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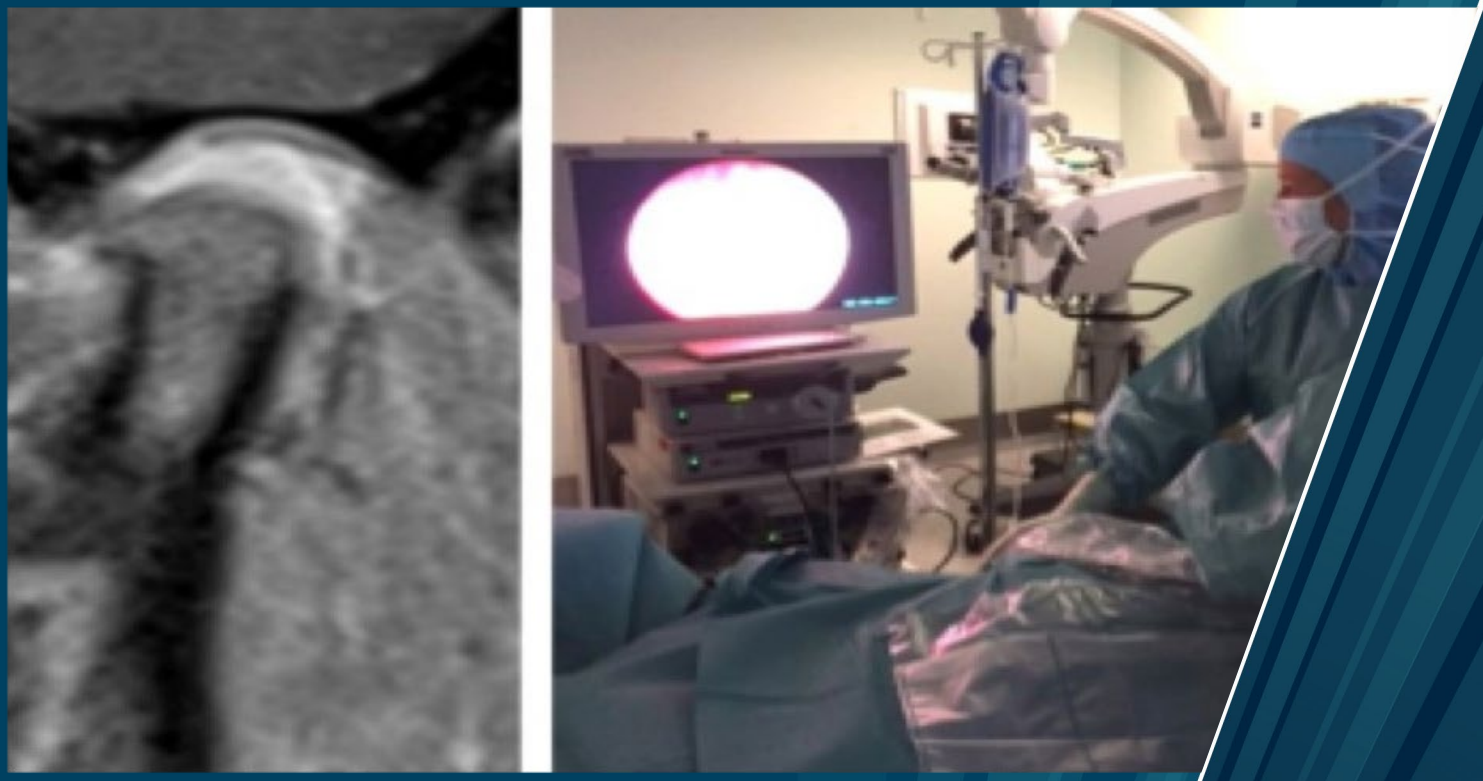
The Temporomandibular Joint in Juvenile Idiopathic Arthritis, focusing on Quality of Life, Oral Microbiome and Intervention

Paula Frid

A dissertation for the degree of Philosophiae Doctor, October 2020



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The Temporomandibular Joint in Juvenile Idiopathic Arthritis, focusing on Quality of Life, Oral Microbiome and Intervention

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ABBREVIATIONS

ACR	American College of Rheumatology
ACPA	Anti-citrullinated Protein Antibody
ADD	Anterior Disc Displacement
AJR	Alloplastic joint reconstruction
CT	Computed Tomography
CHAQ	Child Health Assessment Questionnaire
CHQ	Child Health Questionnaire
CHAQ-DI	Child Health Assessment Questionnaire – Disability Index
DC/TMD	Diagnostic Criteria for temporomandibular disorders
DO	Distraction osteogenesis
DMARDs	Disease-modifying anti-rheumatic drugs
ERA	Enthesitis-related arthritis
euroTMJoint	European temporomandibular joint work group (now TMJaw)
EULAR	European League Against Rheumatism
GBI	Gingival Bleeding Index
HC	Healthy controls
HLA	Human leukocyte antigen
HRQoL	Health Related Quality of Life
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IACs	Intraarticular corticosteroids
JADAS10	The composite juvenile arthritis10-joint disease activity score

JAMAR	Juvenile Arthritis Multidimensional Assessment Report
JCA	Juvenile chronic arthritis
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
LEfSe	Linear discriminant analysis effect size
LOM	Limited range of motion
MDgloVAS	The physician global evaluation of overall disease activity on a 10-cm visual analogue scale (VAS)
MTX	Methotrexate
MIO	Maximal incisal opening
MRI	Magnetic Resonance Imaging
NGS	Next Generation Sequencing
NORJIA	NorJIA Norwegian multicenter study on temporomandibular involvement, oral and bone health in Juvenile Idiopathic Arthritis
NSAIDs	Non-steroidal anti-inflammatory drugs
OCEBM	Oxford Centre for Evidence-based Medicine
OHI-S	Simplified Oral Hygiene Index
OMFS	Oral and Maxillofacial Surgery
OSA	Obstructive Sleep Apnea
PAS	Posterior airway space
PCoA	Principal Component Analysis
PICO criteria	Patients, intervention, comparison and outcome criteria
PRgloVAS	Patient reported global assessment of well-being VAS
PRpainVAS	Patient reported pain VAS
PRINTO	The Pediatric Rheumatology International Trials Organisation

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QIIME	Quantitative Insights Into Microbial Ecology
QoL	Quality of Life
RA	Rheumatoid arthritis
RCT	Randomized Controlled Trial
RF	Rheumatoid factor
ROC	Receiver operating characteristic analysis
sJIA	Systemic onset JIA
TNFα	Tumor necrosis factor α
TMJ	Temporomandibular joint
TMJaw	The Temporomandibular Joint Juvenile Arthritis Work group (previously euroTMJoint)
US	Ultrasound
VAS	Visual Analogue Scale

PREFACE

Research in the field of temporomandibular joint (TMJ) arthritis in juvenile idiopathic arthritis (JIA) has been growing the last decades despite the effective biologic treatment available today, probably because the TMJ arthritis is not always responding. There is increasing focus on this small joint, called “the silent joint” "or “the forgotten joint" in the literature. This may be because TMJ arthritis is not always symptomatic, the general definition of arthritis can not be applied to the TMJ,

and that many specialists share interest in the same facial area, resulting in missing as well as overlapping responsibility for the TMJ. Furthermore, the incidence of JIA in the northern countries is quite high compared to the rest of the world. Therefore, as a specialist in oral and maxillofacial surgery (OMFS) in Tromsø, Northern Norway, I was quite early exposed for these patients, both regarding local TMJ injections and surgical correction of dentofacial deformities.

Together with my main supervisor Associate Professor Ellen Nordal, I am collaborating with several of dental and medical specialists in this field in Norway and also with international researchers and working groups. Going into research was therefore a natural thing to do for me combined with my clinical position as a consultant in OMFS. My wish with this thesis is to bring new knowledge in the field of TMJ arthritis and JIA.

SUMMARY

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children with an incidence of 1-2 per 1000 children per year. The temporomandibular joint (TMJ) is commonly involved in JIA, and may lead to impaired mouth opening, pain, facial growth disturbances, a reduced posterior airway space with related comorbidities. The rate of TMJ arthritis varies from 40-90% in different studies using magnetic resonance imaging (MRI). The management of TMJ arthritis is a challenge because TMJ arthritis may be asymptomatic and diagnosed late in the disease course, and because the generally accepted clinical criteria for arthritis in JIA usually cannot be applied to the TMJ. The overall objectives with this study were therefore to provide new knowledge of disease activity and quality of life (QoL), the oral microbiome and intervention in patients with JIA and TMJ arthritis.

In an international cross-sectional study with JIA the prevalence of clinical TMJ involvement was assessed and found to be 12%. Clinical TMJ involvement was associated with higher levels of disability, higher disease activity, and impaired QoL scores in children with JIA. Special attention should be drawn to TMJ involvement in children with cervical spine involvement, polyarticular course, and longer JIA disease duration.

In a Norwegian cross-sectional study, the oral microbiome was studied in children with JIA. There were no significant differences between JIA and healthy controls salivary microbiome according to species richness (alpha- diversity) or microbial composition, Principal Component Analysis (PCoA) (beta-diversity). We found in JIA overabundance of genera associated with chronic inflammation in saliva such as

TM7-G1, Solobacterium and *Mogibacterium*, together with increased gingival bleeding. *Haemophilus* and *bacillus* species were overabundant in healthy controls. *Gemella morbillorum*, *Leptotrichia* sp. oral taxon 498 and *Alloprevotella* oral taxon 914 positively correlated with the composite juvenile arthritis10-joint disease activity score (JADAS10), while *Campylobacter* oral taxon 44, among others, particularly correlated with the number of active joints.

In a Norwegian 2-year prospective multicenter pilot study we studied single corticosteroid injections in combination with systemic treatment in adolescents with JIA and TMJ arthritis. A single injection was found to improve MRI-assessed inflammation but clinical improvement of maximal mouth opening and pain was minimal. MRI-assessed bone damage was mostly stable, and no side effects were seen.

In a systematic review, including 28 papers and 172 patients with JIA, the surgical correction of patients with JIA induced dentofacial deformity was studied. TMJ function and skeletal alignment was improved by any surgical technique and morbidity was low. Orthognathic surgery is recommended in skeletally mature patients with controlled or quiescent JIA and a stable dentofacial deformity, and distraction osteogenesis for severe deformities. Costochondral grafts were associated with unpredictable postoperative mandibular growth, as reported by some authors. Alloplastic TMJ reconstruction was efficacious but should be used cautiously in skeletally immature patients. However, the level of evidence was low with mostly case reports and case series found in this review.

In conclusion, the present work showed that quality of life scores are reduced in children with JIA and TMJ arthritis compared to those without TMJ arthritis and healthy controls. Taxa associated with chronic inflammation in saliva are more common in JIA compared to healthy children and some of these bacteria were associated to disease activity in JIA. Single corticosteroid injections in adolescents with JIA and TMJ arthritis, with an age not thought of as critical regarding mandibular growth retardation due to steroid injection, seem to be safe and may be efficient as a supplement to systemic treatment. Finally, surgical intervention of dentofacial deformities in patients with JIA-induced TMJ arthritis can be recommended in selected cases even if level of evidence is low.

LIST OF ORIGINAL ARTICLES

The following articles (Papers I-IV) are submitted in partial fulfillment of the requirements for the degree Philosophiae Doctor (Ph.D.) at the Department of Clinical Medicine, UiT the Arctic University of Norway. This thesis is based on work carried out at the Public Service Competence Centre of North Norway and at the University Hospital North Norway, Tromsø, Norway, the Public Service Competence Centre of West Norway and the Haukeland University Hospital, Bergen, Norway and the Oslo University Hospital, Rikshospitalet, Oslo, Norway and in collaboration with the Pediatric Rheumatology International Trials Organisation (PRINTO) and the Temporomandibular Joint Juvenile Arthritis Work Group (TMJaw). In the text the papers will be referred to by their Roman numerals.

Paper I

Frid P, Nordal E, Bovis F, Giancane G, Larheim TA, Rygg M, Pires Marafon D, De Angelis D, Palmisani E, Murray KJ, Oliveira S, Simonini G, Corona F, Davidson J, Foster H, Steenks MH, Flato B, Zulian F, Baildam E, Saurenmann RK, Lahdenne P, Ravelli A, Martini A, Pistorio A, Ruperto N; Paediatric Rheumatology International Trials Organisation.Temporomandibular Joint Involvement in Association with Quality of Life, Disability and High Disease Activity in Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2017 May;69(5):677-686.

Paper II

Frid P, Baraniya D, Halbig J, Rypdal V, Songstad N.T, Rosen A, Berstad J.R, Flatø B, Alakwaa F, Grut Gil E, Cetrelli L, Chen T, Al-Hebshi N.N, Nordal E, Al-Haroni M. Salivary oral microbiome of children with juvenile idiopathic arthritis: A Norwegian cross-sectional study. Submitted to BMC Arthritis Research and Therapy April 16th 2020.

Paper III

Frid P, Augdal T, Larheim T.A, Halbig J, Rypdal V, Songstad N-T, Rosen A, Tylleskär K.B, Berstad J.R, Flatø B, Stoustrup P, Rosendahl K, Kirkhus E, Nordal E. Efficacy and safety of intraarticular corticosteroid injection in adolescents with juvenile idiopathic arthritis in the temporomandibular joint: A Norwegian 2-year prospective multicenter-study. Submitted to Pediatric Rheumatology April 7th 2020.

Paper IV

Frid P, Resnick C, Abramowicz S, Stoustrup P, Nørholt SE. Surgical correction of dentofacial deformities in juvenile idiopathic arthritis: a systematic review; Temporomandibular Joint Juvenile Arthritis Work Group TMJaw. Int J Oral Maxillofac Surg. 2019 Aug;48(8):1032-1042.

INTRODUCTION AND BACKGROUND

General aspects of juvenile idiopathic arthritis

Clinical features

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease in childhood (1-6). It is a heterogeneous group of chronic arthritis of unknown origin persisting for at least 6 weeks with onset before 16 years of age. There is a female predominance of 60-70% (3). Onset of JIA may occur any time before the age of 16, but with a peak onset in girls 1-3 years and in boys 10-15 years of age (7, 8). In contrast to adult rheumatoid arthritis (RA) typically affecting small joints in the hands and feet, JIA may present with a broad range of clinical patterns and often involves large joints including knees, wrists and ankles (7, 8). Because JIA occurs in growing children, a treatment goal is to avoid growth disturbances such as leg length discrepancies and dentofacial deformities with micrognathia and asymmetry (7, 8).

Definition and classification criteria

The definition of arthritis is based on the clinical signs of inflammation: "Swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness (9). Classification of JIA is based on the number of joints affected and the presence or absence of specific serologic findings and systemic manifestations, such as skin rash, fever, iridocyclitis, cardiac disease, generalized lymphadenopathy, serositis, splenomegaly, and hepatomegaly (8, 10).

In the literature there have historically been different classification systems for JIA, making it difficult to compare research results. In 1995, the International League of Associations for Rheumatology (ILAR) introduced a classification system that would unify and replace the JRA and JCA criteria. The term was Juvenile idiopathic arthritis and the classification criteria has been revised twice, lastly in 2001 (9). According to

the ILAR criteria JIA is classified in seven different categories and a set of exclusion criteria for each of them (9) (Table 1.) Many children with JIA fit into no category or more than one JIA category and will therefore be placed in the undifferentiated arthritis category. There is an ongoing debate on the ILAR criteria and criticism has been raised towards the complexity. A new classification criterion for JIA is underway but is not yet validated (11).

Epidemiology

Reported annual incidence of JIA differs from 1.3 to 22.6 per 100 000 children (3, 6). In the Nordic countries, incidence of JIA is reported to be 15 per 100 000 children per year (12). The oligoarticular category of JIA is the most common among Caucasian populations with European ancestries while enthesitis-related arthritis (ERA) and systemic onset JIA categories are most common in some Asian countries such as Taiwan and Japan (13) .

Table 1. International League of Associations for Rheumatology (ILAR) classification of JIA. * **(9)**

Category	Definition	Exclusions
Systemic onset JIA	Arthritis in one or more joints with, or preceded by, fever of at least 2 weeks' duration that is documented to be daily (''quotidian†'') for at least 3 days and accompanied by one or more of the following: 1. Evanescent (non-fixed) erythematous rash 2. Generalised lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis‡	A. Psoriasis or a history of psoriasis in the patient or a first-degree relative B. Arthritis in an HLA-B27 positive male beginning after the 6th birthday C. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative D. The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart
Oligoarthritis	Arthritis affecting 1–4 joints during the first 6 months of disease. Two subcategories are recognised: 1. Persistent oligoarthritis: affecting not more than 4 joints throughout the disease course 2. Extended oligoarthritis: affecting a total of more than 4 joints after the first 6 months of disease	A–D above, plus E. The presence of systemic JIA in the patient
Polyarthritis (RF-negative)	Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative	A, B, C, D, E
Polyarthritis (RF-positive)	Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive	A, B, C, E

Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis§ 2. Nail pitting** and onycholysis 3. Psoriasis in a first-degree relative	B, C, D, E
Enthesitis-related arthritis	Arthritis and enthesitis††, or arthritis or enthesitis with at least 2 of the following: 1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain‡‡ 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis in a first-degree relative	A, D, E
Undifferentiated arthritis	Arthritis that fulfils criteria in no category or in 2 or more of the above categories.	

*Adapted from McCann LJ et al in Arch Dis Child Educ Pract Ed 2006 and Petty R et al in J Rheumatol 1994 (18, 36).
†Quotidian fever is defined as a fever that rises to 39˚C once a day and returns to 37˚C between fever peaks.
‡Serositis refers to pericarditis and/or pleuritis and/or peritonitis.
§Dactylitis is swelling of one or more digits, usually in an asymmetrical distribution, which extends beyond the joint margin.
**A minimum of 2 pits on any one or more nails at any time.
††Enthesitis is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.
‡‡Inflammatory lumbosacral pain refers to lumbosacral pain at rest with morning stiffness that improves on movement.

