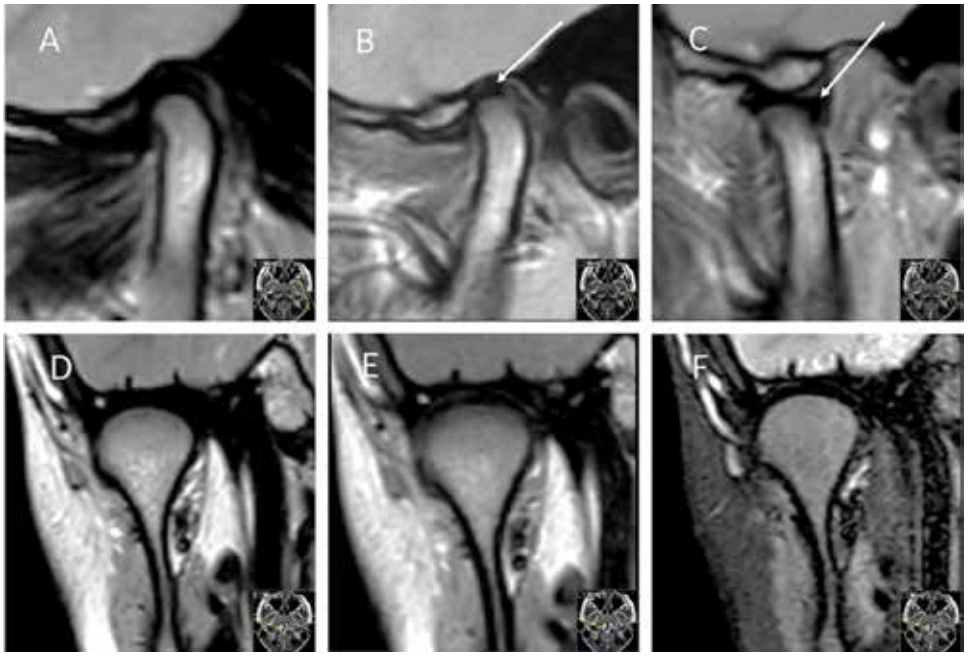


FIG. 1 MR images of a healthy control subject, demonstrating the image protocol sequences used. Upper row: A. T2WI of the TMJ in the closed-mouth oblique sagittal plane. B. PDWI of the TMJ in the closed-mouth oblique sagittal plane. C. PDWI of the TMJ in the open-mouth oblique sagittal plane. Arrows indicate the position of the posterior part of the disk. Lower row: D. T2WI of the TMJ in the closed-mouth oblique coronal plane. E. PDWI of the TMJ in the closed-mouth oblique coronal plane. F. STIR image of the TMJ in the closed mouth oblique coronal plane.
T2WI, T2 – weighted image; PDWI, proton density weighted image; STIR, short tau inversion recovery.