Etiology

The etiology of JIA remains unknown. It is thought to be an autoimmune disease and the result of a combination of genetic and environmental causes. The human microbiome might be a contributing factor to disease etiology and there are reports describing the microbiome to be different in children with JIA compared to healthy children (14-16). Host-microbe interaction is important for recognition and development of the immune system (17). Imbalanced composition, i.e. dysbiosis, of the subgingival microbiome has been associated to the presence of rheumatoid arthritis (RA) and periodontitis (18, 19). Infections and vaccinations have also been suggested as causative agents in JIA but there is so far very little evidence for this, except for in Lyme´s disease (20, 21). The species borrelia burgdorferi has been isolated from the joint cavity in Lyme´s disease, an infectious disease with joint inflammation. Probably, in a genetically predisposed individual, a series of environmental events may lead to the onset of JIA (20). Early life antibiotic use is associated with the development of JIA (22, 23). Arvonen et al. found that previous early and repeated exposure to antibiotics may predispose individuals to develop JIA. Alternatively, the apparent association may reflect shared susceptibility to infections and JIA (22). Furthermore, antibiotic exposure may play a role through alterations in the human microbiome (23).

Genetic susceptibility

Multiple specific susceptibility genes have been identified, which can be broadly subdivided in human leucocyte antigen (HLA) and non-HLA genes and differ between subtypes of JIA. Oligoarticular and polyarticular rheumatoid factor (RF)-negative JIA categories are associated with HLA-DRB1*13 (24). In the juvenile psoriatic arthritis category no genetic associations have been found (24) but

associations are seen between systemic JIA (sJIA) and the HLA-DRB*11 (25). HLA-DRB1*13 has been found to be a risk factor in both seropositive rheumatoid arthritis (RA) in adults and in rheumatoid factor (RF)- positive category where a glycine residue at the same amino acid position drives the association (26). Only 8 to 13% of the variation in JIA susceptibility is explained by HLA-genotypes, the remaining part should therefore be explained by non-HLA genes or environmental influences (27).

Non-HLA genes linked to JIA mostly relate to the innate immune system and its cytokines. For example gene variants linked to elevation of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin (IL)-6, IL-8, and intracellular adhesion molecules are found (28). In systemic onset JIA (sJIA) some authors have found dysregulation of the pro-inflammatory IL-1, IL-18 and the anti-inflammatory cytokine IL-10 (29, 30).

Pathogenesis

The most common clinical feature in JIA is joint swelling due to increased joint fluid, hypertrophy and hyperplasia of the synovial lining layer. The synovium becomes hyperemic and edematous due to infiltration by immune cells such as T- and B-lymphocytes, plasma cells, macrophages, and synoviocytes. This infiltration leads to production of cytokines, i.e. pro-inflammatory mediators. Increased number of inflammatory cells are recruited and activated by the cytokines and may lead to fever, fatigue, and pain as well as destruction of bone and cartilage through proliferating synovium (7, 8, 20).

The oral microbiome and the immune system

The human microbiota is a collecting term for all the microorganisms that inhabit the gut, the respiratory tract and the skin. The human microbiome is the collection of genes encompassed by the microbiota i.e. the oral microbiome code for the oral microbiota. In recent years increasing evidence has emerged on contribution of the microbiota to development of immune-mediated diseases such as inflammatory bowel disease, type 1 diabetes, rheumatoid arthritis and JIA (15, 31-33). There is a complex interplay between the immune system and the microbiota, which is essential for normal development of the immune system and for protecting the host against pathogens (15). If this interplay is disrupted, an imbalance in the composition of the microbiota, i.e. "dysbiosis", will occur (Figure 1). Composition of both the gut (34) and the oral microbiota (35, 36) have been investigated. Today new methods such as the Next generation sequencing (NGS) are used for exploring microbiota (37). Environmental factors associated with dysbiosis are lifestyle, diet, pathogens and antibiotics (38-40). As mentioned above, increased antibiotic use in childhood is associated with increased risk of developing JIA (22, 23). Dysbiosis may lead to immunological imbalance and trigger inflammation, where immune cells can reach extra-intestinal and also extra-oral sites such as joints, and trigger local inflammation with the release of different inflammatory mediators, including cytokines (41, 42).

There are several theories of how microbes can trigger autoimmune responses and contribute to autoimmune disease:

Bacterial translocation hypothesis refers to bacteria migrating through the gut epithelium due to increased permeability, enters the circulation and then finally distal tissues like the joints where local immune responses are triggered (43).

Cross-reactive epitope hypothesis or Molecular mimicry refers to a foreign antigen with structural similarities with self-antigens, typically leading to the formation of cross-reactive antibodies and T cells (44). Rheumatic fever is a well-known example in which severe systemic disease is caused by the generation of cross-reactive antibodies against group A streptococcus.

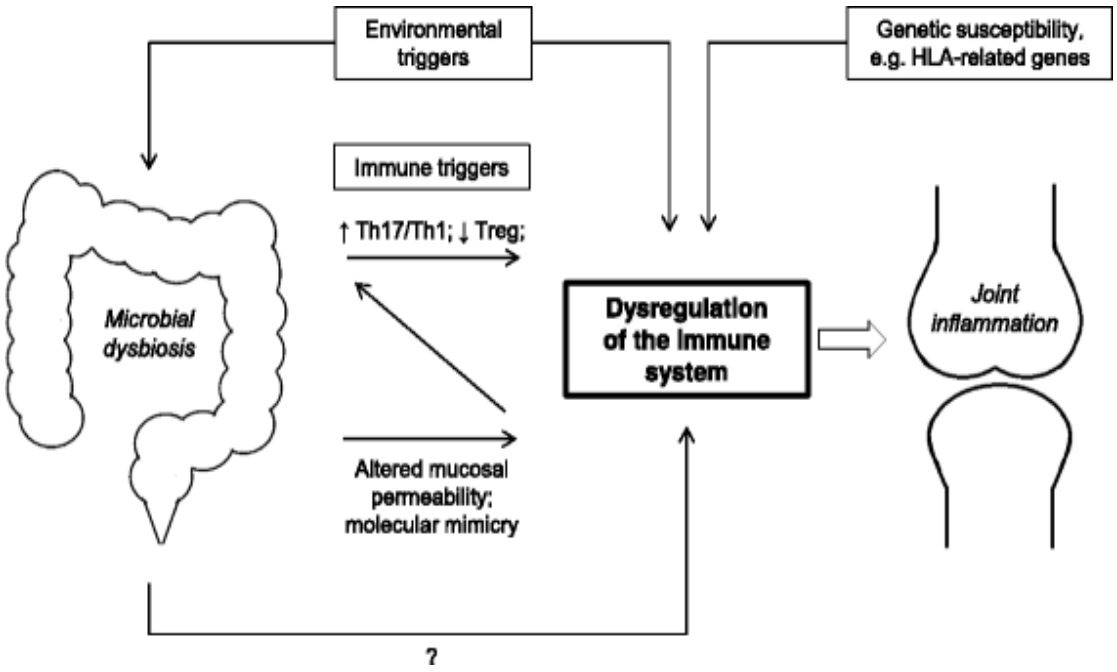
Bacterially derived metabolite hypothesis or Bystander activation refers to an indirect activation of autoreactive cells caused by the release of pro-inflammatory cytokines during inflammation or tissue damage, for example as a result of a dysbiotic environment.

Mucosal immune dysregulation hypothesis. When dysbiosis occur **some microbes might alter host proteins,** thereby creating new antigens that are recognized by the adaptive immune system as non-self (45). An example is *Porphyromonas gingivalis*, inducing antibodies to citrullinated protein antigens (ACPAs) in RA. (46).

The microbiome in JIA is reported to differ from healthy individuals (14-16) where a lower abundance of Firmicutes and a higher abundance of Bacteroidetes, on the phylum level, were found in the gut microbiota in patients with new-onset JIA (16). Furthermore, the genera Actinobacteria and Fusobacteria have been seen only in gut microbiota in JIA patients and Lentisphaerae only in healthy controls (16). The patterns of the JIA gut microbiome also resembles the microbiome reported in other autoimmune diseases such as type 1 diabetes, Crohn's disease and ankylosing spondylitis (32, 47). Different studies present different changes in microbiota, so it is possible that the impact of disruption of microbial ecology is more important for the host than the actions of just one single microbe in both JIA and RA (43, 48). Most studies on the human microbiome in JIA have investigated the gut microbiome and

not the oral microbiome (16, 34, 49-54). There is a need for more studies on the oral microbiome and JIA.

Figure 1. Possible associations between microbial dysbiosis, dysregulation of the immune system and joint inflammation.



Verwoerd, A, Ter Haar, N.M., de Roock, S. *et al.* The human microbiome and juvenile idiopathic arthritis. *Pediatr Rheumatol* **14,** 55 (2016). https://doi.org/10.1186/s12969-016-0114-4 (14).

Disease activity and Quality of Life

Disease activity measures. Validated tools for assessment of disease activity and outcome in JIA are important. Reliable assessment of self-reported health, functional status, remission and damage is necessary when evaluating treatment effects in clinical studies (55). Examples of disease activity measures are: the number of active joints, tender joints, joints with limited range of movement, laboratory markers, visual analogue scales (VAS) of pain, and global assessment of disease severity. The Juvenile Arthritis Disease Activity Score (JADAS) is a validated composite disease activity measure that is increasingly used and available in several versions. JADAS includes the sum of four measures: 1, number of joints with active arthritis assessed in 10, 27, or 71 joints 2, parent/patients global assessment of well-being 3, physician´s global assessment of well-being and 4, erythrocyte sedimentation rate (ESR) (56). The ACR pediatric response criteria (ACRpedi30, 50, 70) define clinical change over time by calculating improvement between two time points in a core set of six variables: the JADAS variables, the CHAQ score and the number of joints with restricted movements (57).

Patient-reported outcome. Different validated questionnaires on Health Related Quality of Life (HRQoL) are developed. This is important for evaluating the patient´s subjective assessment of the impact of the disease and its treatment on daily life, physical, psychological, social functioning and overall well-being. In younger children questionnaires on the self-reported measures are filled in by the parents / proxies. Two commonly used HRQoL-questionnaires are the Child Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) validated and translated into several languages, also available in Norwegian (58, 59). CHAQ evaluates physical functioning with 30 items divided into 8 domains: dressing,

arising, eating, walking, hygiene, reach, grip, and activities. Using aids and devices and help from another person for physical functioning are also registered. CHAQ further includes two visual analogue scales (VAS) on pain and overall well-being. This questionnaire is the most commonly used patient-reported outcome measure in JIA reported to have a high reliability, a moderate correlation to other disease activity indices, and with a low responsiveness to change. Many children with JIA report low levels of disability according to the CHAQ, thus a ceiling effect may be a problem (59). The CHQ is a generic quality of life measurement tool with in total 15 subscales (physical and psychosocial domains), covering daily functioning. The CHQ includes a physical and psychosocial summary score (60).

Disease status is defined as active disease, inactive disease, clinical remission on medication, or clinical remission off medication according to the ACR provisional criteria (61). Inactive disease status require all the following: 1) no active joints; 2) no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA 3) no active uveitis; 4) normal ESR or CRP; 5) the physician global evaluation of overall disease activity on a 10-cm visual analogue scale (MDgloVAS) =0; and 6) duration of morning stiffness of ≤15 minutes.

As mentioned earlier, assessment of HRQoL is important when evaluating treatment effects in clinical studies. There are few studies on HRQoL and TMJ arthritis in JIA and therefore a need for more research in this field.

Treatment

There is no cure for JIA. However, with optimal medical treatment and multidisciplinary follow-up disease activity in JIA can often be controlled and many children can live active lives (61-63). The primary goals in treatment are therefore to eliminate active disease, to normalize joint function, to preserve optimal growth and to prevent long-term joint damage (64). The ACR recommendations for treatment in JIA are published in 2011, in 2013 on systemic arthritis and in 2019 with a consensus on medical treatment of non-systemic polyarthritis, sacroiliitis, and enthesitis (65-68).

Disease-modifying antirheumatic drugs

Early aggressive intervention with **disease-modifying antirheumatic drugs (DMARDs)** is recommended in JIA children with high or moderate disease activity and / or features of poor prognosis (65, 69). **Methotrexate** is the most commonly used DMARD and often considered the gold standard of treatment in JIA. It is effective on improving joint inflammation, health-related quality of life, and physical function (70-72). However, its effect on radiological progression is poorly documented. Other synthetic DMARDs such as **salazopyrine** and **leflunomide** are also available.

Biologic treatment

Biologic treatment was introduced and available first time in 1999, interfering with key cytokines of inflammation. These targeted drugs are biologic products and generally larger complex molecules in contrast to methotrexate and the other synthetic DMARDs. The first available biologic agents were the TNF-antagonists **etanercept,**

infliximab and **adalimumab**. A range of potent cytokine inhibitors has become available including **anakinra** targeting IL-1, **tocilizumab** targeting IL-6 and also **abatacept** inhibiting the T-cell co-stimulation among many others (73) . There is today a trend of treating the JIA patients more aggressively, with earlier use of methotrexate and biologic drugs, adjusted to disease category, manifestations, and response. The biologic drugs are not only highly effective but also expensive. There is also an increased risk of infections with biologic treatment. Concerns has been raised on associations with malignancies (74), even if recent data seem to suggest that JIA itself, as in the case of RA, is associated with an increased risk of malignancy and that this risk is not further increased with anti-TNF treatment (75).

Intraarticular and systemic corticosteroids

Regardless of concomitant therapy and JIA category, the use of intraarticular corticosteroid joint injections (IACs) is recommended in active arthritis for most joints (65, 67). **Triamcinolone hexacetonide** is shown to be superior to other glucocorticoids in a randomized controlled trial (RCT) (76, 77), and may be used also in TMJ arthritis in children with JIA (78). Due to unwanted side effects such as growth retardation, metabolic alterations, and loss of bone-mass density, minimal use of **systemic glucocorticoids** in children is recommended (66, 69, 79).

Nonsteroidal antiinflammatory drugs (NSAIDS)

NSAIDS are used for pain but with a less anti-inflammatory effect than steroids and with unwanted side effects present such as an increased risk of gastrointestinal

bleeding. **Paracetamol** is well tolerated and used for pain as an alternative or supplement to NSAIDS. **Opioids** are associated with addiction problems and are not recommended for long-term use in children.

Non-medical treatment

Physiotherapy can maintain and restore function and prevent disability. **Surgical intervention** may be an option to correct growth deformities or to reconstruct or replace joints due to contractures, dislocations or ankylosis (7, 8, 80). Splint therapy has historically been used to prevent contractures in many joints, but is generally less used because of other effective therapies. Stoustup et al. currently suggest implementation of **distraction splint therapy** to normalize mandibular vertical growth in case of asymmetry in JIA with unilateral TMJ arthritis (81).

Temporomandibular joint anatomy and physiology

The temporomandibular joints (TMJs) connect the lower jaw (mandible) with the skull (temporal bone) by a bilateral synovial articulation (82). The TMJ consists of: the joint capsule, articular disc, mandibular condyle, articular surface of the temporal bone, temporomandibular ligament, stylomandibular ligament, sphenomandibular ligament, and lateral pterygoid muscle (Figure 2).

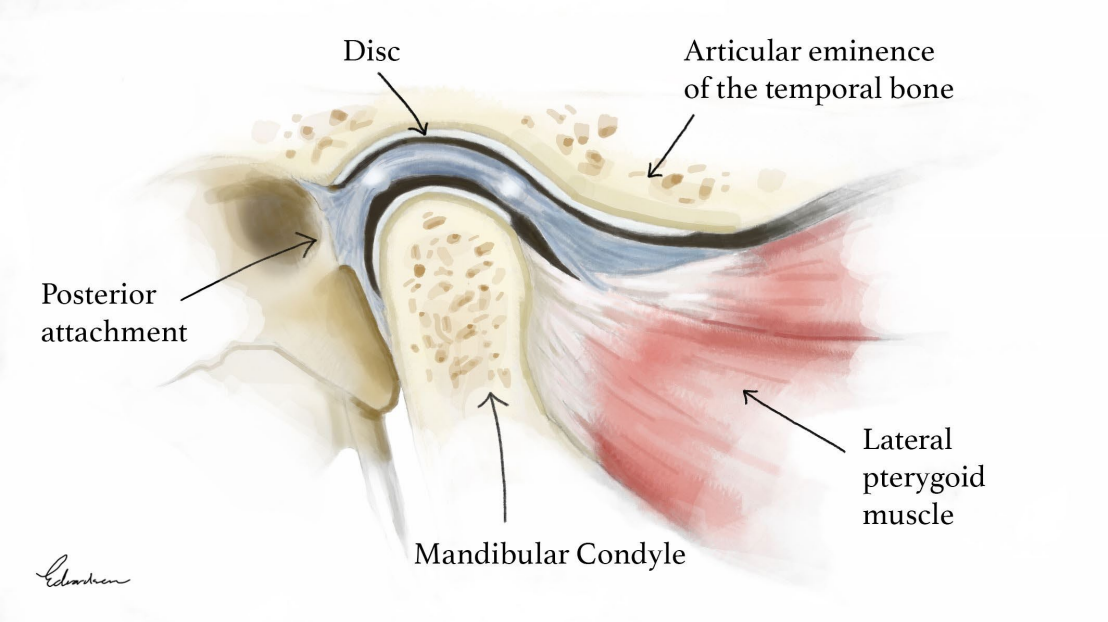


Figure 2. The temporomandibular joint and surrounding structures, illustration: Even Elias Edvardsen *(2020). Used with permission from the artist.*

A capsule with a dense fibrous membrane surrounds the TMJ and the articular eminence. The disc is unique, with a fibro- cartilaginous biconcave tissue, attached to the condyle medially and laterally. The lateral pterygoid muscle is coincident with the anterior part of the disc. The posterior part of the disc or the "retrodiscal tissue" is vascular and innervated, in contrast to the central thin part of the disc that gets nutrition from the surrounding synovial fluid. The disc divides the TMJ into the lower and the upper compartments with synovial fluid that is produced by the synovial

membrane lining TMJ capsule. The TMJs, the sternoclavicular joints and the radioulnar joints are the only synovial joints in the body with an articular disc. Branches from the external carotid artery, mainly the superficial temporal branch, but also the deep auricular artery, anterior tympanic artery, ascending pharyngeal artery and maxillary artery, provide arterial blood supply to the TMJ. The TMJ is innervated by the auriculotemporal and masseteric branches of the mandibular nerve (V_3) of the trigeminal nerve.

The TMJs develops at around 12 weeks in utero. The growth center is located in the head of the mandibular condyles, and consists of hyaline cartilage. This center grows by appositional growth in all directions, unlike a typical long bone. Over time the cartilage is replaced by bone, using endochondral ossification. The mandibular growth follows the pattern of the general human growth in children and adolescents.

The TMJ is a hinging and a sliding joint ("ginglymoarthrodial" joint). After 25mm of rotation (lower joint compartment), the translational movement (upper joint compartment) of mouth opening follows. The muscles of mastication are the masseter, the medial and the lateral pterygoid and the temporalis muscle. The lateral pterygoid muscle protrudes the mandible, while the other three muscles are involved in closing the mouth.

JIA in the temporomandibular joint

The classical clinical signs of inflammation in a joint with swelling or limitation in the range of joint movement with joint pain or tenderness (9), are seldom seen in the TMJ. TMJ arthritis is sometimes even asymptomatic (83, 84). The TMJ has therefore been described as "the forgotten joint" (83) and imaging has an important role in diagnosing TMJ arthritis (85, 86). In 2018 a new standardized terminology for assessment of orofacial conditions in JIA were published, with recommendations

from an international, multidisciplinary expert group aiming to unify TMJ terminology in JIA (87).

Magnetic resonance imaging (MRI) plays an important role in diagnosis and assessment of TMJ involvement in children with JIA (88). Common findings seen on MRI are synovial enhancement, joint fluid, bone edema and condylar head articular surface flattening (89, 90). Also, synovial enhancement and joint fluid fluctuate over time (91). Adolescents with anterior disc displacement (ADD) often have similar inflammatory changes in the TMJ as adolescents with JIA. However, TMJs with ADD showed a better-preserved and often normal shape of the glenoid fossa in the study of Kellenberger et al. (90). Even if ADD is not common in JIA it may occur, representing a challenge in differential diagnostics with regard to rheumatic or non-rheumatic disease (92).

Depending on the study design and examination methods used (i.e. classification systems, inclusion criteria, age of the subjects, applied diagnostic clinical criteria and differences in the imaging methods) the prevalence of TMJ arthritis varies substantially (40-90%) in different JIA studies, as reviewed by Larheim et al (93).

A frequency of 40–45% TMJ involvement in consecutive series of patients with JIA has usually been found using panoramic radiography (85, 94). When using MRI frequencies of 39 - 43% are reported (95, 96). Arvidsson et al reported a frequency of 70% TMJ involvement when the adult JIA patients were examined longitudinally for 27 years, with both computed tomography and MRI at last follow-up. Both lower and higher prevalence have been reported in clinical and radiologic studies (97, 98) and in particular with MRI (99, 100) higher prevalence of TMJ arthritis have been found. However, many studies regarding TMJ in JIA are characterized by a low number of patients. MRI may detect findings that indicate TMJ arthritis in children with JIA

without symptoms or clinical findings. Contrast enhancement may also be seen in healthy children and adolescents (101-103). Thus, the reliability of contrast-enhanced MRI to assess TMJ arthritis can be discussed (101), reflecting the complex diagnostics of pathology in the TMJ. Tolend et al. (104) and Kellenberger et al. (105) have recently presented a new scoring system for MRI and JIA in the TMJ. Ultrasound (US) is often found less helpful in early diagnosis of TMJ arthritis (106).

Jaw treatment

Intraarticular corticosteroid injections to the TMJ

Some observational studies report short-term symptomatic efficacy of intraarticular corticosteroid injections (IACs) to the TMJ, while other studies show no or little improvement (107-120) (Table 2).

Table 2. Observational studies on intraarticular corticosteroids (IACS) to the temporomandibular joints (TMJs)

Source	Study design	No.patients (TMJ inj.)	No.of patients at Follow-up	Mean age Years (range or SD)	Intervention	Drug/Dose per TMJ	Outcome variable(s)	Mean Follow-up Months (range)	Number of IACs per TMJ	Severe side-effects bone TMJ	MIO improvement	Orofacial pain improvement	Radiology improvement
Arabshahi et al. 2005 (107)	Retrospective	23 (49)	23/23MIO 14/23MRI	9 (14-16)	CT-guided IACs	T.Hexacetonide 20mg/ml (n=7), T.acetonide 40mg/ml (n=16)	Jaw pain, MIO, MRI	6-12	1	3/19 TMJs (16%) bony resorption	Mean 5.1mm 10/23 >5mm	10/13 (77%)	11/23 TMJs (48%) MRI
Cahill et al. 2007 (110)	Retrospective	15 (27)*	12/15clinic 10/17 MRI	8.3 (4.5-16)	CT-guided IACs	T.acetonide 40mg/ml	Pain, MIO, MRI	3-4 clinical 9 (5-15) MRI	1-2	Not reported	5/11 patients	7/8 (88%)	11/15 (73%) TMJs MRI
Ringold et al. 2008 (111)	Retrospective	25 (74)*	Unclear	8.9 (1-16)	IACs	T.Hexacetonide 20mg/ml, T.acetonide 40mg/ml	MIO, pain, clinical/radiological findings	26 (5-52)	1-5	N=2 Intraarticular Ossifications (10/15=67% signs of worsening)	One IAC: 6.6mm, additional IAC: 0.4mm increase	8/12 (67%)	2/15 TMJs (13%) CT
Weiss et al. 2008 (112)	Prospective	21	16/21MIO, 5/21 MRI	8.6 (1.5-17.2)	CT-guided IACs	T.Hexacetonide 10mg	MIO, MRI	2.4 (1.4-7.3)	1	Not reported	9/16 patients, 5/16 >5mm	NA	5/6 TMJs (83%) MRI
Parra et al. 2010 (113)	Retrospective	83 (180)*	Unclear	12 (4.3-17)	US-guided IACs	T.Hexacetonide 5-10mg, T.acetonide 5-10mg	Accuracy, clinical findings (MIO, pain)	6 weeks	1-6	Not reported	81% good, 10% partial, 9% poor response (based on MIO, clinical signs and symptoms, jaw deviation)		NA
Habibi et al. 2012 (114)	Retrospective	38 (63)	38	12.25 (5-18)	US-guided IACs	T.Hexacetonide 10-20mg	Safety, clinical findings	6-8 weeks	1		Not reported	17/17 (100%)	NA
Stoll et al. 2012 (108)	Retrospective	63 (125)*	MIO 55/63, MRI 31/63	10	IACs	T.Hexacetonide 5-10mg	Safety, MRI, MIO	MRI: 5.3 (0.5-23)	1-2	15/47 TMJs (32%) new onset erosions / flattening	Mean 2.7mm	NA	24/47 TMJs (51%) MRI
Olsen-Bergem et al. 2014 (119)	Prospective	21 (38)	21 (38) at 3 and 8 months	11.4 (6-18)	Arthrocentesis with and without steroids	T.Hexacetonide 0.5ml = 10mg	Pain, function	8 months	1	Not reported	Significant improvement in pain on opening and laterotrusive movement	Significant improvement in palpation muscles No sign.difference between arthrocentesis with and without steroid	No radiology
Stoustrup et al. 2015 (109)	Prospective observational pilot study	13	-	Median 17.2, IQR 15-18.4	IACs	T.Hexacetonide 20mg	Orofacial symptoms and signs	Mean 333 days	1-2	Not reported	No significant changes, great inter-patient variation in MIO, laterotrusive and	Total resolution of pain was rare after 34 days, pain worsened between 34 – 333 days	No radiology

											protrusive movements		
Lochbûhler et al. 2015 (120)	Retrospective	33 (19 TMJs inj once and 45 repeatedly)	33 (156 IACS)	Median 5.2 yrs	IACs	T.Hexacetonide 6-20 mg	MRI: inflammation and bone damage and growth	Median 5 yrs	2.4±1.4 (0-7)	45/66 (68%) TMJs progressive osseous deformation, 24% intraarticular ossifications Reduced mandibular growth	Not reported	Not reported	53% (intraarticular location) 20% (extraarticular location)
Kinard et al. 2016 (115)	Case-series	3 (5)	3 (5)	12.5	Artroscopy (lysis / lavasje with steroid)	T.Hexacetonide	Pain, MIO	(?)	1 (?)	Not reported	Improvement in pain and mouth opening		?
Resnick et al. 2016 (116)	Retrospective	29 (50)	-	12.1±1.9	IACs	T.Hexacetonide 0.5ml = 10mg	Patient reported pain, MIO; ER (MRI)	22.9 ±4.3 (5-48)	1	Not reported	89% of patients reduction pain	5.8±2.6mm	18% of the TMJs MRI (reduction of synovial enhancement ratio, ER)
Resnick et al. 2017 (117)	Retrospective	45 (71)	-	<16 y	IACSs with and without image guiding; ultrasonic or computed tomography	T.Hexacetonide 0.5ml = 10mg	Patient reported pain, MIO; ER (MRI), total procedure time	22.9 (5-48)		Not reported	No statistical differences in short-term outcomes between image-guiding or landmark technique, with regard to pain, MIO, synovial enhancement ratio, ER, but procedure times were longer for the image-guided group		
Antonarakis et al. 2018 (118)	Retrospective	41	-	13.6±4.0	Arthrocentesis with and without steroids and no intervention (3 groups)		MIO, Helkimo dysfunction index scores, pain intensity, acute inflammation (MRI)	(?)	1 (?)	Not reported	TMJ lavage with or without IACS injection cannot be claimed to systematically decrease pain, increase mouth opening, or resolve acute inflammation. Despite a tendency for improvement, response to this treatment is very patient dependent and can be determined by an array of other variables.		

* Repeated IACS. ER; enhancement ratio. Adapted from Stoustrup et al. (78) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence.

Other studies however, demonstrate mandibular growth impairment that may be induced by the arthritis itself and/or the treatment with repeated IACs (120, 121). The use of IACs is recommended for treatment of active arthritis in other joints of the body, regardless of concomitant therapy (65, 66). Triamcinolone hexacetonide seem to be superior to other corticosteroids in a RCT of IACs to the knee joint (76). In TMJ arthritis in children with JIA, IACs with triamcinolone hexacetonide is reported in several studies to be a useful treatment (78) and can be safely performed with or without radiologic guidance by trained specialists (108, 117). However, the role of IACs in the treatment of TMJ arthritis is not clarified. There are no prospective studies in children with JIA and TMJ arthritis showing the short and long-term safety and efficacy of IACs in terms of improving clinical symptoms and findings, reducing disease progression on MRI, and improving mandibular growth (78).

Surgical correction of dentofacial growth disturbances

If not timely and successfully treated, TMJ arthritis can lead to reduced mouth opening, impaired mastication, pain, reduced mandibular growth, and dentofacial deformities (122). Facial asymmetry and/or an occlusal cant may be the result of unilateral TMJ arthritis (123). Clockwise rotation of the mandible due to bilateral involvement may lead to micrognathia, anterior open bite, and a reduction in posterior airway space (PAS) (124) (125). A small PAS is associated with obstructive sleep apnea (OSA) and related comorbidities (126). Orthodontic and orthognathic treatment aiming to improve occlusion, facial esthetics, and self-confidence can be important because facial attractiveness may influence education, relationships, and employment (127).

The treatment of dentofacial deformities can sometimes be improved with orthopedic/orthodontic treatment during growth (81). It is however, many times a need for reconstructive surgery in most cases after final growth is reached for normalization of TMJ function and/or occlusion, skeletal alignment, facial esthetics, and/or OSA. Two strategies are found in the literature for the surgical correction of JIA-induced dentofacial deformities: (1) TMJ preservation (i.e. orthognathic surgery, distraction osteogenesis (DO)), and (2) TMJ reconstruction (i.e. resection of the remaining condyle, synovial lining, and disc, and reconstruction with an autologous graft (128) or an alloplastic prosthesis (129).

There is no consensus regarding the most appropriate reconstructive approach of dentofacial deformities in JIA. Therefore, there is a need for more research in this field with systematic reviews and prospective clinical studies leading to intervention algorithms.

AIMS OF THE STUDY

The overall objectives with this dissertation was to provide new knowledge of TMJ arthritis in JIA with regard to QoL and disease activity, the oral microbiome and intervention in patients with JIA and TMJ arthritis, with the following specific aims:

I. To describe in a cross-sectional cohort with JIA: (1) the prevalence of clinical TMJ involvement, (2) the associations between TMJ involvement and other disease characteristics, and (3) the associations between TMJ involvement and QoL measures (Paper I).

II. To describe the oral microbiome in saliva of children with JIA and relate this to disease activity, including presence of TMJ arthritis and gingival bleeding (Paper II).

III. To assess efficacy and safety of single IACs in the TMJ in terms of (I) improving maximal mouth opening capacity and pain, and (II) reducing disease inflammation and bone damage, in a 2-year prospective multicenter pilot study of adolescents with JIA and TMJ arthritis, by using validated clinical outcome measures and a newly established MRI scoring system (Paper III).

IV. To assess the level of evidence for surgical correction of dentofacial deformities in patients with JIA-related TMJ involvement (Paper IV).

MATERIAL AND METHODS

Collaboration

All papers in this thesis are based on an interdisciplinary collaboration between dental and medical specialists through local, national and international research networking.

Paper I was initiated and designed in collaboration with The Pediatric Rheumatology International Trials Organisation (PRINTO). PRINTO is a not for profit, non-governmental, international research network founded by Alberto Martini and Nicolino Ruperto in 1996. PRINTO include today about 90 countries, 656 centers with 1383 members worldwide, with the goal to foster, facilitate and coordinate the development, conduct, analysis, and reporting of multicenter studies and international clinical trials and/or outcome standardization studies in children with pediatric rheumatic diseases (www.printo.it).

Paper II and Paper III is part of a larger Norwegian multicenter cohort study on JIA; "NorJIA multicenter study on temporomandibular involvement, oral and bone health in Juvenile Idiopathic Arthritis (NorJIA)". Dr. Karen Rosendahl, professor and specialist in radiology at the Haukeland University Hospital and at the University Hospital of North-Norway, is the initiator of this cohort study (www.norjia.com) registered in Clinical Trials.gov (NCT03904459). The multidisciplinary national collaboration between medical and dental specialists at the main four University Hospitals of Norway and Public dental competence centers makes this project unique.

Paper IV was initiated and conducted by the TMJ Surgical Task Force through the Temporomandibular Joint Juvenile Arthritis Work group (TMJaw) (earlier:

euroTMJoint), an international, multidisciplinary research network founded in Oslo, Norway in 2010, which focus research of TMJ arthritis related to JIA. The terminology of Paper (II), (III) and (IV) adheres to the TMJaw consensus-based standardized terminology by Stoustrup et al. (87). Drs. Ellen Nordal, Josefine Halbig and Paula Frid are members of the working groups on clinical examination, IACs, medical and surgical intervention in the TMJaw. Professor Tore A. Larheim has been leading the working group on imaging since the first European Meeting in Oslo 2010, until the second meeting in Oslo 2018.

Study design

All papers in this thesis are based on projects with different study design and cohorts, with the purpose to answer our aims on gaining more knowledge of TMJ arthritis in JIA, including two cross-sectional studies with multicenter cohorts, one prospective intervention study and one systematic review on surgical intervention.

Paper I is based on a descriptive cross-sectional multicenter study about clinical TMJ-involvement in children with JIA, with data extracted from two studies of the Pediatric Rheumatology International Trials Organisation (PRINTO); the MTX-trial (72) and the HRQoL-study (130). The MTX-trial was a RCT comparing standard dose to high dose of MTX in JIA with 633 study subjects. The HRQoL-study with 2715 study subjects was a multicenter-study validating the CHAQ and CHQ in different languages.

Paper II is based on a descriptive Norwegian cross-sectional multicenter study on the oral microbiome in saliva in children with JIA and TMJ arthritis.

Paper III reports on a Norwegian 2-year prospective multicenter pilot study on efficacy and safety of single IACs in the temporomandibular joint (TMJ) in adolescents with JIA.

Paper IV is a systematic literature review on surgical correction of dentofacial deformities in patients with JIA and TMJ arthritis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (131).

Inclusion criteria

All papers in this thesis include children with JIA and TMJ arthritis with different study inclusion criteria and different time periods. However, all children with JIA were classified as per the ILAR criteria (9) (Figure 5).

In paper I a total of 3343 children with JIA and 3409 healthy pears were included from 32 different countries (Figure 5) in the time period of 1998-2001 (MTX-trial) and in the time period of 1998-2000 (HRQoL-study). Disease activity was assessed by the JIA core set activity variables (9). In this study assessment of TMJ activity was defined as; presence of TMJ pain and/or limited range of motion (LOM), registered by the local pediatric rheumatologist in the PRINTO joint examination form, according to standard pediatric rheumatology textbooks.