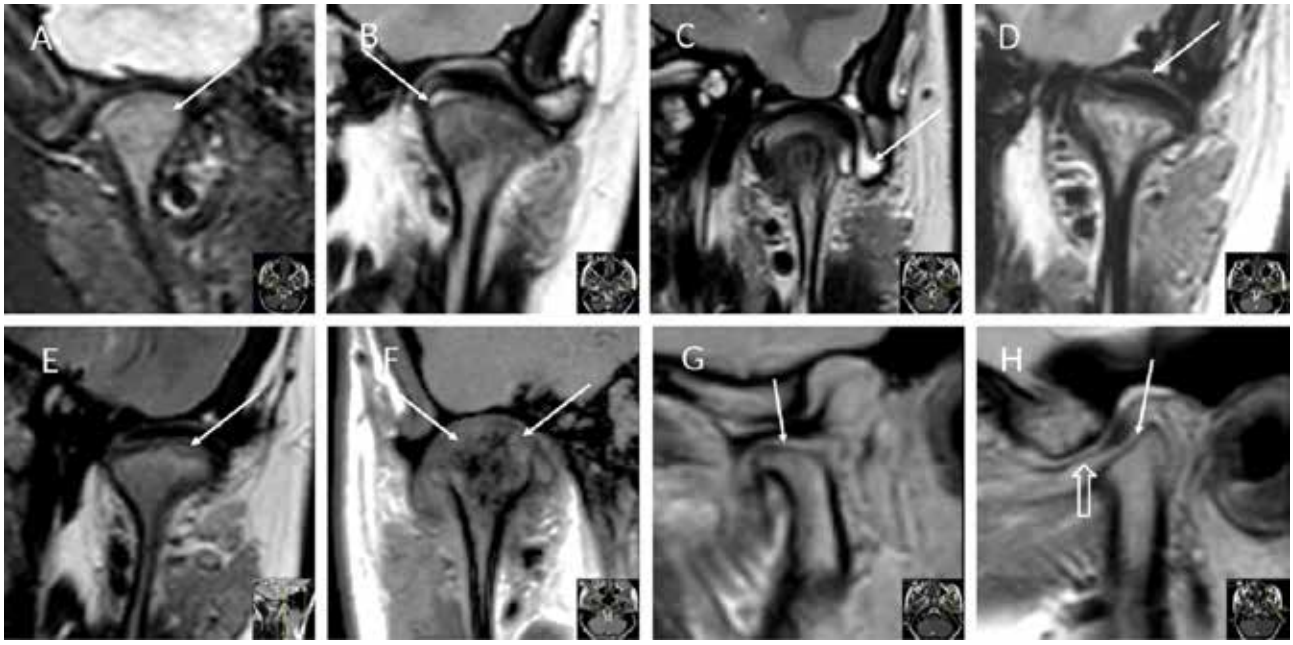


FIG. 2 MR images of JIA patients, demonstrating examples of the different findings and grades. Arrows indicate the findings.
Upper row: Images A-D demonstrate findings in the inflammatory domain. A. STIR image in the closed-mouth oblique coronal plane exhibiting bone marrow oedema in the TMJ condyle. B. T2WI in the closed-mouth oblique coronal plane exhibiting a small amount of joint effusion. C. T2WI in the closed-mouth oblique coronal plane exhibiting a large amount of joint effusion. D. T2WI in the closed-mouth oblique coronal plane exhibiting moderate synovial thickening.
Lower row: Images E-H demonstrate findings in the damage domain. E. T2WI in the closed-mouth oblique coronal plane exhibiting mild erosion of the condyle. F. PDWI in the open-mouth oblique coronal plane exhibiting severe erosion of the condyle. G. PDWI in the open-mouth oblique sagittal plane exhibiting mild flattening of the condyle. H. T2WI in the closed-mouth oblique sagittal plane exhibiting severe flattening of the TMJ condyle. The open arrow indicates the disk anterior to the TMJ condyle.
T2WI, T2 – weighted image; PDWI, proton density weighted image; STIR, short tau inversion recovery.

were assessed with the Graded Chronic Pain Scale (GCPS). The two GCPS subscales used in the current research were characteristic pain intensity and pain-related disability. Jaw function limitation was assessed using the Jaw Functional Limitation Scale (JFLS-8), including eight items regarding jaw function (jaw mobility, mastication, and verbal and emotional expression), graded separately by the patients on an 11-point scale (from no limitation to severe limitation). The four-item Patient Health Questionnaire (PHQ–4) was used to assess the degree of symptoms associated with depression and anxiety. There are established cut-off limits for "normal", "mild", "moderate", and "severe" degrees of symptoms from depression and anxiety. The Pain Catastrophizing Scale (PCS) was used to assess the degree of catastrophising (a cognitive distortion that prompts an individual to jump to the worst possible conclusion, usually with very limited information or objective reason to despair) and includes three subscales: rumination, magnification, and helplessness (total score range of 0–52). The 10-item Perceived Stress Scale (PSS-10) was used to assess the degree of stress. High scores correlate to high levels of perceived stress. The disease-specific Childhood Health Assessment Questionnaire (CHAQ) was used to assess functional ability in daily life activities for children with JIA. CHAQ is designed to capture the physical and psychosocial well-being of children with JIA.

Venous blood samples were obtained to assess markers of disease activity, i.e., erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anti-nuclear antibodies (ANA), and anti-cyclic citrullinated peptide antibodies (anti-CCP). The Juvenile Arthritis Disease Activity Score-71 (JADAS-71) was calculated based on active joint count (number of joints among 71 pre-defined joints with either swelling, palpation pain, or both), physician's global assessment, parental global evaluation, and erythrocyte sedimentation rate [Consolaro et al., 2009].