In paper II in the period of 2015-2019, 93 Norwegian children in total were consecutively recruited at the participating pediatric rheumatology centers in Tromsø, Oslo and Bergen. Children with JIA and TMJ arthritis (JIA-TMJ) (n=15), JIA without

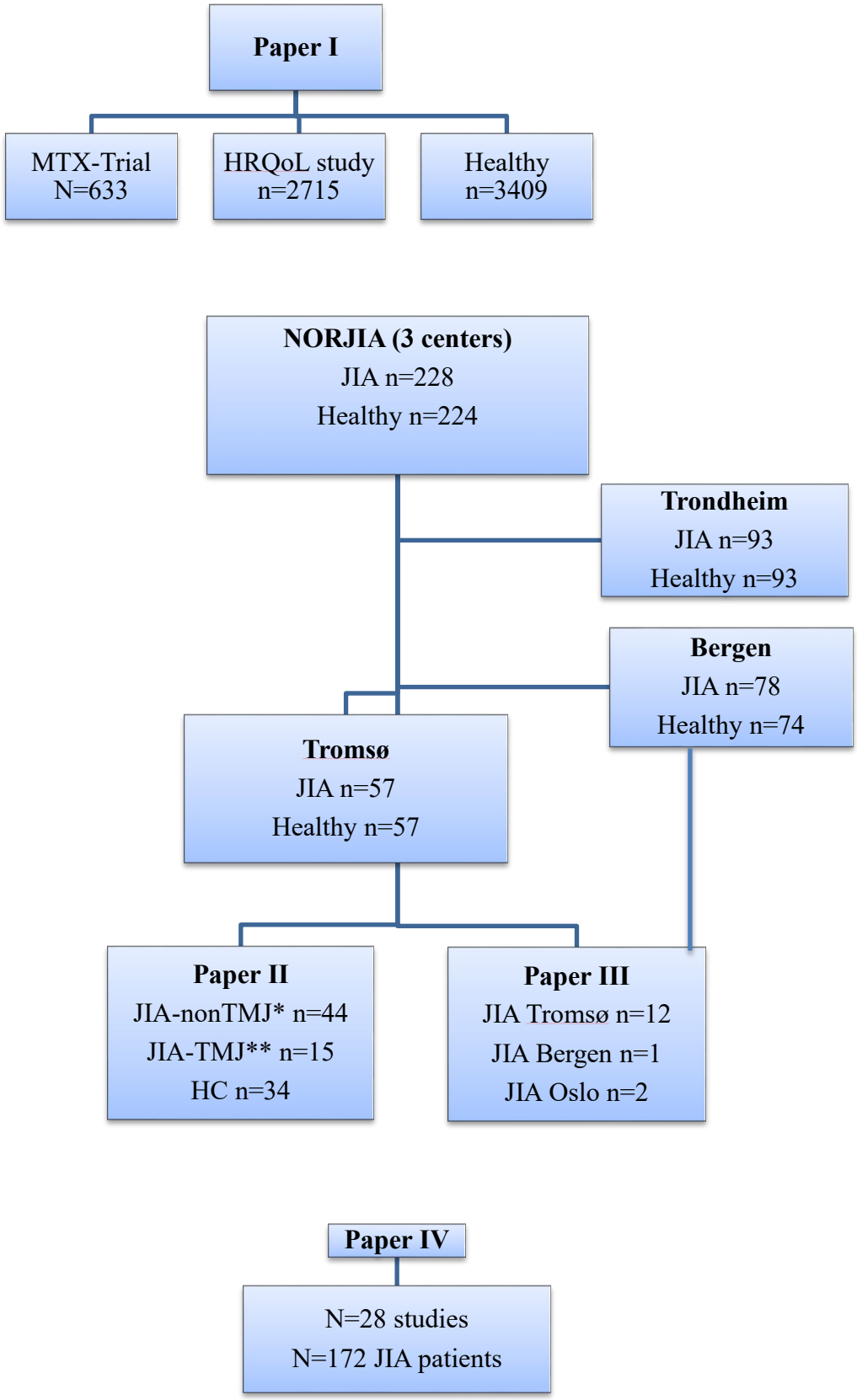
TMJ arthritis (JIA-nonTMJ) (n=44) and healthy controls (HC) (n=34) (Figure 5). All eligible children with a diagnosis of JIA aged <18 years and with a saliva sample available were included. Among the totally 59 children with JIA in this study three were not included in the main NORJIA study in Tromsø, due to either origin in Oslo (n=2) or an age older than 16 years at time of inclusion (n=1). We included the 34 healthy children from Tromsø with available saliva samples also participating in the main NorJIA multicenter study.

In paper III in the period of 2015-2019, 15 children with JIA and TMJ arthritis from three participating centers received IACs (Figure 5). Children with JIA aged <18 years at time for inclusion in the study, and arthritis activity in one or both TMJs were included. Children requiring sedation or general anesthesia for MRI and/or IACs were included in this study only if there was a clear clinical indication for imaging and intervention. Alternative treatment options for TMJ arthritis such as systemic medication, physiotherapy/specific jaw exercises and activation device/splint for myalgia were first considered. Due to emerging findings of possible negative effect of steroids on mandibular growth in the study period, IACs were used in our study in treatment resistant symptomatic TMJ arthritis in adolescents in whom most of the expected growth had taken place. IACs were performed on the following indications, judged by each participating center: (1) Clinical signs of TMJ-inflammation such as pain on movement, limitation of MIO, limitation of laterotrusive or protrusive jaw movements and/or dentofacial growth disturbance AND (2) MRI signs of TMJ arthritis (i.e. active arthritis in the TMJ) such as contrast enhancement of synovial tissue, bone marrow edema and/or effusion. TMJ-injections were not performed in Trondheim

during this time period, and children with active TMJ arthritis that did not receive any IACs to the TMJs were not included in this study.

In paper IV the primary search was conducted in June 2017 and updated in February 2018. The following studies were included according to the PICO criteria (patients, intervention, comparison and outcome): patients with a diagnosis of JIA and involvement of the TMJ, receiving a reconstructive or orthognathic surgical intervention (Figure 5). 28 papers were finally included in this systematic review for full-text evaluation; 24 were case reports or case series, three were retrospective chart reviews and one was a prospective cohort study. A total of 172 subjects with JIA were included.

Figure 5. Flow chart of the participants enrolled in Paper I-IV.



* JIA without TMJ arthritis ** JIA with TMJ arthritis from Tromsø (n=12), Bergen (n=1), Oslo (n=2)

Data collection

All papers in this thesis collect data from children with JIA and TMJ arthritis: demographic data, laboratory data reported according to the PRINTO case report form (CRF) for study I, NORJIA CRF for studies II and III, PRISMA guidelines and the Oxford Centre for Evidence-based Medicine (OCEBM) level of evidence guide for study IV. In paper II and III all specialists performing the examinations of the study subjects and healthy controls were calibrated repeatedly.

In paper I demographic, clinical and laboratory data was collected by the local pediatric rheumatologist according to the PRINTO CRF together with validated patient/ proxy-reported outcomes; CHQ, PRgloVAS and PRpainVAS score.

In paper II demographic and clinical data were collected from clinical registrations of the NorJIA CRF including a modified version of the validated DC/TMD examination and diagnosis protocol (132) and the validated EuroTMJoint Clinical Recommendations protocol (133) . Laboratory data including saliva samples for microbiological analyses was also collected. A modified version of the Gingival bleeding index (GBI) (134) was used for registering gingival inflammation according to a gingival bleeding cut-off score ≥ 10% (135). A modified version of the Simplified Oral Hygiene Index (OHI-S) was used for registering dental plaque and calculus (136).

In paper III demographic, clinical and laboratory data was collected from clinical registrations using a modified version of the validated diagnostic criteria of temporomandibular disorders (DC/TMD) examination and diagnosis protocol (132) and the validated EuroTMJoint Clinical Recommendations protocol (133) together with

MRI assessments according to the recently published MRI scoring systems for TMJ arthritis in JIA .

In paper IV data was collected and independently assessed by two authors (PF, SEN) in a systematic literature search at three occasions. The first selection was based on titles, the second on abstracts, and the third on full text review. The selected studies were assessed for risk of bias: prospective study design, sufficient description of the outcome variable, uniform inclusion criteria, standardized examination protocol, outcome assessor blinded to imaging findings, and information on outcome variable variation. The level of evidence was scored according to the Oxford Centre for Evidence-based Medicine (OCEBM) level of evidence guide.

Statistical methods

In the statistical analyses of thesis the SPSS software, version 21, 24, 25 and 26 was used, except for paper IV being a systematic review where the collected data was not sufficient for a meta-analysis. Paper I also used the SAS software version 9.3. In paper II Downstream bioinformatics analysis was performed with QIIME and LEfSe software. In all studies a p-value <0.05 was considered statistically significant, except for p-values adjusted for multiplicity with Benjamini-Hockberg method (FDR ≤ 0.1) in paper II.

Paper I, II, III: For clinical and demographic data, descriptive statistics were used, such as median (1^{st} and 3^{rd} quartile), mean (standard deviation) and frequencies (percentage). In paper I associations between TMJ and other disease characteristics were analyzed by chi-square test for categorical variables, and Student´s t-test for continuous variables if normally distributed, otherwise Wilcoxon test was used. To

identify factors differentiating JIA patients with or without TMJ involvement (Paper I), univariate logistic regression was performed, using as exploratory measures the JIA core set, the CHAQ and the CHQ domains. Multivariable logistic regression was performed to identify factors independently associated with TMJ involvement. In both univariate and multivariable regression analyses the continuous variables were dichotomized as per Receiver Operating Characteristics (ROC) analysis (Paper I).

Paper II: Associations between microbiome and different disease characteristics were analyzed by chi-square test for categorical variables (Fisher´s exact test) and Student´s t-test for continuous variables if reasonably normally distributed, otherwise Wilcoxon´s test was used. Significant differences between three different medication groups were analyzed with the Kruskal Wallis test. Associations between gingival bleeding index (GBI) and JIA were analyzed with multivariable logistic regression analysis.

Paper III: When testing continuous variables for differences between two time-points, Wilcoxon Signed Ranks Test was used for not normally distributed data and paired sample t-test for normally distributed data. For nominal data and dependent samples tested for differences between two time-points; McNemar Chi-square test was used. Multiple testing of four time-points and Bonferroni correction for 6 comparisons with a p-value <0.008 was analyzed and considered, but not used in the final manuscript. Percentage of patients was used for absolute improvement of the variables pain, MIO and MRI. For the MRI assessment, the intra-observer agreement for the MRI-scoring was assessed with Cohen's kappa.

Ethical approval and considerations

Approval from appropriate medical ethical committees and data authorities was obtained according to the requirements of each participating country (Paper I-III). In paper IV all of the included studies had the necessary approvals.

Research involving children is strictly regulated because this patient group is considered a vulnerable group. Research should be in accordance with the United Nations Convention on the Rights of the Child (Article 24): *"States Parties recognize the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services".*

Children included in Paper I-III had reduced autonomy and were dependent on parental/proxies responsibilities and rights. Age-adapted informed written consent was therefore obtained from the child and his/her parents/proxies and information about the study (aims, benefits, potential adverse events, principle of voluntary participation etc.) was given. However, if a situation had arisen where the child of any age did not want to further participate in the study, he or she would of course have been excluded from the study. One example of this in my thesis was a child participating in the study and described in paper III, who did not prefer to take follow-up MRIs after the baseline, but she was still included and participated in the clinical assessments of the study. All papers in this PhD were performed according to the Declaration of Helsinki: ethical guidelines for research with human subjects (137). Furthermore, the authors were not influenced by any financial support or other conflicting interests in the present research projects presented in papers I-IV.

SUMMARY OF THE RESULTS

Paper I

Temporomandibular joint involvement in association with quality of life, disability, and high disease activity in juvenile idiopathic arthritis.

Paula Frid, Ellen Nordal, Francesca Bovis, Gabriella Giancane, Tore A.Larheim, Marite Rygg, Denise Pires Marafon, Donato De Angelis, Elena Palmisani, Kevin J.Murray, Sheila Oliveira, Gabriele Simonini, Fabrizia Corona, Joyce Davidson, Helen Foster, Michel H.Steenks, Berit Flato, Francesco Zulian, Eileen Baildam, Rotraud K. Saurenmann, Pekka Lahdenne, Angelo Ravelli, Alberto Martini, Angela Pistorio, Nicolino Ruperto for the Paedriatic Rheumatology International Trials Organisation (PRINTO).

- Clinical temporomandibular joint (TMJ) involvement is associated with higher levels of disability, high disease activity, and impaired quality of life in children with juvenile idiopathic arthritis (JIA).
- Clinicians should pay special attention to TMJ involvement in children with JIA and cervical spine involvement, polyarticular course, and longer disease duration.
- Observations were based on 387 of 3343 children with JIA, representing those with clinically evident TMJ involvement.

Paper II

Salivary oral microbiome of children with juvenile idiopathic arthritis: A Norwegian cross-sectional study.

Frid P, Baraniya D, Halbig J, Rypdal V, Songstad N.T, Rosen A, Berstad J.R, Flatø B, Alakwaa F, Grut Gil E, Cetrelli L, Chen T, Al-Hebshi N.N, Nordal E, Al-Haroni M.

- A total of 216 bacterial species belonging to 58 genera and 8 phyla were identified across all samples, with *Prevotella, Streptococcus, Actinomyces, Haemophilus*, *Porphyromonas* and Rothia accounting for the bulk of the average microbiome.
- There were no significant difference between JIA and healthy controls in species richness or in principal component analysis (PCoA), i.e. alpha or beta diversity. Differential abundance analysis revealed genera *TM7-G1, Solobacterium* and *Mogibacterium* to be associated with JIA, while *Haemophilus* and *Bacillus* were overabundant in healthy subjects.
- *Gemella morbillorum*, *Leptotrichia sp. oral taxon 498* and *Alloprevotella oral taxon 914* correlated positively with the composite juvenile arthritis10-joint disease activity score (JADAS10), while *Campylobacter oral taxon 44*, among others, correlated with the number of active joints.
- We found a significantly higher gingival bleeding index (GBI), plaque-index and simplified oral hygiene index (OHI-S) in the JIA group compared to the healthy group**.** When adjusted for dental plaque and calculus (OHI-S), GBI was not found strictly significantly associated to JIA.

- There was no significant difference in GBI between the three groups of children with JIA using no systemic medication, methotrexate or biologic agents.
- Overabundance of microbiota associated to chronic inflammation in JIA did not overlap with microbiota associated to increased GBI, even if the periopathogenic species *s.sputigena* was associated with GBI in our study.

Paper III

Efficacy and safety of intraarticular corticosteroid injections in adolescents with juvenile idiopathic arthritis in the temporomandibular joint: A Norwegian 2-year prospective multicenter pilot study.

Frid P, Augdal T, Larheim T.A, Halbig J, Rypdal V, Songstad N.T, Rosen A, Tylleskär K.B, Berstad J.R, Flatø B, Stoustrup P, Rosendahl K, Kirkhus E, Nordal E.

- Most patients received a single IAC, including five (33%) with bilateral IACs. In two patients the IACs were repeated once unilaterally.
- The majority of patients had persistent oligoarthritis or polyarthritis RF negative JIA category.
- Systemic medication was adjusted during the 2-year observation period in 10/15 (66.7%) patients.
- At the 2-months study visit after injection there was a minimal improvement in maximal incisal opening (MIO) from median 44.0 (36.0, 48.0) mm to 45.0 (43.0, 47.0) mm, p= 0.045 and decreased MRI mean additive inflammatory score from 4.4±1.8 standard deviations (SD) to 3.4±2.0, p= 0.040.
- Pain improved in 6/11 patients but pain scores were not significantly improved at the 2-months follow-up.
- MRI-assessed damage was mostly stable, but increased in two patients with repeated IACs, and improved in three other patients over the 2-year follow-up.
- Intra-rater repeatability of the domains of the MRI scoring systems varied from poor to excellent. Synovial thickening and disc abnormalities had the best scores for intra-rater repeatability.
- No side effects were seen.

Paper IV

Surgical correction of dentofacial deformities in juvenile idiopathic arthritis: a systematic literature review

P.Frid, C.Resnick, S.Abramowicz, P.Stoustrup, S.E.Nørholt, on behalf of the Temporomandibular Joint Juvenile Arthritis Work Group TMJaw.

- The database search identified 255 citations, of which 28 met the eligibility criteria.
- Of these, 24 were case reports with a low level of evidence that did not allow for meta-analysis, three were retrospective and one a prospective cohort study (n=172 participants with JIA in total).
- Extrapolated evidence supports orthognathic surgery in skeletally mature patients with controlled or quiescent JIA and a stable dentofacial deformity.
- Distraction osteogenesis may be recommended for severe deformities.
- Some authors demonstrated unpredictable postoperative mandibular growth with costochondral grafts.
- Alloplastic TMJ reconstruction was reported efficacious, but should be used cautiously in skeletally immature patients.
- TMJ function and skeletal alignment was reportedly improved with reconstruction by any technique and morbidity was low.

GENERAL DISCUSSION

Methodological considerations

Study design and strength and limitations

Papers I and II was designed as descriptive cross-sectional studies. The advantage with this study design is that the participants are not deliberately exposed, treated or not treated; therefore this seldom imposes ethical dilemmas. The studies are also relatively inexpensive to perform and it is possible to study multiple outcomes. However, cross-sectional studies do not provide an explanation for the results, only information on associations and not on causation. It is impossible to control for confounding factors.

A strength with paper I is the large international cohort and healthy controls included. However, selection bias may have occurred because many children with high disease activity were included in this study. Data was extracted from two different studies of the PRINTO; the HRQoL study to validate the CHAQ and the CHQ into 32 different languages, and the second study was the PRINTO high dose of MTX trial with patients in high disease activity state.