### Statistical methods

Non-parametric statistical analysis of the data was performed. For descriptive statistics, median, 25th, and 75th percentiles were reported. For analytical statistics, the Mann-Whitney U-test was used to calculate the significance of differences between groups. $P < 0.05$ was considered significant. The Cohen Kappa coefficient was calculated for inter- and intra-observer agreement [Landis and Koch, 1977]. Interpretation of the Kappa coefficients were made according to the following intervals: < 0.00 "Poor"; 0.01 to 0.20 "Slight"; 0.21 to 0.40 "Fair"; 0.41 to 0.60 "Moderate"; 0.61 to 0.80 "Substantial" and 0.81 to 1.00 "Almost Perfect"[Landis and Koch, 1977] .The Spearman ranked correlation test was used to calculate the significance of correlations between variables. All calculations were performed with Stata 15.1 Special Edition software (StataCorp, College Station, TX, USA). A correction for multiple testing was performed for the results from the correlations tests and $P < 0.02$ was therefore considered significant.

## Results

### TMJ MRI findings in JIA patients and healthy individuals

The distribution and grading of MRI findings in the patients with JIA and healthy individuals is shown in Figure 3 and Table 3. No significant differences were observed between JIA patients and healthy individuals in any of the TMJ MRI findings.

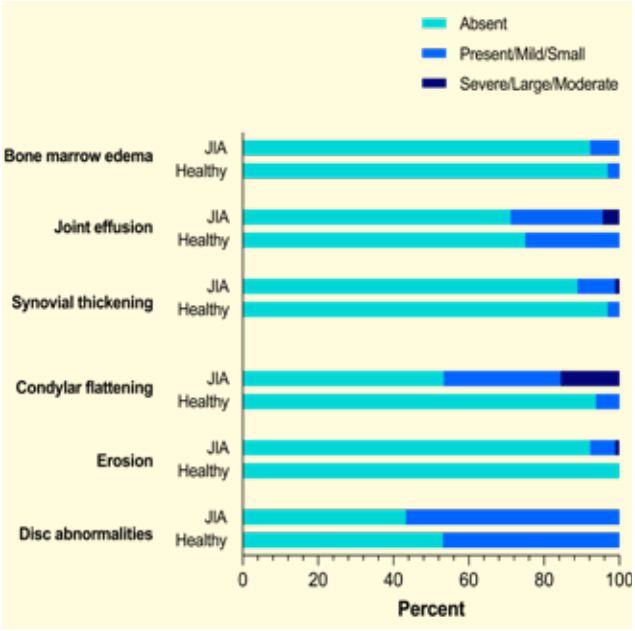


FIG. 3 Presence and severity of temporomandibular joints with magnetic resonance imaging findings in 45 patients with juvenile idiopathic arthritis and 16 healthy individuals. See Table 2 for definition of the criteria for the categories of evaluation. No significant differences were observed between patients and healthy individuals for any of the conditions in the inflammatory and damage domains.

Moderate/severe changes were found only in JIA patients and for effusion, synovial thickening, condylar flattening, and erosion. Healthy individuals did not exhibit any moderate/severe TMJ changes.

Among the 45 JIA patients, 28 of the 90 TMJs (31%) had at least one finding in the inflammatory domain. Ten of the 32 TMJs (31%) in the 16 healthy individuals had at least one finding in the inflammatory domain (Fig. 3).

### Relationships between clinical, psychosocial, and MRI findings in JIA patients

Table 4 shows the clinical and psychosocial variables in JIA patients and healthy individuals. There were no statistically significant differences between JIA patients and healthy individuals regarding these variables. In addition, there were no statistically significant differences between JIA patients with or without presence of MRI signs in the inflammatory or damage domains for maximum mouth opening, TMJ pain on maximum mouth opening, masticatory muscle pain on jaw movement, number of sites with referred pain, characteristic orofacial pain intensity, jaw function limitation scale, pain-related disability, depression and anxiety, stress, catastrophising, or activity of daily living limitation.

Table 5 shows significant correlations between clinical findings and the severity of the MRI findings in the JIA patients. There were significant correlations between masticatory muscle pain on maximum mouth opening and severity of erosion and between C-reactive protein and severity of erosion. Figure 4 illustrates the significant correlation of characteristic orofacial pain intensity (0–10 numerical rating scale) in JIA patients with the presence of TMJ bone marrow oedema in the 45 JIA patients ($p = 0.020$).