Furthermore, the primary research questions in the two original studies did not include assessment of TMJ involvement and in addition TMJ imaging was not performed. Also, we do not know to what extent children with asymptomatic TMJ arthritis and growth disturbances in terms of dentofacial deformities from previously active arthritis were identified as TMJ arthritis in this study. Pediatric rheumatologists and not trained dental specialists performed the TMJ examination. The prevalence of TMJ involvement was therefore probably underreported in this study. Another limitation was to distinguish clinical variables associated with TMJ involvement from associations with arthritis in any specific joint or polyarticular disease in general.

Adjustments for polyarticular disease course and other disease activity measures were therefore performed in the multivariable logistic regression analyses.

In the cross-sectional study in paper II, the cohort consisted of children with JIA without TMJ arthritis (n=44), JIA with TMJ arthritis (n=15) and healthy controls (n=34). A limitation regarding this cohort was that the children with JIA were not new-onset nor treatment naïve.

Paper III was designed as a prospective Norwegian multi-center pilot study, where a cohort of 15 children with TMJ arthritis treated with IACs was followed for 2 years according to potential effect and safety. The prospective study-design has the advantage of being tailored to collect specific exposure data and may be more precise than cross-sectional studies. The disadvantage of a prospective cohort study is the need for the long follow-up period while waiting for events or diseases to occur, thus the risk for loss to follow-up increases with longer follow-up time, and thereby inflicting selection bias. The ideal research design would have been to randomize the children in a RCT to either corticosteroid or saline injection. However, recruiting enough patients for sufficient statistical power would have been time-consuming and very difficult for our study. Furthermore, it would have been interesting to compare mandibular growth in children with JIA and TMJ arthritis after IACs, with healthy controls. We were not able in our study to assess mandibular growth because the children had mostly finished their growth at time for IACs, and a suitable control group with active TMJ arthritis and alternative treatment strategy was not available. The low number of patients (n=15) is a limitation in this cohort.

Paper IV was designed as a systematic literature review according to the PRISMA-guidelines. The level of evidence was scored according to the Oxford Centre for Evidence-based Medicine (OCEBM) level of evidence guide (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/). A limitation with this systematic review was that no meta-analysis could be performed due to the low level of evidence of the included studies and the high risk of bias. The risk of bias was assessed according to the following variables: prospective study design, sufficient description of the outcome variable, uniform inclusion criteria, standardized examination protocol, outcome assessor blinded to imaging findings, and information on outcome variable variation. Of the 28 included papers, 24 were case-reports; three were retrospective studies and only one prospective. Most of the studies had a small patient sample, and no study had a control group. Only 172 of the 232 included patients had JIA, the remaining patients had different craniofacial syndromes including a dentofacial deformity, thus having the same surgical procedure done. Therefore, it is difficult to ascertain that the results are specific to JIA and not to other conditions. The majority of the outcome assessors, i.e. the oral and maxillofacial surgeons that performed the surgical procedure, were obviously not blinded to the intervention performed in the included studies. Only two databases were used for the literature search, which may have inflicted bias at the review level. The study heterogeneity did therefore not allow for meta-analysis. The strength of this review is that it to our knowledge includes all manuscripts on JIA and dentofacial reconstruction.

Discussion of main findings

The present papers contribute to the current understanding of JIA and TMJ arthritis, by describing in papers I-IV disease activity and quality of life, the oral microbiome and intervention with both IACs to the TMJ and surgical correction of dentofacial deformities in children with JIA.

Disease activity and quality of life

The TMJ is a special joint because of few symptoms and diagnostics may be challenging (122). Paper I pointed out to the need for an internationally accepted definition of TMJ arthritis based on clinical findings and symptoms as well as MRI. Standardizations of terminology according to orofacial examination in JIA have later been published by Stoustrup et al (87). It is a short clinical protocol assessing orofacial symptoms, TMJ dysfunction, and dentofacial deformity, taking less than three minutes to complete. In addition, suggested MRI scoring systems for the TMJ is published by Tolend et al (104), and Kellenberger et al. (105). Prospective longitudinal studies using these new internationally suggested definitions will hopefully make it easier to identify and compare future studies on early predictors of severe facial growth disturbances, intervention and outcome over time.

There has been increasing focus on the TMJ in recent years, and the rate of TMJ arthritis varies significantly (40-90%) in different JIA-cohorts using magnetic resonance imaging (MRI) (95, 99, 138). In our international cohort comprising a large number of children with JIA with or without TMJ arthritis and healthy children, **the prevalence of clinical TMJ involvement** was found to be low (12%), most probably

because diagnostic imaging was not used. TMJ involvement was based on clinical assessment of the variables “active arthritis” and “limitation in range of movement”.

We found associations between clinical TMJ involvement and impaired QoL, polyarticular disease course, longer disease duration, physical disability, and cervical spine involvement in children with JIA. To our knowledge, this is the first study to analyze the relationship between QoL and TMJ involvement in children with JIA. We found an association with increased pain, difficulties in eating, arising, and reaching, and having limitations in physical functioning measured by the child health assessment questionnaire (CHAQ) in multivariable analyses compared to the non-TMJ group. This is in agreement with studies on healthy children, young adult JIA and adult JIA patients, showing that temporomandibular disorders (TMD) may lead to impaired oral health and influence daily life (139-143). Many JIA cohorts are small, adjustment for disease severity is not always done and general orofacial symptoms are most often studied. In our study the TMJ involvement was specifically studied. Furthermore, we found associations between clinical TMJ involvement and impaired physical and emotional wellbeing according to the TMJ (144). However, lower self-esteem (SE of the child health questionnaire (CHQ)) and eating difficulties (CHAQ) were not significantly associated with clinical TMJ involvement in multivariable analysis, only in univariate analysis. A lower self-esteem may be explained by dentofacial deformities, but also by high disease activity in general, because it was not significantly associated to clinical TMJ involvement in the adjusted analyses in our study. Several studies show a positive psychosocial effect in JIA patients after orthognathic surgery (145, 146). It is reported that facial attractiveness may influence education, relationships, and employment (127).

The TMJ plays an important role for daily life activities (141, 147, 148). Our results of the association between TMJ involvement and eating problems and also with oral hygiene are in agreement with other studies (147-149), even if medication and general disease activity also might have an impact on these problems (147). CHAQ used in our study is not a specific tool for assessing TMJ dysfunction. Other questionnaires such as "Juvenile Arthritis Multidimensional Assessment Report (JAMAR)" (150) and the EuroTMJoint Clinical Recommendations protocol similar to, but shorter than the established and validated Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) (151, 152), is now developed in the EuroTMJoint network, and may better explore eating difficulties and TMJ involvement.

We found longer disease duration in the group with TMJ involvement in contrast to the other children with JIA (95). Evolving growth disturbances can influence this finding and asymmetries following active TMJ arthritis that may be increasingly easier to recognized over time. Peak onset of TMJ arthritis according to age and time after disease onset are best studied in prospective JIA cohorts with radiographic assessment.

In line with other studies, we found associations between TMJ involvement and upper limb involvement and also with a higher ESR (85, 95). We found a significant association between TMJ involvement and cervical spine involvement, and in contrast to other studies, this association was confirmed in multivariable analysis adjusting for higher disease activity (85, 95). Cervical pain and limitation in movement may be caused by cervical spine arthritis, but could also be the result of stiffness in neck and masticatory muscles.

The oral microbiome

The aim of this study was to investigate the salivary oral microbiome in children with JIA and relate this to JIA disease activity including gingival inflammation. There is increasing evidence that the human microbiome may contribute to the development of JIA (15, 31-33) through an imbalance in the composition of the microbiota, i.e. a dysbiosis (15). In patients with rheumatoid arthritis, the oral microbiota is suggested to be involved in the pathogenesis by activation of mucosal immunity (153). Dysbiosis and periodontitis are reported to be associated with increasing severity of rheumatoid arthritis (18).

The next generation sequencing (NGS) method was used in our study for oral bacterial DNA sequencing (154), allowing analysis of microbiota at a reasonable cost and with less extensive laboratory work compared to the earlier method of Sanger sequencing of 16S rRNA clones. The NGS target one or more regions of the 16S rRNA gene, which due to their hypervariability serve as good markers of bacterial taxa in samples. In our study, we chose the V1-V3 region of the 16S rRNA gene to study the salivary oral microbiome. This region proved to provide the most resolution to study oral microbiome, even at the subspecies level.

We found no significant differences between JIA and healthy controls (HC) regarding alpha- and beta-diversity. Alpha-diversity refers to the average species diversity in saliva and beta-diversity to the ratio between species diversity i.e. microbial composition in saliva between the two communities JIA and HC in our study. The average microbiome in our study in both JIA and healthy saliva were found to be *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria*, and *Fusobacteria* at the phyla level (accounting for more than 98% of the reads). Thirteen genera accounted for 90% of the average microbiome, with *Prevotella*, *Streptococcus*,

Haemophilus, *Actinomyces*, *Porphyromonas* and *Rothia* alone making 70% of the genera. At the species level, *Prevotella melaninogenica*, *Haemophilus parainfluenzae*, *Rothia mucilaginosa*, *Porphyromonas sp. oral taxon 279*, *Prevotella histicola*, *Actinomyces odontolyticus* were the most abundant species, constituting around 40% of the microbiome on average.

Operational taxonomic unit (OUT) differential abundance testing is commonly used to identify OTUs that differ between two sample categories (i.e. saliva in two groups). OTUs are proxies for species at different taxonomic levels.

In our study, differential abundance analysis revealed that taxa associated with chronic inflammation also was associated to JIA: *TM7-G1, Solobacterium* and *Mogibacterium* at the genus level; and *Leptotrichia oral taxon 417, TM7-G1 oral taxon 352* and *Capnocytophaga oral taxon 864*, among others, at the species level. An overabundance of *Haemophilus* and *Bacillus* was found in saliva in healthy subjects. Overabundance of taxa associated with chronic inflammation, i.e. dysbiosis, may explain the significantly higher gingival bleeding found in patients with JIA compared to HC in our study. The higher gingival bleeding found in JIA in our study is in line with some authors (147-149, 155, 156). Other authors found, however, no significant difference between JIA and healthy (157-163). In univariate regression analyses JIA was associated to higher GBI. When adjusting for the simplified oral hygiene index (OHI-S) including dental plaque and calculus in multivariable logistic regression analyses, we found that the association between JIA and gingival bleeding lost the clear significance, but OHI-S was significantly associated to gingival bleeding index.

The differences across studies may be caused both by different study designs and different measure indices for gingival inflammation, thus making it difficult to compare the results. In our study a cut-off score ≥10% for the GBI was used for

gingival inflammation in the analyses, even if this only is validated in adults. No cut-off score is established for children. In addition, the gingival bleeding index (GBI) used in our study was modified by measuring only the upper part of the gingival sulcus and only 6 index-teeth were used.

We did not find overabundance of the same microbiota associated to gingival bleeding that was found associated to JIA. However, microbiota associated to chronic inflammation were found in both GBI and JIA. *S.sputigena* associated to GBI in our study is found associated to general aggressive periodontitis in other studies (164). Even if GBI and OHI-S was higher among children with JIA in our study, there was no difference in the frequency of tooth brushing between the groups. Therefore, we hypothesize that the dysbiosis more than specific bacteria may contribute to increased gingival bleeding and dental plaque formation in JIA compared to healthy. Maspero et al found reduced gingival bleeding in patients treated with biologic medication (162). We did not find significant differences in GBI between children with JIA on no systemic medication, methotrexate or biologics.

Furthermore, we found JADAS10 to be positively correlated to *Gemella morbillorum, Leptotrichia sp. oral taxon 498* and *Alloprevotella oral taxon 914,* while *Campylobacter oral taxon 44,* among others, particularly correlated with **the number of active joints**. Association between increased disease activity and certain bacteria is in line with other studies on RA (18).

An altered microbiome profile is in accordance to other studies about the gut microbiota in JIA (16, 34, 49, 50, 52, 53). However, no single species has been identified and different studies on the gut microbiome in JIA show changes in different taxa (16, 34, 49-54). The species found in our study on the salivary oral microbiome in JIA are not found in the studies of the gut microbiome in JIA.

However, disruption of microbial ecology was found and this dysbiosis may have community effects on the host that are more powerful than the actions of just one or a few single microbes (43).

Intervention with IACs to the TMJ

In some patients with JIA, systemic treatment is not sufficient to treat TMJ-arthritis. In these cases other treatment options are sought, such as IACs. When we initiated this study 5 years ago, many clinicians worldwide had a liberal attitude towards performing IACs, and this local treatment was widely recommended (108). However, after several case series reporting severe side effects of mostly repeated IACs, including intra-articular calcifications and inhibited mandibular growth, there is today recommendations towards a more cautious use of IACs (165).

Based on the results from our Norwegian 2-year prospective multicenter pilot study of adolescents with JIA and TMJ arthritis, we suggest, that a single IAC after the peripubertal growth might be beneficial as a supplement to systemic treatment. **We found reduced inflammation at both 2-months and 2-year follow-up with a newly established MRI scoring system, but minimal improvement of MIO.** Validated clinical outcome measures were used in our pilot study. **Pain improved in 6 of 11 adolescents in our study but did not reach significance,** in contrast to some retrospective studies in children with JIA (107, 110, 111, 113, 114). Stoustrup et al. found improvement in pain one month after IACs but worsened pain after one year in his prospective pilot study using the same validated pain index score that was used in our study (109).

Improved MIO is in line with other retrospective studies (107-111, 113, 114, 117), even if MIO was minimally improved in our study and is associated with variation (166,

167), increases with age, show a wide normal range in children of the same age (168) and is associated with measurement biases even if standardized protocols are used (132) (133). The smallest detectable difference is found to be 5mm when MIO is repeatedly measured in patients with JIA.

We found a significant improvement in the reduction of MRI-assessed inflammation using two newly validated scoring systems, both at 2-month- and at 2-year follow-up after IACs (104, 105). Studies of IACs to the TMJs in JIA patients report a variable MRI improvement of 18-83% probably because of variable definitions of MRI improvement (107, 108, 110, 112, 117). There has been a clear need for a standardized MRI scoring system differentiating normal findings in growing children from pathology, and also grading the pathologic changes that are identified.

We did not find any significant improvement in bone damage on MRI. Two patients with repeated IACs worsened during the 2-year follow-up and 3 patients improved. This is in line with other studies showing either stable condylar changes or worsening with intraarticular ossifications after IACs (107, 108, 111, 120, 169). The authors cannot say if these ossifications are the result of repeated IACs or due to the long-standing TMJ inflammatory process. Also reduced mandibular growth has been reported after IACs in children with JIA and TMJ arthritis (120). We were not able to evaluate growth since most of the study participants in our study were in the phase of finishing their growth at the time the injection was performed. Furthermore, the effect of naturally fluctuating JIA disease activity, systemic treatment changes, and TMJ lavage versus IACs could not be discerned in our study. Our study may still add evidence by assessment of efficacy and safety of *one single* injection and not *repeated*

injections in adolescents with an age not thought of as critical regarding mandibular growth retardation due to steroid injection.

Intervention with jaw surgery

If systemic treatment with/or without IACs to the TMJ do not prevent the development of dentofacial deformities in patients with JIA and TMJ arthritis, surgical correction may be the treatment of choice. There is no consensus regarding the most appropriate reconstructive approach, which may be influenced by the degree of skeletal maturity, level of TMJ arthritis activity, severity of TMJ and dentofacial deformity, and surgeon preference and experience.

We found in our systematic review that **orthognathic surgery is supported in skeletally mature patients with controlled or quiescent JIA and a stable dentofacial deformity.** The reason for performing this kind of surgery after growth is to maximize stability (124, 170). However, reduced stability or "skeletal relapse" after surgery may be a problem in patients with JIA even after growth, because they are so called "high-angle cases" with a TMJ deformity causing posterior rotation of the mandible resulting in an anterior open bite (171). Early surgical intervention, before growth is finished, has therefore been recommended in order to provide better conditions for normal development of the facial skeleton (170, 172).

Distraction osteogenesis (DO) was recommended for severe deformities, even if DO require careful vector planning, patient collaboration during device activation and a second surgery to remove the device (173).

In growing individuals, autologous reconstruction may be preferred because the graft has the potential to grow with the child. Our review found an improvement in functional outcome and esthetics (128, 145, 174-177), self-confidence (174, 176), and

OSA (176, 178), after the use of costochondral-grafts (CCG). However, there is controversy in the literature regarding the use of CCG, due to the risk of graft overgrowth (145, 177), graft resorption and ankylosis, and donor site morbidity (179, 180).

A temporomandibular joint prosthesis was found efficacious because the TMJ could be mobilized early after surgery. However, in growing individuals it should be used cautiously because of the risk of mechanical failure requiring reoperation. Furthermore, long-term outcomes of TMJ prostheses beyond 15 years are unknown (129). We conclude in our review that TMJ function and skeletal alignment was improved by all the mentioned surgical techniques and morbidity was low. Even if available articles were mainly case-series, we believe there is an indication for surgical correction of dentofacial deformities in certain patients with JIA.

Clinical implications of the results

Clinicians should pay special attention to TMJ involvement in children with JIA and cervical spine involvement, polyarticular course and longer disease duration. Furthermore, TMJ diagnostics should include both a standardized clinical TMJ examination and an MRI examination (Paper I).

Children with JIA are vulnerable for oral infections and should have regular dental follow-up. In addition, the oral microbiome may contribute to the pathogenesis and disease severity in JIA. This may give implications in support of a more restrictive use of antibiotics in children (Paper II).

A single IAC in the TMJ in adolescents with JIA may be a supplement to systemic treatment in refractory cases with JIA and TMJ arthritis (Paper III).

The surgical correction of JIA-induced dentofacial deformities is indicated and the specific reconstructive approach may be chosen based on the degree of skeletal maturity, level of TMJ arthritis activity, severity of TMJ and dentofacial deformity, and surgeon preference and experience (Paper IV).