There were no statistically significant relationships between psychosocial variables and MRI findings.

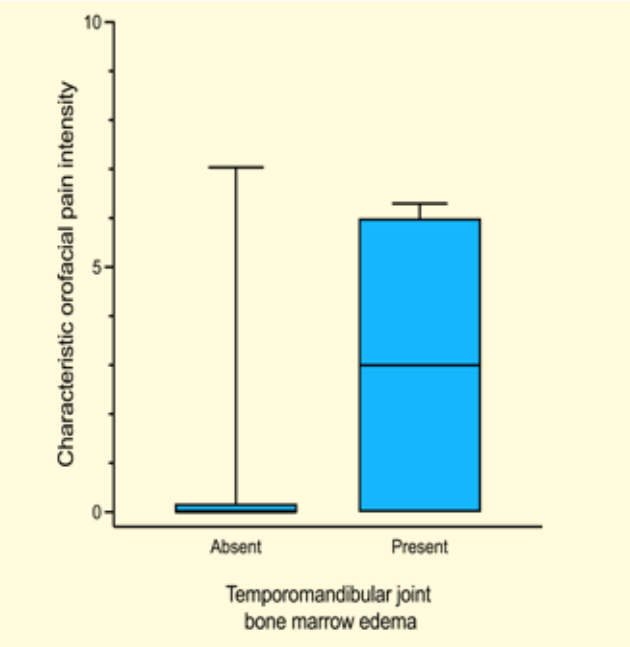


FIG. 4 Box-plot showing the characteristic orofacial pain intensity (0-10 numerical rating scale) in patients with and without presence of temporomandibular joint bone marrow oedema (according to magnetic resonance imaging) in 45 patients with juvenile idiopathic arthritis.

### Intra- and interobserver agreement for magnetic resonance imaging findings

The inter-observer Kappa values ranged from slight (0.15) to moderate (0.56) and the intra-observer Kappa values ranged from fair (0.33) to almost perfect (0.88).

## Discussion

This study indicates a substantial overlap of TMJ MRI findings in both the inflammatory domain and the damage domain between JIA patients and healthy individuals, with no significant differences between the groups in any of the six conditions that were evaluated. In JIA patients, the inflammatory MRI sign of bone marrow oedema seems to influence orofacial pain intensity.

MRI findings of abnormalities in the inflammatory domain and damage domain seemed to be as prevalent in healthy individuals as in JIA patients. This similarity has been shown before. MRI findings consistent with minimally active TMJ arthritis were found to be equally likely in children with JIA and non-inflamed controls, a result that supports our findings [Stoll et al., 2018a]. Small amounts of synovial fluid are a common MRI finding in TMJs among children without JIA, and this finding should not be considered diagnostic for early arthritis [Kottke et al., 2015]. Increased signal intensity in TMJ synovial tissue has been reported in a majority of healthy children [von Kalle et al., 2013]. Therefore, minor TMJ MRI changes may be considered part of the normal spectrum in children and adolescents and not evidence of disease [Angenete et al., 2018]. The changes found in healthy children may be part of normal growth or perhaps changes due to disc displacement, trauma or degenerative disease [Giannakopoulos et al., 2009]. However, no healthy individual in the present study fulfilled clinical criteria for degenerative joint disease or disc displacement, although 47% of these had MR signs of disc displacement.

In the TMJs of JIA patients, abnormal immune system reactions including inflammation may result in pain, destruction of cartilage and bone tissue, and growth inhibition that may result in micrognathia. This may cause life-long consequences including chronic pain, altered occlusion, and micrognathia that require surgery [Stoustrup et al., 2019]. Early diagnosis of active TMJ arthritis is therefore crucial to the timely provision of treatment that can reduce the impact of the inflammation/immune system.

Moderate/severe changes in effusion, synovial thickening, condylar flattening, and erosion were only found in the JIA patients, suggesting that severe alterations may be a sign of inflammatory activity. Severe synovial thickening and erosion have been suggested to indicate active disease, which further supports our findings [Stoll et al., 2018a]. However, using contrast-enhanced MRI, Stoll et al. [2018a] found very few chronic changes in JIA patients and no chronic changes in the healthy individuals. A likely explanation for this difference in chronic alterations is that the JIA patients in the study by Stoll et al. [2018a] were recently diagnosed with JIA and were younger than the JIA patients in our study population.

Erosion severity was associated with the systemic

| | | JIA patients | | | Healthy individuals | | |
|---|---|---|---|---|---|---|---|
| MRI findings | | 0 | 1 | 2 | 0 | 1 | 2 |
| Inflammatory domain | | | | | | | |
| Bone marrow oedema | *0-1: Absent, present* | 83 (92%) | 7 (8%) | n.a. | 31 (97%) | 1 (3%) | n.a. |
| Joint effusion | *0-2: Absent, small, large* | 64 (71%) | 22 (24%) | 4 (4%) | 24 (75%) | 8 (25%) | 0 (0%) |
| Synovial thickening | *0-2: Absent, mild, moderate/severe* | 80 (89%) | 9 (10%) | 1 (1%) | 31 (97%) | 1 (3%) | 0 (0%) |
| Damage domain | | | | | | | |
| Condylar flattening | *0-2: Absent, mild, moderate/severe* | 48 (53%) | 28 (31%) | 14 (16%) | 30 (94%) | 2 (6%) | 0 (0%) |
| Erosions | *0-2: Absent, mild, moderate/severe* | 83 (92%) | 6 (7%) | 1 (1%) | 32 (100%) | 0 (0%) | 0 (0%) |
| Disc abnormalities | *0-1: Absent, present* | 39 (43%) | 51 (57%) | n.a. | 17 (53%) | 15 (47%) | n.a. |

TABLE 3 Distribution (number and percentage) of temporomandibular joint (TMJ) magnetic resonance imaging (MRI) findings, assessed according to Tolend et al (2018), in 90 TMJs in 45 patients with juvenile idiopathic arthritis (JIA) and 32 TMJs in 16 age- and sex-matched healthy individuals. There was no statistically significant difference between the patients and the healthy individuals regarding any of the MRI findings.
n.a. = not applicable; n.s. = not significant (P>0.05)

| | Patients | | | | | | Healthy individuals | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Percentiles | Percentiles | | | | | | Percentiles | | | |
| | Q/C | Unit | Median | 25th | 75th | n | Median | 25th | 75th | n |
| Clinical vaiables | | | | | | | | | | |
| Maximum mouth opening | C | mm | 47 | 44 | 51 | 45 | 51 | 48 | 53 | 16 |
| TMJ pain on maximum mouth opening | C | Y/N | | | | 6/39 | | | | 0/16 |
| Masticatory muscle pain on jaw movement | C | 0-16 | 0 | 0 | 2 | 45 | 0 | 0 | 0 | 16 |
| Number of sites with referred pain | C | 0-12 | 0 | 0 | 0 | 45 | 0 | 0 | 0 | 16 |
| Characteristic pain intensity | C | 0-10 | 0 | 0 | 3 | 45 | 0 | 0 | 0 | 16 |
| Jaw function limitation scale | Q | 0-80 | 0 | 0 | 3 | 45 | 0 | 0 | 0 | 16 |
| Psychosocial status | | | | | | | | | | |
| Pain-related disability | Q | 0-10 | 0 | 0 | 0 | 26 | 0 | 0 | 0 | 16 |
| Depression and anxiety | Q | 0-12 | 0 | 0 | 2 | 26 | 0 | 0 | 2 | 9 |
| Stress | Q | 0-40 | 8 | 2 | 16 | 26 | 4 | 1.3 | 13 | 9 |
| Catastrophizing | Q | 0-52 | 8 | 1 | 15 | 26 | 2 | 0.3 | 12 | 9 |
| Activity of daily living limitation | Q | 0.0-3.0 | 0.2 | 0 | 0.5 | 45 | n.a | | | |

TABLE 4 Clinical and psychosocial data from 45 patients with juvenile idiophatic arthritis and 16 age-and sex-matched healhy individuals
Q/C = data obtained from questionnaire (Q) or the clinical examination (C); n.a. = not applicable; TMD = temporomandibular disorders; Pain-related disability was assessed with Graded Chronic Pain Scale; Depression and anxiety was assessed with the Patient Health Questionnaire-4; Stress was assessed with Percieved Stress Scale-10; Catastrophizing was assessed with Pain Catastrophizing Scale-10 and activity of daily life limitation was assessed with the Childhood Health Assessment Questionnaire.

inflammatory activity, as assessed with C-reactive protein. Our findings thus suggest that erosion could indicate ongoing inflammatory activity. Active TMJ inflammation, as revealed by MRI, has been associated with higher incidences of recent involvement of other joints [Ma et al., 2015]. This is an interesting and important matter to study as a next step.