CONCLUSIONS

The work in this dissertation has contributed to new knowledge of TMJ arthritis in JIA with regard to quality of life (QoL) and disease activity, oral microbiome and intervention with the following conclusions:

I. Clinical TMJ involvement is associated with impaired QoL in children with JIA. The prevalence of TMJ involvement is surely an underestimate of TMJ arthritis, but most children with clinically evident TMJ involvement were probably identified. Special attention should be paid to the TMJ in children with cervical spine involvement, polyarticular course, longer disease duration, and physical disability (Paper I).

II. Microbiota associated with chronic inflammation was enriched in the saliva of children with JIA. Increased disease activity in terms of JADAS10 and number of active joints were associated to specific bacteria. The disrupted microbial ecology may have triggered a local pathological immune response resulting in increased gingival bleeding and dental plaque formation in JIA (Paper II).

III. A single IAC to the TMJ in combination with systemic treatment improved MRI-assessed inflammation during a 2-year follow-up in adolescents with JIA and TMJ arthritis. However, short-term clinical improvement was minimal in MIO and no significant improvement in pain was seen. Bone changes in the

TMJ were mostly stable and no side effects were seen during the 2-year follow-up (Paper III).

IV. Surgical correction of JIA-induced dentofacial deformities may be indicated in selected patients but the level of evidence on treatment outcome is low (Paper IV).

FUTURE STUDIES

There is a need for an internationally accepted definition of TMJ arthritis whether based on clinical findings and/or imaging. Longitudinal TMJ studies with clinical assessment and imaging are warranted to identify early predictors of severe facial growth disturbances, the most efficacious and safe treatment modalities and outcome over time.

Orofacial examinations and imaging of children with JIA and TMJ arthritis with validated standardized protocols are important basis for future research in the field.

Studies on other biomarkers including cytokine levels in saliva, serum and TMJ joint fluid may expand our understanding of TMJ inflammation in JIA. Analyses of cytokines are ongoing in the study participants described in paper II on the oral salivary microbiome. Prospective studies with treatment-naive recent onset patients are warranted to further explore the possible role of the oral microbiome in the etiology of JIA.

Prospective multi-center studies with larger samples of patients and with an age not critical for mandibular growth retardation due to steroid injection including a control group, may further explore the efficacy, safety and role of single IACs in the treatment of active TMJ arthritis in children with JIA.

The different surgical reconstructive interventions performed in the management of dentofacial deformities found in children with JIA and TMJ arthritis should be monitored by establishing prospective intervention studies and a multi-center registry. A prospective multi-center study with Tromsø and Århus on surgical intervention is now ongoing. The TMJaw group may be a networking platform with a key role in establishing an international registry of surgical reconstructive interventions of the TMJ in JIA.

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PAPER I

Temporomandibular Joint Involvement in Association with Quality of Life, Disability and High Disease Activity in Juvenile Idiopathic Arthritis.

Frid P, Nordal E, Bovis F, Giancane G, Larheim TA, Rygg M, Pires Marafon D, De Angelis D, Palmisani E, Murray KJ, Oliveira S, Simonini G, Corona F, Davidson J, Foster H, Steenks MH, Flato B, Zulian F, Baildam E, Saurenmann RK, Lahdenne P, Ravelli A, Martini A, Pistorio A, Ruperto N; Paediatric Rheumatology International Trials Organisation.

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ORIGINAL ARTICLE

Temporomandibular Joint Involvement in Association With Quality of Life, Disability, and High Disease Activity in Juvenile Idiopathic Arthritis

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Objective. **To evaluate the demographic, disease activity, disability, and health-related quality of life (HRQOL) differences between children with juvenile idiopathic arthritis (JIA) and their healthy peers, and between children with JIA with and without clinical temporomandibular joint (TMJ) involvement and its determinants.**

Methods. **This study is based on a cross-sectional cohort of 3,343 children with JIA and 3,409 healthy peers, enrolled in the Pediatric Rheumatology International Trials Organisation HRQOL study or in the methotrexate trial. Potential determinants of TMJ involvement included demographic, disease activity, disability, and HRQOL measures selected through univariate and multivariable logistic regression.**

Results. **Clinical TMJ involvement was observed in 387 of 3,343 children with JIA (11.6%). Children with TMJ involvement, compared to those without, more often had polyarticular disease course (95% versus 70%), higher Juvenile Arthritis Disease Activity Score (odds ratio [OR] 4.6), more disability, and lower HRQOL. Children with TMJ involvement experienced clearly more disability and lower HRQOL compared to their healthy peers. The multivariable analysis showed that cervical spine involvement (OR 4.6), disease duration >4.4 years (OR 2.8), and having more disability (Childhood Health Assessment Questionnaire Disability Index >0.625) (OR 1.6) were the most important determinants for TMJ involvement.**

Conclusion. **Clinical TMJ involvement in JIA is associated with higher disease activity, higher disability, and impaired HRQOL. Our findings indicate the need for dedicated clinical and imaging evaluation of TMJ arthritis, especially in children with cervical spine involvement, polyarticular course, and longer disease duration.**

INTRODUCTION

Temporomandibular joint (TMJ) arthritis in childhood is recognized as a common problem in children with juvenile idiopathic arthritis (JIA) and may lead to reduced mouth opening and pain, as well as craniomandibular growth disturbances. The growth disturbances in childhood TMJ arthritis are different from arthritis in other joints because of the special anatomy of the TMJ, with fibrous cartilage and the intraarticular condylar growth pattern (1). Bilateral involvement may lead to micrognathia and dental malocclusion (2,3), and unilateral involvement may lead to

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Significance & Innovations

- Clinical temporomandibular joint (TMJ) involvement is associated with high levels of disability, high disease activity, and impaired quality of life in children with juvenile idiopathic arthritis (JIA).
- Clinicians should pay special attention to TMJ involvement in children with JIA and cervical spine involvement, polyarticular course, and longer disease duration.
- Observations were based on 387 of 3,343 children with JIA, representing those with clinically evident TMJ involvement.

facial asymmetry (4). TMJ arthritis may also hamper oral hygiene and lead to dental caries (5,6).

Depending on the examination methods and study design used, the prevalence of TMJ arthritis varies in different JIA studies. Rheumatologists may not have the same awareness for TMJ as for other joints, and standardized examination of TMJ range of motion is challenging in small children. Tenderness is very subjective, and young children often do not report pain in even obviously swollen chronically inflamed joints. An overall TMJ prevalence of approximately 40–45% has usually been found using panoramic radiography (7,8). In 2 large series of children examined with magnetic resonance imaging (MRI), frequencies of approximately 39% and 43% were reported (9,10). In 47 patients followed longitudinally for 27 years, Arvidsson et al (11) reported a frequency of 70% when the adult JIA patients were examined with both computed tomography and MRI. Both lower and higher prevalences have been reported in clinical and radiologic studies (12,13), and in particular with MRI (14,15) higher prevalences of TMJ arthritis have been found. However, many TMJ studies are characterized by a low number of patients. It is a fact that MRI may detect TMJ arthritis in children with JIA without symptoms or clinical findings. However, contrast enhancement is also seen in healthy children and adolescents (16,17), and thus the reliability of contrast-enhanced MRI to assess synovial inflammation is discussed (18), reflecting the complex diagnostics of the TMJ.

TMJ pain has a negative impact on health-related quality of life (HRQOL) in adult rheumatoid arthritis patients (19), and a high prevalence of temporomandibular disorders (TMDs) in adult JIA patients has also been reported (20). TMDs in general lead to reduced HRQOL in preadolescents (21). Orofacial symptoms are frequent, and are reported to influence daily life severely for almost a quarter of a series of children with JIA (22). However, little is known about the effect of TMJ involvement on HRQOL and disability in children with JIA.

The purpose of the present study was to examine the difference in clinical characteristics, disease activity, disability, and HRQOL in a large cohort of children with JIA with and without clinical TMJ involvement, to compare the results with those obtained in healthy peers, and to identify the factors that have the greatest influence on TMJ arthritis. The overall hypothesis was that children with JIA and TMJ involvement have distinctive clinical features when compared to children without TMJ involvement.

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MATERIALS AND METHODS

Patients. This is a cross-sectional study based on data extracted from 2 studies of the Pediatric Rheumatology International Trials Organisation (PRINTO) (23). The first relates to the HRQOL study, which enrolled 3,235 children with JIA and 3,409 healthy controls to validate the translation of the Childhood Health Assessment Questionnaire (C-HAQ) and the Child Health Questionnaire (CHQ) into 32 different languages (24). The second study was the PRINTO high dose of methotrexate (MTX) trial with 633 participants (25); for the MTX trial, only baseline data, from patients in a high disease activity state, were used. Children were classified as per the International League of Associations for Rheumatology criteria (26). Children with psoriatic or enthesitis-related arthritis were excluded.

Assessment of functional disability and HRQOL measures. The national version of the C-HAQ questionnaire was completed by one of the parents, or by the child if age >9 years. The C-HAQ is used to assess the patient's ability to carry out daily life activities (24,27) and the child's ability to perform different functions, grouped in 8 domains (range 0–3): dressing, grooming, arising, eating, walking, hygiene, reach, grip, and activities. The C-HAQ

disability index (C-HAQ DI) is calculated with a range from 0 (no or minimal physical disability) to 3 (very severe physical disability). A parent's/patient's global assessment of the child's overall well-being in the previous week was scored on a 0–10-cm visual analog scale (PRgloVAS) (where 0 = very well and 10 = very poor), and a parent's/patient's global assessment of the child's pain in the previous week was scored on a 0–10-cm VAS (where 0 = no pain and 10 = very severe pain) (PRpainVAS).

The national language version of the parent's administered 50-item version of the CHQ (also called CHQ-PF 50) was used to assess HRQOL of patients and healthy children. The CHQ is a generic self-administered instrument designed to capture the physical, emotional, and social components of health status of children ages 5–18 years, which comprises 15 health concepts (range 0–100): global general health, physical functioning, role/social limitations emotional/behavioral, role/social limitations physical, bodily pain/discomfort, behavior, general behavior, mental health, self-esteem, general health perception, change in health, parent impact emotional, parent impact time, family activity, and family cohesion. The CHQ comprises 2 summary measures, based on a US normative standard, the physical summary score (PhS) and the psychosocial summary score (PsS) (mean ± SD 50 ± 10). Higher scores in the scales indicate better HRQOL (28).

Assessment of disease activity. The JIA core set activity variables (29) were assessed: the number of joints with active arthritis (i.e., swelling within a joint or limitation in the range of joint movement with joint pain or tenderness) (26,29), the number of joints with limitation of motion (LOM), the physician global evaluation of disease activity on a 10-cm VAS (MDgloVAS), erythrocyte sedimentation rate (ESR), the C-HAQ, the PRgloVAS, and the Juvenile Arthritis Disease Activity Score 71 (JADAS) (30–32).

Assessment of TMJ involvement. For this study, we defined TMJ involvement as a clinical evaluation of TMJ arthritis based on the presence of TMJ pain or LOM, registered by the local pediatric rheumatologist in the PRINTO joint examination form. Jaw deviation during opening and maximal mouth opening capacity were not registered, but LOM was assessed according to standard pediatric rheumatology textbooks.

Statistical analysis. For clinical and demographic data, descriptive statistics were used, such as median (1st to 3rd quartile) and frequencies (percentage). Associations between TMJ and other disease characteristics were analyzed by chi-square test for categorical variables and Student's *t*-test for continuous variables if reasonably normally distributed, otherwise Wilcoxon's test was used. A *P* value less than 0.05 was considered statistically significant. To identify factors differentiating JIA patients with or without TMJ involvement, univariate logistic regression was performed, using as exploratory measures the JIA core set, the C-HAQ, and the CHQ domains. Multivariable logistic regression was performed to identify factors independently associated with TMJ involvement. In both univariate and multivariable regression analyses, the continuous variables were dichotomized as per receiver operating characteristics analysis. Statistical analysis was performed using SAS software, version 9.3, and SPSS software, version 21. Approval from appropriate medical ethical committees and data authorities was obtained according to the requirements of each participating country.

Figure 1. Flow chart of the participants enrolled in the study. MTX = methotrexate; HRQoL = health-related quality of life; JIA = juvenile idiopathic arthritis.

RESULTS

Study population. Of the original 2 studies we used, 2,715 of 3,235 JIA patients (84%) from the HRQOL study, 628 of 633 (99%) from the MTX trial, and all 3,409 healthy participants from the HRQOL study, in total 6,752 subjects, were analyzed (Figure 1). Participants from the MTX trial had higher levels of disease activity and disability and worse HRQOL when compared to the participants from the cross-sectional HRQOL study (see Supplementary Tables 1 and 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23003/abstract). Of the 3,343 children with JIA included, 2,278 of 3,243 (70.2%) were female, and 1,530 (45.8%) were diagnosed with persistent or extended oligoarthritis (Table 1).

Demographic and disease activity parameters. Demographic and disease activity characteristics and univariate analysis for the TMJ group and non-TMJ group are given in Table 1. Of the 387 children with clinical TMJ involvement (11.6% of the entire cohort), 75 (19.4%) had unilateral and 312 (80.6%) had bilateral TMJ involvement. In the TMJ group there was a female predominance (75.5%) and longer disease duration, versus the non-TMJ group,

Table 1. Demographic and disease activity characteristics according to clinical TMJ involvement among 3,343 children with JIA*

	Clinical TMJ involvement (n = 387)	No clinical TMJ involvement (n = 2,956)	Cutoff	Clinical TMJ involvement OR (95% CI)
Demographic characteristics				
Female, no. (%)	292 (75.5)	1,986 (67.3) (n = 2,951)	–	1.5 (1.2–1.9)
Age at visit	11.6 (8.5–14.9)	10.0 (6.5–13.6)	>9.2	1.8 (1.4–2.3)
Age at onset	4.9 (2.3–8.3)	5.2 (2.5–8.8) (n = 2,948)	≤8.9	1.2 (0.9–1.5)
Disease duration	5.1 (2.1–8.6)	3.2 (1.3–6.0) (n = 2,948)	>4.4	2.2 (1.8–2.8)
JIA category, no. (%)				
Persistent oligoarthritis	19 (4.9)	887 (30.0)	–	–
Extended oligoarthritis†	78 (20.2)	546 (18.5)	–	6.7 (4.0–11.1)
Polyarthritis†	93 (24.0)	585 (19.8)	–	7.4 (4.5–12.3)
Systemic arthritis†	197 (50.9)	938 (31.7)	–	9.8 (6.1–15.8)
ANA	142 (38.6) (n = 368)	1,057 (37.4) (n = 2,823)	–	1.1 (0.8–1.3)
RF	43 (11.4) (n = 377)	216 (7.6) (n = 2,831)	–	1.6 (1.1–2.2)
MTX study	116 (30.0)	512 (17.3)	–	2.0 (1.6–2.6)
Disease activity variables				
JADAS score	20.6 (11.1–30.3) (n = 354)	9.2 (3.2–17.9) (n = 2,627)	>18.1	4.6 (3.7–5.8)
MDgloVAS	4.2 (2.2–6.2) (n = 385)	2.3 (0.6–4.5) (n = 2,944)	>2.6	2.7 (2.2–3.4)
ESR	32.0 (18.0–52.0) (n = 357)	22.0 (11.0–41.0) (n = 2,652)	>15.0	2.8 (2.1–3.7)
No. of patients with active joints, no. (%)	259 (66.9)	1,044 (35.3)	≥5.0	3.7 (3.0–4.6)
No. of joints with swelling	4.0 (1.0–12.0)	2.0 (0.0–5.0)	>2.0	2.3 (1.8–2.8)
No. of joints with pain	7.0 (2.0–15.0)	1.0 (0.0–5.0)	>5.0	4.5 (3.6–5.6)
No. of joints with LOM	13.0 (6.0–29.0)	2.0 (0.0–7.0)	>4.0	8.9 (6.8–11.7)
No. of active joints	8.0 (3.0–17.0)	2.0 (0.0–6.0)	>5.0	3.9 (3.1–4.8)
Cervical spine involvement, no. (%)	239 (61.8)	508 (17.2)	–	7.8 (6.2–9.8)

* Values are the median (1st to 3rd quartile) unless indicated otherwise. Chi-square test is used for testing associations with temporomandibular joint (TMJ) (categorical variables) together with Student's *t*-test and Wilcoxon's test (continuous variables). Cutoff values for continuous variables were dichotomized as per receiver operating curve analyses. $P < 0.05$ for all variables, except for age at onset and antinuclear antibody (ANA), which were not statistically significant. The variables are known for >95% of the total participants, except for the following: erythrocyte sedimentation rate (ESR) (90%), Juvenile Arthritis Disease Activity Score (JADAS) (89%). JIA = juvenile idiopathic arthritis; OR = odds ratio; 95% CI = 95% confidence interval; RF = rheumatoid factor; MTX = methotrexate; MDgloVAS = physician global evaluation of disease activity using a visual analog scale; LOM = limited range of motion.
† JIA category versus persistent oligoarthritis used as a reference.

but no statistically significant difference in age at onset. Polyarticular disease course (extended oligoarthritis, polyarthritis rheumatoid factor [RF]–positive or -negative, and systemic arthritis) was more common in the TMJ group (95.1%) compared to the non-TMJ group (70.0%), and a polyarticular RF-positive or -negative JIA category was reported in 50.9% of the children in the TMJ group compared to 31.7% in the non-TMJ group (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23003/abstract). Disease activity measures as measured by the JADAS score, MDgloVAS, ESR, and the number of active joints were significantly higher in the TMJ group compared to the non-TMJ group.

Disability and HRQOL. Disability and HRQOL are reported in Figures 2 and 3 and in the related descriptive statistics in Supplementary Tables 2 and 3 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23003/abstract). Children with clinical TMJ involvement had more disability compared to children without TMJ involvement, as measured by the 8 C-HAQ subscales, PRpainVAS, PRgloVAS, and C-HAQ DI. As shown by the arrows in Figure 2, children with clinical TMJ involvement had scores more than 2 SD above the mean values of healthy controls in the domains of dressing, eating, and activities.