Erosion severity was associated with masticatory muscle pain on maximum mouth opening in the present investigation. This finding is supported in a previous study of 45 JIA patients with masticatory muscle pain who had higher systemic inflammatory activity and reduced jaw function compared to JIA patients without such pain [Dimitrijevic Carlsson et al., 2019]. Masticatory muscle pain associated with inflammatory signs of the TMJ may be explained by the general decrease in pain thresholds that can be seen in JIA patients [Leegaard et al., 2013].

In general, associations between clinical and MRI variables were either weak, non-significant or completely absent. Together with the substantial overlap between JIA patients and the healthy individuals regarding TMJ MRI parameters, this means that MRI findings should be interpreted with caution in the clinical setting. The value of MRI in the assessment of TMJ inflammatory activity in JIA can therefore be debated from the findings in the present and other studies. However, this must be regarded in the light of the absent or minor clinical signs or TMJ symptoms in JIA. It is therefore important to include controls also in future studies of TMJ MRI changes.

| | Correlation | | |
|---|---|---|---|
| Variables | rs | n | P |
| Masticatory muscle pain on maximum mouth opening | | | |
| Erosion severity | 0.36 | 45 | 0.014 |
| C-reactive protein | | | |
| Erosion severity | 0.39 | 45 | 0.008 |

TABLE 5 Significant correlations (Spearman) between clinical and laboratory variables versus temporomandibular joint changes on magnetic resonance imaging in 45 patients with juvenile idiopathic arthritis.
rs = Spearman's ranked correlation coefficient; n = number of observations; p = p-value

The results for bone marrow oedema, condylar flattening, and disc abnormalities in the present investigation were very similar to the results of a previous study, which had a sample size similar to our study [Abramowicz et al., 2011]. The presence of erosion and synovial thickening were lower in our study. The extensive development of systemic pharmacological treatment regimens is most likely the main reason for these differences, although the difference in imaging protocols may contribute.

The Tolend et al. scoring system [Tolend et al., 2018] assigns erosion in the damage domain. However, several studies point to presence of erosion being strongly related to ongoing inflammatory activity, especially when combined with bone marrow oedema [Sudoł-Szopińska et al., 2015]. Both bone erosion and bone marrow oedema, as detected by MRI without contrast, has been found to be due to inflammatory infiltrates [Jimenez-Boj et al., 2007]. In our study sample, none of the healthy TMJs had a combination of erosion and bone marrow oedema, but the TMJs of 4 patients did have this combination. However, it is impossible to base any conclusion on this small number of joints. The combination of erosion and bone marrow oedema in the TMJ warrants further study.

More than half of the TMJs in the patients showed condylar flattening, an abnormality discovered in only two TMJs in the healthy individuals. Condylar involvement has been found in previous research to be more frequent in younger JIA patients at disease onset, and these patients experience longer disease activity [Argyropoulou et al., 2009]. The present study did not observe such relations despite a similar number of patients. However, in the study of Argyropoulou et al. [2019], the patients' ages varied between 2 and 37 years, which may

explain the difference between these two studies.

This study could not find any difference in clinical or psychosocial variables between the JIA patients and the healthy individuals. JIA patients are generally difficult to diagnose since presence of clinical signs and symptoms are rare (Stoustrup et al., 2020) and the JIA patients in our study were all taken care of and monitored by paediatric rheumatologists and orofacial pain specialists. This means that the systemic inflammatory activity among our study sample was well-controlled, which likely contribute to the only few orofacial signs and symptoms.

A strength of the present study is the case-control design with JIA patients as well as healthy individuals. The use of the strictly standardised clinical examination protocol according to DC/TMD further strengthens the methodology. In addition, the radiological assessments were made by calibrated specialists in oral and maxillofacial radiology, and the clinical examination was performed by a trained and calibrated specialist in orofacial pain and jaw function.

## Conclusions

This study indicates a substantial overlap of TMJ MRI findings in both the inflammatory domain and the damage domain between JIA patients and healthy individuals. In JIA patients, the inflammatory MRI sign of bone marrow oedema seems to influence orofacial pain intensity.

## Conflict of interest

No conflict of interest was reported by the authors.

## Availability of data

Supplementary files for MRI protocol and intra-and inter-observer agreement for assessment of TMJ findings are available from the corresponding author at reasonable request.

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## References


- Abramowicz S, Cheon JE, Kim S, Bacic J, Lee EY. Magnetic resonance imaging of temporomandibular joints in children with arthritis. J Oral Maxillofac Surg 2011;69:2321-2328.
- Angenete OW, Augdal TA, Jellestad S, Rygg M, Rosendahl K. Normal magnetic resonance appearances of the temporomandibular joints in children and young adults aged 2-18 years. Pediatric radiology 2018;48:341-349.
- Argyropoulou MI, Margariti PN, Karali A, Astrakas L, Alfandaki S, Kosta P, Siamopoulou A. Temporomandibular joint involvement in juvenile idiopathic arthritis: clinical predictors of magnetic resonance imaging signs. Eur Radiol 2009;19:693-700.
- Berntson L, Andersson Gare B, Fasth A, Herlin T, Kristinsson J, Lahdenne P, Marhaug G, Nielsen S, Pelkonen P, Rygg M. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. J Rheumatol 2003;30:2275-2282.
- Berthold E, Mansson B, Kahn R. Outcome in juvenile idiopathic arthritis: a population-based study from Sweden. Arthritis Res Ther 2019;21:218.
- Cannizzaro E, Schroeder S, Müller LM, Kellenberger CJ, Saurenmann RK. Temporomandibular joint involvement in children with juvenile idiopathic arthritis. J Rheumatol 2011;38:510-515.
- Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, Malattia C, Viola S, Martini A, Ravelli A. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009;61:658-666.
- Dimitrijevic Carlsson A, Wahlund K, Kindgren E, Skogh T, Starkhammar Johansson C, Alstergren P. Orofacial pain in juvenile idiopathic arthritis is associated with stress as well as psychosocial and functional limitations. Pediatr Rheumatol Online J 2019;17:83.
- Eriksen ES, Hellem S, Skartveit L, Brun JG, Bøe OE, Moen K, Geitung JT. Temporomandibular joint pain and associated magnetic resonance findings: a retrospective study with a control group. Acta Radiol Open 2020;9:2058460120938738.
- Fair DC, Rodriguez M, Knight AM, Rubinstein TB. Depression and anxiety in patients with juvenile idiopathic arthritis: current insights and impact on quality of life, a systematic review. Open Access Rheumatol Res Rev 2019;11:237-252.
- Giannakopoulos HE, Quinn PD, Granquist E, Chou JC. Posttraumatic temporomandibular joint disorders. Craniomaxillofac Trauma Reconstr 2009;2:91-101.
- Jimenez-Boj E, Nobauer-Huhmann I, Hanslik-Schnabel B, Dorotka R, Wanivenhaus AH, Kainberger F, Trattnig S, Axmann R, Tsuji W, Hermann S, Smolen J, Schett G. Bone erosions and bone marrow oedema as defined by magnetic resonance imaging reflect true bone marrow inflammation in rheumatoid arthritis. Arthritis Rheum 2007;56:1118-1124.
- Kottke R, Saurenmann RK, Schneider MM, Muller L, Grotzer MA, Kellenberger CJ. Contrast-enhanced MRI of the temporomandibular joint: findings in children without juvenile idiopathic arthritis. Acta Radiol 2015;56:1145-1152.
- Kristensen KD, Stoustrup P, Kuseler A, Pedersen TK, Twilt M, Herlin T. Clinical predictors of temporomandibular joint arthritis in juvenile idiopathic arthritis: A systematic literature review. Semin Arthritis Rheum 2016;45:717-732.
- Kuijper TM, Luime JJ, Xiong H, de Jong P, van der Lubbe P, van Zeben D, Tchetverikov I, Hazes J, Weel A. Effects of psychosocial factors on monitoring treatment effect in newly diagnosed rheumatoid arthritis patients over time: response data from the tREACH study. Scand J Rheumatol 2018;47:178-184.
- Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-174.