All CHQ health concept and summary scores (PhS and PsS) in children with clinical TMJ involvement were significantly lower than in children without TMJ involvement, except for behavior and general behavior. In addition, children with clinical TMJ involvement had values more than 2 SD below the mean of healthy controls for the following health concepts: global general

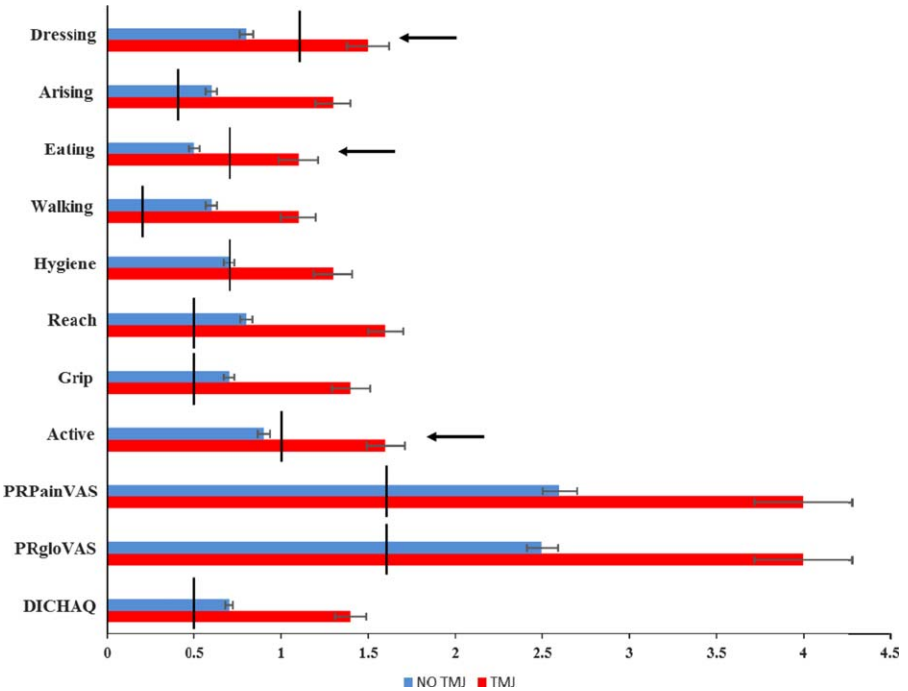

Figure 2. Mean and 95% confidence intervals for the Childhood Health Assessment Questionnaire (CHAQ) for children with and without clinical temporomandibular joint (TMJ) involvement. Vertical bars represent +2 SD of the mean of healthy children. Higher scores indicate more disability. Arrows indicate the 3 CHAQ domains (dressing, eating, and active) in which only children who have juvenile idiopathic arthritis with clinical TMJ involvement have scores >2 SDs of the mean of healthy children. DICHAQ = CHAQ disability index; PRpainVAS = parent's/patient's global assessment of the child's pain using a visual analog scale; PRgloVAS = parent's/patient's global assessment of the child's overall well-being using a visual analog scale.

health, role/social limitations emotional/behavioral, role limitations physical, and bodily pain/discomfort.

Univariate analysis. To evaluate the association of disease activity, disability, and HRQOL with clinical TMJ involvement, we report the results of the univariate analyses (odds ratios [ORs] and 95% confidence intervals), with continuous variables dichotomized as per operating characteristics analysis in Table 1 and Table 2. A significant association with clinical TMJ involvement was found for extended oligoarticular, polyarticular, and systemic arthritis categories, using the oligoarticular persistent category as a reference (OR range 6.7–9.8). Disease activity measures as measured by the JADAS score (OR 4.6), MDgloVAS (OR 2.7), ESR (OR 2.8), and number of active joints (OR 3.9) were significantly higher in the TMJ group compared to the non-TMJ group. Children with clinical TMJ involvement had more frequent cervical spine involvement (OR 7.8) or upper extremity involvement (data not shown).

All the C-HAQ domains had higher scores in the TMJ group compared with the non-TMJ group, particularly for the domains of reach (OR 5.5), difficulties concerning arising, grip, and activities (OR > 3.5 for all). In addition, the TMJ group had higher scores for C-HAQ DI (OR 4.1) compared with the non-TMJ group. The TMJ group also had higher scores compared to the non-TMJ group for PRgloVAS and for PRpainVAS (OR 3.1 and OR 2.7, respectively). An adverse impact on physical and psychosocial well-being was found in the TMJ group, with lower PhS score (OR 3.2) and to a lesser extent PsS score (OR 1.7) compared with the non-TMJ group. There were significantly lower scores for the specific CHQ health concepts concerning self-esteem, global general health, bodily pain/discomfort, impact on general health, family activity, parent impact emotional, child's physical and emotional behavior, and physical functioning in the TMJ group, with an OR between 2.0 and 2.9 (Table 2). A univariate analysis was performed for the same continuous variables, dividing them into quartiles, and the results were overlapping (data not shown).

Multivariable logistic regression. In the final regression model, we entered all variables that were found to be significantly associated with clinical TMJ involvement at the univariate analysis based on OR as follows: sex, disease duration, RF, cervical spine involvement, ESR, number of active joints, MDgloVAS, PRpainVAS, PRgloVAS, C-HAQ DI, PhS, and PsS (CHQ). We excluded JIA categories (the number of joints with pain in lower and upper extremities, LOM, and swelling) that were significant in the univariate analysis, but for which there was collinearity with other variables entered in the model. The 8 C-HAQ domains and 13 of 15 CHQ health concepts were excluded, since they were collinear with the respective total scores of the C-HAQ DI, PhS, and PsS (CHQ). In the final model, to

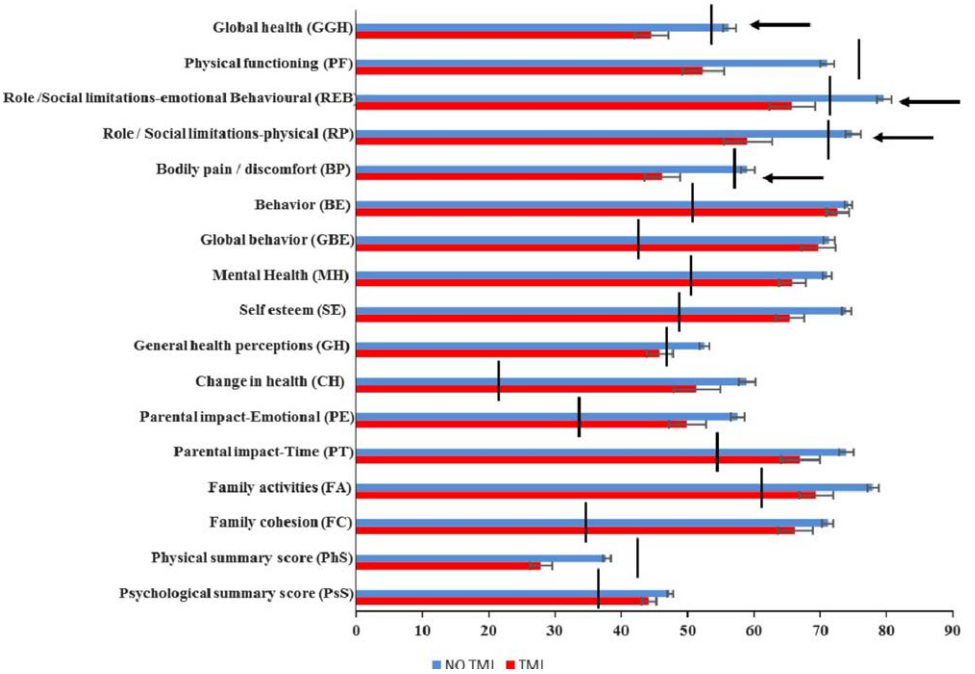

Figure 3. Mean and 95% confidence intervals of the 15 subscales (range 0–100) and the 2 summary scores (norm-based values with mean ± SD of 50 ± 10) of the Child Health Questionnaire (CHQ) for children with and without clinical temporomandibular joint (TMJ) involvement. Higher scores indicate better health. Vertical bars represent −2 SD of the mean of healthy children. Arrows indicate the 4 CHQ health concepts (global general health, role/social limitations emotional/behavioral, role/social limitations physical, and bodily pain/discomfort), in which only children with juvenile idiopathic arthritis with clinical TMJ involvement have scores less than −2 SDs of the mean of healthy children.

control for the level of disease activity, we also adjusted (with adjusted OR) for the following measures: participation in the MTX trial, number of active joints, ESR, and RF. The multivariable analysis (Table 3) showed that cervical spine involvement (adjusted OR 4.6), disease duration >4.4 years, being female, and having higher C-HAQ DI were the most important determinants for TMJ involvement (OR 2.8–1.5).

DISCUSSION

The present study demonstrated an association between clinical TMJ involvement, disability, and HRQOL in children with JIA, as well as independent associations between TMJ and cervical spine involvement. We found a female predominance, longer disease duration, polyarticular course, and higher level of disease activity in the group with clinical TMJ involvement, and we found that the majority had bilateral involvement.

The strength of the present study is the large international cohort of 3,343 children with JIA, with as many as 387 children with clinical TMJ involvement. In this cohort, systemic arthritis is overrepresented compared to population-based JIA cohorts, and enthesitis-related arthritis and psoriatic arthritis are not included, but otherwise our cohort is representative of most JIA populations according to sex and JIA category distribution (9,10,13,33,34). Moreover, the observed associations between clinical TMJ involvement and a number of disease variables are in accordance with studies based on radiologic TMJ involvement (7,9).

An obvious weakness in the present study is the assessment of TMJ involvement. No data on imaging were available. Since recognizable swelling in the TMJ is rare, the general definition of arthritis could not be applied (26). We are not aware of any TMJ studies in children with JIA that have used this general definition of arthritis. In line with other studies (7,9,15,35), clinical TMJ involvement (whether active or not) in our study was based on the presence of TMJ pain and/or LOM. The observed low frequency of clinical TMJ involvement was therefore not surprising. TMJ imaging and in particular MRI may detect TMJ abnormalities, even in JIA children without any clinical symptoms or signs of TMJ arthritis.

However, in a recent study using the same criteria for assessing clinical TMJ involvement in JIA, Kirkhus et al (35) reported that contrast-enhanced MRI demonstrated TMJ arthritis in 85% of the children with clinical TMJ involvement. Mostly, they found a combination of synovitis (78%) and bone abnormalities (72%). This finding is also in accordance with others (15,33). Koos et al (15) found a specificity of 0.86 for TMJ pain and 0.83 for LOM when comparing with MRI-detected TMJ arthritis in children with JIA. Sensitivity of these clinical signs of TMJ involvement was, however, low (15). We therefore anticipate that in the present study, the vast majority of the children with clinical symptoms actually had TMJ arthritis.

It must be emphasized that symptoms and signs in these joints are quite unspecific. We could expect that a

Table 2. Disability and HRQOL measures for children with (n = 387) and without (n = 2,956) clinical TMJ involvement*

	Cutoff	Clinical TMJ involvement OR (95% CI)
C-HAQ		
Dressing	>0.0	3.1 (2.4–3.9)
Arising	>0.0	3.7 (3.0–4.7)
Eating	>0.0	3.4 (2.7–4.2)
Walking	>0.0	2.6 (2.1–3.3)
Hygiene	>0.0	3.0 (2.4–3.7)
Reach	>0.0	5.5 (4.1–7.2)
Grip	>0.0	3.6 (2.8–4.4)
Active	>1.0	3.5 (3.3–5.6)
C-HAQ DI	>0.6	4.1 (3.2–5.2)
PRpainVAS	>1.8	2.7 (2.2–3.5)
PRgloVAS	>2.2	3.1 (2.5–4.0)
CHQ		
Global general health	≤30.0	2.0 (1.6–2.5)
Physical function	≤72.2	2.9 (2.3–3.6)
Role emotional behavior	≤77.8	2.4 (1.9–3.0)
Role physical	≤66.7	2.4 (2.0–3.1)
Bodily pain	≤50.0	2.2 (1.7–2.7)
Behavior	NA	NA
General behavior	NA	NA
Mental health	≤70.0	1.7 (1.3–2.1)
Self-esteem	≤70.8	2.0 (1.6–2.4)
General health	≤51.0	2.0 (1.6–2.5)
Change in health	≤25.0	1.6 (1.2–1.9)
Parental impact emotional	≤75.0	2.3 (1.7–3.0)
Parental impact time	≤77.8	1.9 (1.5–2.3)
Family activities	≤66.7	2.0 (1.6–2.5)
Family cohesion	≤30.0	1.7 (1.3–2.3)
Physical score	≤35.1	3.2 (2.5–4.1)
Psychosocial score	≤50.3	1.7 (1.4–2.2)

* Cutoff values for continuous variables were dichotomized as per receiver operating curve analyses. $P < 0.05$ for all variables except for behavior and general behavior, which were not significant in the univariate analysis. HRQOL = health-related quality of life; TMJ = temporomandibular joint; OR = odds ratio; 95% CI = 95% confidence interval; C-HAQ = Child Health Assessment Questionnaire; C-HAQ DI = C-HAQ disability index; PRpainVAS = parent's/patient's global assessment of the child's pain using a visual analog scale; PRgloVAS = parent's/patient's global assessment of the child's overall well-being using a visual analog scale; CHQ = Child Health Questionnaire; NA = not applicable.

minority, as discussed by Kirkhus et al (35), might have TMJ symptoms/signs due to myalgia or mechanical disorders, such as disc displacement. MRI would have been highly valuable for differential diagnostics. In the present study, we do not know to what extent dentofacial growth disturbances were registered. In other studies, approximately one-third of children with JIA and TMJ arthritis have been observed with micrognathia (2,3).

Children with JIA ages <7 years are reported to have almost no subjective TMJ dysfunction or symptoms (36). They may not be able to give a precise description of their symptoms and may develop severe facial growth disturbances, apparently without previous symptoms (2). With an average age at visit ≥10 years in the present study, the majority should have been old enough to report symptoms. The subgroup with TMJ arthritis constituted a rather large number of patients, although being only a small percentage of the whole series. Therefore, the present study can provide valuable characteristics of a large group of children with symptomatic TMJ involvement.

To our knowledge, no study has actually analyzed the relationship between TMJ involvement in children with JIA and HRQOL measures, although 1 study has reported an impact on the daily life activities (22). Our results showed an association with increased pain, and difficulties in eating, arising, and reaching in univariate analysis, and being disabled measured by the C-HAQ DI in multivariable analyses compared to the non-TMJ group. The associations between TMJ involvement and impaired HRQOL are in agreement with studies on non-JIA children and young adult JIA patients, showing that TMD may lead to impaired oral health and influence daily life (21,22,37). This finding is in accordance also with Leksell et al (22), who found that almost 80% of their children with JIA reported pain from the TMJs or the face, and nearly a quarter was severely influenced by orofacial pain in daily life. However, their findings were based on a small JIA cohort of 41 children, and adjustment for disease severity was not performed. Leksell et al (22) studied general orofacial symptoms, while the present study focused on clinical TMJ involvement. A high prevalence of TMD problems in adolescent and adult JIA patients is also reported by other authors (11,20).

The present study showed associations between clinical TMJ involvement and impaired HRQOL factors such as activity and physical and emotional wellbeing (38). A lower self-esteem (CHQ) and eating difficulties (C-HAQ) were significantly associated with clinical TMJ

Table 3. Disease activity, disability, and HRQOL characteristics associated with clinical TMJ involvement, adjusted for measures of high disease activity (n = 387)*

	Crude OR (95% CI)	Adjusted OR (95% CI)
Cervical joint involvement	7.8 (6.2–9.8)	4.6 (3.5–6.1)
Disease duration >4.4 years	2.2 (1.8–2.8)	2.8 (2.1–3.8)
C-HAQ DI >0.6	4.1 (3.2–5.2)	1.6 (1.2–2.3)
Female	1.5 (1.2–1.9)	1.5 (1.1–2.1)
PRgloVAS >2.2	3.1 (2.5–4.0)	1.3 (0.9–1.8)
CHQ PhS ≤35.1	3.2 (2.5–4.1)	1.2 (0.9–1.7)
CHQ PsS ≤50.3	1.7 (1.4–2.2)	1.2 (0.9–1.6)
PRpainVAS >1.8	2.7 (2.2–3.5)	1.1 (0.8–1.6)
MDgloVAS >26.0	2.7 (2.2–3.4)	0.9 (0.6–1.3)

* Multivariable logistic regression analysis adjusted for the following measures of high disease activity: methotrexate trial participation, number of active joints >5, erythrocyte sedimentation rate >15, and rheumatoid factor positive. HRQOL = health-related quality of life; TMJ = temporomandibular joint; OR = odds ratio; 95% CI = 95% confidence interval; C-HAQ DI = Child Health Assessment Questionnaire disability index; PRgloVAS = parent's/patient's global assessment of the child's overall well-being using a visual analog scale; CHQ = Child Health Questionnaire; PhS = physical summary score; PsS = psychosocial summary score; PRpainVAS = parent's/patient's global assessment of the child's pain using a visual analog scale; MDgloVAS = physician global evaluation of disease activity using a visual analog scale.

involvement in univariate analysis, but not in multivariable analysis. A lower self-esteem may be explained by craniofacial growth disturbances resulting in asymmetries and micrognathia, or related to high disease activity, since it is not significantly associated with clinical TMJ involvement in the adjusted analyses. However, several studies show a positive psychosocial effect in JIA patients after orthognatic surgery (39,40).