- Leegaard A, Lomholt JJ, Thastum M, Herlin T. Decreased pain threshold in juvenile idiopathic arthritis: a cross-sectional study. J Rheumatol 2013;40:1212-1217.
- Ma GM, Amirabadi A, Inarejos E, Tolend M, Stimec J, Moineddin R, Spiegel L, Doria AS. MRI thresholds for discrimination between normal and mild temporomandibular joint involvement in juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2015;13:53.
- Nerurkar L, Siebert S, McInnes IB, Cavanagh J. Rheumatoid arthritis and depression: an inflammatory perspective. Lancet Psychiatry 2019;6:164-173.
- Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-392.
- Rongo R, Alstergren P, Ammendola L, Bucci R, Alessio M, D'Anto V, Michelotti A. Temporomandibular joint damage in juvenile idiopathic arthritis: Diagnostic validity of diagnostic criteria for temporomandibular disorders. J Oral Rehabil 2019;46:450-459.
- Rozenfeld MN, Podberesky DJ. Gadolinium-based contrast agents in children. Pediatr Radiol 2018;48:1188-1196.
- Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, Michelotti A, Brooks SL, Ceusters W, Drangsholt M, Ettlin D, Gaul C, Goldberg LJ, Haythornthwaite JA, Hollender L, Jensen R, John MT, De Laat A, de Leeuw R, Maixner W, van der Meulen M, Murray GM, Nixdorf DR, Palla S, Petersson A, Pionchon P, Smith B, Visscher CM, Zakrzewska J, Dworkin SF. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Groupdagger. J Oral Facial Pain Headache 2014;28:6-27.
- Stoll ML, Guleria S, Mannion ML, Young DW, Royal SA, Cron RQ, Vaid YN. Defining the normal appearance of the temporomandibular joints by magnetic resonance imaging with contrast: a comparative study of children with and without juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2018a;16:8.
- Stoll ML, Kau CH, Waite PD, Cron RQ. Temporomandibular joint arthritis in juvenile idiopathic arthritis, now what? Pediatr Rheumatol Online J 2018b;16:32.
- Stoustrup P, Glerup M, Bilgrau AE, Küseler A, Verna C, Christensen AE, Kristensen KD, Nørholt SE, Twilt M, Herlin T, Pedersen TK. Cumulative Incidence of Orofacial Manifestations in Early Juvenile Idiopathic Arthritis: A Regional, Three-Year Cohort Study. Arthritis Care Res (Hoboken) 2020 Jul;72(7):907-916.
- Stoustrup P, Twilt M, Spiegel L, Kristensen KD, Koos B, Pedersen TK, Kuseler A, Cron RQ, Abramowicz S, Verna C, Peltomaki T, Alstergren P, Petty R, Ringold S, Norholt SE, Saurenmann RK, Herlin T. Clinical orofacial examination in juvenile idiopathic arthritis: International Consensus-based Recommendations for Monitoring Patients in Clinical Practice and Research Studies. J Rheumatol 2017;44:326-333.
- Sudoł-Szopińska I, Jurik AG, Eshed I, Lennart J, Grainger A, Østergaard M, Klauser A, Cotten A, Wick MC, Maas M, Miese F, Egund N, Boutry N, Rupreht M, Reijnierse M, Oei EH, Meier R, O'Connor P, Feydy A, Mascarenhas V, Plagou A, Simoni P, Platzgummer H, Rennie WJ, Mester A, Teh J, Robinson P, Guglielmi G, Åström G, Schueller-Weiderkamm C. Recommendations of the ESSR Arthritis Subcommittee for the Use of Magnetic Resonance Imaging in Musculoskeletal Rheumatic Diseases. Semin Musculoskelet Radiol 2015;19:396-411.
- Tolend MA, Twilt M, Cron RQ, Tzaribachev N, Guleria S, von Kalle T, Koos B, Miller E, Stimec J, Vaid Y, Larheim TA, Herlin T, Spiegel L, Inarejos Clemente EJ, Moineddin R, van Rossum MA, Saurenmann RK, Doria AS, Kellenberger CJ. Toward Establishing a standardized magnetic resonance imaging scoring system for temporomandibular joints in juvenile idiopathic arthritis. Arthritis Care Res 2018;70:758-767.
- von Kalle T, Winkler P, Stuber T. Contrast-enhanced MRI of normal temporomandibular joints in children--is there enhancement or not? Rheumatol 2013;52:363-367.