The TMJ is important for many daily life activities such as eating, chewing, talking, and oral health (5,37,41). Our results on eating problems in univariate analyses are in accordance with Leksell et al (41), who report problems with eating and oral health among JIA patients ages 10–19 years compared to healthy controls. Welbury et al (5) report significantly increased levels of poor oral hygiene and dental decay in children with JIA in general compared to controls. Ahmed et al (6) report a greater gingivitis score for the permanent teeth in the children with JIA and greater TMJ dysfunction in children with JIA compared to controls. Leksell et al (41), however, believe the problems with eating and performing good oral hygiene, are not only due to TMJ pain, but also due to medication and general disease activity. Adequate nutrition is essential for growth and general wellbeing in children with chronic inflammation. Eating difficulties is 1 of the 8 domains in the C-HAQ, and one question is "Is your child able to: Cut his/her own meat?" This question probably mainly reflects problems with fine motor skills due to finger and wrist arthritis more than eating problems due to TMJ. The C-HAQ is therefore not a specific tool for assessing TMJ dysfunction. The newly developed questionnaire Juvenile Arthritis Multidimensional Assessment Report may better explore eating difficulties and TMJ involvement in the question "Difficulties/limitations with bite into a sandwich or an apple" (42). Also, a standardized protocol for a proper diagnostic and classification system of TMJs in children with JIA, similar to, but shorter than, the established and validated Diagnostic Criteria for Temporomandibular Disorders (43,44), is under development in the EuroTMjoint network. Jaw opening is also included in the pediatric Gait, Arms, Legs, and Spine screening tool for musculoskeletal examination in children (45).

In contrast to Cannizzaro et al (9), we found longer disease duration in the TMJ group, but not significant differences between the 2 groups according to age at onset. Peak onset of TMJ arthritis according to age and time after disease onset are best studied in prospective JIA cohorts with imaging. In line with other studies, we found associations between TMJ involvement and upper extremity involvement as well as higher ESR (7,9). We also found a significant association between TMJ and cervical spine involvement, and in contrast to Cannizzaro et al, the association was confirmed in multivariable analysis, adjusting for higher disease activity (7,9).

A diagnosis of cervical spine arthritis is often based on clinical criteria such as cervical pain and stiffness. However, these symptoms could also be the result of myalgia, in the same way as clinical TMJ involvement may represent muscular pain instead of TMJ arthritis. The close proximity of the neck and masticatory muscles might partly explain this association.

Bilateral involvement was registered in 80.6% of the children with clinical TMJ involvement, in agreement with observations in adult JIA patients (11). At the baseline radiographic examination of the longitudinal followup study by Larheim et al (7), approximately 60% of the children with TMJ arthritis were assessed with bilateral TMJ involvement. This figure seems to be in accordance with most radiographic TMJ studies of JIA children (2,11,46,47), but the occurrence of bilateral TMJ involvement seems to be higher when using MRI (10,48,49). Children may have difficulties distinguishing whether there is pain in 1 or both TMJs.

There are some limitations in the present study. It was not designed to study TMJ arthritis specifically, and no imaging was performed. Furthermore, pediatric rheumatologists and not trained dental specialists performed the TMJ examination. Since TMJ involvement is most common in children with polyarthritis, another limitation of our study is to distinguish clinical variables associated with TMJ involvement from associations with arthritis in any specific joint or polyarticular disease in general. Therefore, we have performed a multivariable analysis, adjusting for measures of high disease activity such as participation in the PRINTO MTX trial, higher number of active joints, higher ESR, and being RF positive. However, other activity variables not adjusted for may still have interfered with our analyses.

In conclusion, clinical TMJ involvement is associated with impaired HRQOL in JIA children. The prevalence of TMJ involvement is surely an underestimate of TMJ arthritis, but most children with clinically evident TMJ involvement were probably identified. Special attention should be paid to the TMJ in children with cervical spine involvement, polyarticular course, longer disease duration, physical disability, and female sex. There is a need for an internationally accepted definition of TMJ arthritis, whether based on clinical findings and/or imaging. Longitudinal TMJ studies with clinical assessment and imaging are warranted to identify early predictors of severe facial growth disturbances, treatment modalities, and outcome over time.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Frid had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Frid, Nordal, Ravelli, Martini, Ruperto.

Acquisition of data. Rygg, De Angelis, Palmisani, Murray, Oliveira, Simonini, Corona, Davidson, Foster, Steenks, Flato, Zulian, Baildam, Saurenmann, Lahdenne, Ravelli, Ruperto.

Analysis and interpretation of data. Frid, Nordal, Bovis, Giancane, Larheim, Marafon, De Angelis, Flato, Ravelli, Martini, Pistorio, Ruperto.

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Paper II

Salivary oral microbiome of children with juvenile idiopathic arthritis: A Norwegian cross-sectional study.

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Salivary oral microbiome of children with juvenile idiopathic arthritis: A Norwegian cross-sectional study

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ABSTRACT

Background: The oral microbiota has been connected to the pathogenesis of rheumatoid arthritis through activation of mucosal immunity. The objective of this study was to characterize the salivary microbiome associated with juvenile idiopathic arthritis (JIA), and correlate it with the disease activity including gingival bleeding.

Methods: Fifty-nine subjects with JIA (mean age 12.6 ± 2.7 years) and 34 healthy controls (HC; mean age 12.3± 3.0 years) were consecutively recruited in this Norwegian cross-sectional study. Information about demographics, disease activity, medication history, gingival bleeding index (GBI), simplified oral hygiene index (OHI-S), and frequency of tooth brushing was obtained. Microbiome profiling of saliva samples was performed by sequencing of the V1-V3 region of the 16S rRNA gene, coupled with a species-level taxonomy assignment algorithm; QIIME, LEfSe and R- package were used for downstream analysis.

Results: There were no significant differences between JIA and HC in alpha- and beta-diversity. However, differential abundance analysis revealed several taxa to be associated with JIA: *TM7-G1*, *Solobacterium* and *Mogibacterium* at the genus level; and *Leptotrichia* oral taxon 417, *TM7-G1* oral taxon 352 and *Capnocytophaga* oral taxon 864 among others, at the species level. *Haemophilus* species, *Leptotrichia* oral taxon 223, *and Bacillus subtilis*, were associated with healthy controls. *Gemella morbillorum, Leptotrichia* sp. oral taxon 498 and *Alloprevotella* oral taxon 914 correlated positively with the composite juvenile arthritis10-joint disease activity score (JADAS10), while *Campylobacter* oral taxon 44 among others, correlated with the number of active joints. Of all microbial markers identified, only *Bacillus subtilis* and *Campylobacter* oral taxon 44 maintained false discovery rate (FDR) < 0.1.

Conclusions. Several taxa associated with chronic inflammation were found to be associated with JIA and disease activity. Our results suggest that oral microbial disruption may be involved in the chronic inflammatory burden in JIA, which warrants further investigation.

Keywords: Gingivitis; Juvenile idiopathic arthritis; Microbiome; Oral health; Next Generation Sequencing (NGS); 16S rRNA

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children, with an annual incidence of 1-2 per 1000 children (1, 2). The pathogenesis of JIA remains unknown, although environmental triggers of disease in genetically predisposed individuals have been suggested (3). Infectious agents are suspected to be environmental triggers for JIA and one of several possible mechanisms is molecular mimicry between bacterial molecules and self-antigens. It is well-known that host-microbe interaction is important for recognition and development of the immune system (4). The human microbiome includes the collective genomes of the microbiota, which is the term for all microbes in the body (3). A dysbiotic imbalance in the host microbiota might contribute as a potential trigger in the development of immune-mediated diseases, including JIA. The patterns of the JIA gut microbiome reportedly resemble the microbiome associated with other autoimmune diseases such as type 1 diabetes, Crohn's disease and ankylosing spondylitis microbiota (5, 6).The gut microbiome in children with JIA is reported to differ from healthy individuals (7-14), where a lower abundance of Firmicutes and a higher abundance of Bacteroidetes were found in the gut microbiota of subjects with oligoarticular and polyarticular rheumatoid factor (RF) negative new-onset JIA (7). Furthermore, Actinobacteria and Fusobacteria have been seen only in subjects with JIA while Lentisphaerae is reported exclusively in healthy controls (7). Higher abundance of Bacteroides is also seen in enthesitis-related-arthritis (11). In all studies on the gut microbiome in JIA, however, no single species has been identified and different studies show changes in different taxa (7-14). These studies suggest that dysbiosis in the microbiome with overabundance in pathogenic microbes, may result in dysregulation of the immune system through disruption of the integrity of mucosal barrier and altered interaction with gut immune cells (15). Aberrations in mucosal homeostasis may be associated with the increased bacterial urease activity, reportedly found in fecal samples of JIA

subjects as compared to healthy controls. The increase of urease activity is hypothesized to be the result of alterations in the anaerobic bacterial flora (16). It is still an open question whether the observed microbial dysbiosis is a cause or an effect of the disease itself.

The oral microbiome has been proposed to play a role in rheumatoid arthritis by contributing to systemic inflammation (17), and may also play a similar role in JIA. Furthermore, dysbiosis and periodontitis has been found to be associated to increased severity of rheumatoid arthritis (18). Gingivitis or gingival bleeding, which is a reversible inflammation of the gingiva caused by dental biofilm accumulation is a prerequisite for progression to periodontitis (19). Gingival bleeding is found to be higher in subjects with JIA compared to healthy ones (20, 21). So far, there have been no attempts to characterize the salivary oral microbiome associated with JIA with the next generation sequencing method (NGS). *The aim of this study was therefore to investigate the oral microbiome in saliva of children with JIA and relate it to the disease activity including gingival bleeding.*

MATERIALS AND METHODS

Study design and subject recruitment

The present cross-sectional study is a project within NorJIA, a larger Norwegian prospective multicenter cohort study on JIA registered in Clinical Trials.gov (NCT03904459). The clinical and demographic data was collected between November 2015 and December 2018 at the Department of Pediatrics and Adolescence Medicine, University Hospital North Norway (UNN), Public Dental Service Competence Centre of North Norway (PCNN), Tromso, and Haukeland University Hospital Bergen, and Oslo University Hospital, Rikshospitalet, Oslo. Informed consent was collected from all study participants and the study was approved by the Institutional Medical Research Ethics Committee (2015/318). Ninety-three children in total were consecutively recruited; Fifty-nine participants with JIA: participants with JIA and newly diagnosed TMJ arthritis (n=15) at the departments above, participants with JIA without TMJ arthritis (n=44) at UNN, and healthy controls (HC; n=34) matched for age and gender at PCNN (Table 1). HC were recruited from the larger multicenter study NorJIA,

and consisted of children attending the regular Norwegian community dental care. The clinical characteristics of the two groups are presented in Table 1. Inclusion criteria for subjects with JIA were fulfillment of the JIA classification criteria defined by the International League of Associations for Rheumatology (ILAR) (22), and age at the study visit <18 years, with or without arthritis activity in one or both TMJs. Subjects on antibiotics prior to sampling were excluded.

Demographics and assessment of JIA disease activity

Patient demographics, subtype of JIA, duration and onset of JIA, medication, general clinical examination, measures of disease activity and severity were collected by pediatric rheumatologists.. Number of active joints was defined according to the general definition of arthritis: swelling within a joint or limitation in the range of joint movement with joint pain or tenderness (23), while TMJ arthritis was based on both clinical signs and symptoms, and MRI imaging. Patient-reported global assessment of overall well-being (PRgloVAS) and patient-reported pain (PRpainVAS) within the last week on a 10-cm visual analogue scale (VAS) were collected. On this scale, 0 indicates no activity/no pain/best global health, and 10 indicate the maximum activity/worst pain/poorest global health, respectively. A routine complete blood cell count, including rheumatoid factor (RF) and human leukocyte antigen B27 (HLA-B27) was registered. The composite juvenile arthritis disease activity score (JADAS10, range from 0 to 40) was calculated as the simple sum of the physician global evaluation of overall disease activity on a 10-cm visual analogue scale (VAS), (MDgloVAS, range 0–10), patient-reported global assessment of well-being (PRgloVAS, range 0–10), active joint count (up to maximum 10 joints), and the erythrocyte sedimentation rate (ESR) (normalized to 0–10) (24, 25). Inactive disease was defined according to the ACR provisional criteria (26) requiring all the following: 1) no active joints; 2) no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA; 3) no active uveitis; 4) normal ESR or C-reactive protein (CRP); 5) MDgloVAS =0; and 6) duration of morning stiffness of ≤15 minutes (26).

Intraoral examination and collection of saliva.

A modified version of the Gingival bleeding index (GBI) (27) and a modified version of the Simplified Oral Hygiene Index (OHI-S) (28) were used (Table 1). For GBI, a dental probe was carefully applied without any pain, in the upper part of the gingival sulcus, and then removed without doing a horizontal movement along the tooth surface. Bleeding on probing within 10 seconds was registered. Angulation of the dental probe of 60 degrees to the vertical axis of the tooth was applied if possible. The mesial, distal and central surface of the index teeth 16, 26, 36, 46, 11 and 31 were chosen. The number of bleeding tooth surfaces were divided to the total number of tooth surfaces examined and finally presented as the mean percentage (%), range 0-100% where a higher percentage represents a worse score in bleeding. Gingival bleeding was diagnosed according to a gingival bleeding score ≥ 10% (29).

OHI-S is a sum score of plaque-index and dental calculus index and is presented as a mean score index, where a higher index represents a worse score in OHI-S. Plaque-index and dental calculus index is the buccal scores + the lingual scores divided by the total number of examined buccal and lingual surfaces. OHI-S was not calculated in children with orthodontic appliances and subgingival status was not evaluated. All children ≥12 years filled out an oral health related questionnaire and the parents/proxies filled out for children <12 years. One of the questions were; How often do you brush your teeth: 1, never 2, most days 3, once daily 4, twice daily or more.

Two calibrated specialists in oral and maxillofacial surgery and pediatric dentistry (PF, JH) collected before oral examination, unstimulated whole saliva (UWS) for 6 minutes and paraffin chewing stimulated whole saliva (SWS) for 3 minutes, according to a standardized protocol (i.e. restrictions to food and drinks 2 hours prior to sampling). Furthermore, medications taken the same day or the day before sampling was recorded. Only SWS were used for microbial analyses. Immediately after collection, each saliva sample was aliquoted and placed in a −80°C freezer until further analyses.

DNA extraction

Seven-hundred and fifty microliters from each SWS sample was mixed with an equal amount of phosphate buffer saline (PBS) and spun down at 9600 *g* for 5 minutes, before the supernatant was carefully removed. The pellet was resuspended in 155 mL PBS and 25 mL MetaPolyzyme multilytic enzyme mix (Zigma-Aldrich, USA) and incubated on a 37^{o} C heat block for 4 hours, for digestion of the bacterial cell wall. The digests were then transferred to a QIAcube (Qiagen, Hilden, Germany) for DNA extraction using preprogramed protocol using the QIAamp DNA Mini Kit (Qiagen, Germany) with 100 µL elution volume.The quality of the isolated DNA (high molecular weight and non-fragmented DNA) was assessed by running extracted DNA samples on agarose gel (1%) with 1kb ladder (Termo Fisher Scientific, Invirtogen, USA). The amount of yield DNA was then measured using Invitrogen Qubit 3.0 Fluorometer (Termo Fisher Scientific, Invirtogen, USA) according to the manufacturer's instructions.

16S rRNA sequencing and bioinformatic analysis

16S rRNA gene library preparation and sequencing were done at the Australian Center for Ecogenomics (Brisbane, Australia) as detailed previously (30). Briefly, the V1-3 region was amplified using the degenerate primers 27FYM (31) and 519R (32) in standard PCR conditions. The amplicons (~ 520 bp) were purified and indexed with unique 8-base barcodes in a second PCR. The tagged libraries were then pooled together in equimolar concentrations and sequenced using MiSeq v3 2x300 bp chemistry (Illumina, USA). Preprocessing of data (merging of reads, primer trimming, quality-filtration, alignment and chimera removal) was performed as detailed elsewhere (33). The high quality, merged reads were assigned species-level taxonomies using our BLASTn-based algorithm (33, 34). The resultant microbial profiles were used as input to QIIME (Quantitative Insights Into Microbial Ecology) software package version 1.9.1 (35) for downstream analysis including subsampling, generation of taxonomy plots/tables and rarefaction curves, and calculation of species richness, coverage, alpha diversity indices and beta diversity distance matrices. Principal component analysis

(PCoA) was used for clustering samples based on overall microbial similarity, while Linear discriminant analysis (LDA) effect size (LEfSe) (36) was used to detect differentially abundant taxa between the groups. To assess the association between the bacterial profiles and disease activity (JADAS10 and number of active joints) a Spearman correlation matrix was computed with R package. Correlations with P-value ≤ 0.01 were considered significant.

Statistical and bioinformatic analyses

For description of clinical and demographic data, median (IQR), mean (standard deviation) and frequencies (percentage) were used. Associations between study participants with JIA and HC and different disease characteristics were analyzed by chi-square test for categorical variables (Fisher´s exact test) and Student´s t-test for continuous variables if reasonably normally distributed, otherwise Man-Whitney U test was used. A multivariable logistic regression analysis was performed to adjust for OHI-S, age and gender in the association between JIA and GBI. A *P*-value ≤ 0.05 was considered statistically significant for clinical parameters. For testing correlation between species and measures of disease activity (JADAS10, number of active joints), p-values were adjusted for multiplicity with Benjamini-Hockberg method (FDR ≤ 0.1).

RESULTS

Demographic and disease activity parameters

Demographics and disease activity parameters for the group with JIA, and HC are given in **Table 1**. There was a female predominance in both groups, and RF negative polyarthritis was the most common category among children with JIA (25%). The simplified oral hygiene index (OHI-S) was significantly higher among children with JIA with median 0.5 (IQR 0.3-0.7) compared to median 0.3 (IQR 0.0-0.4) in HC. Also, the plack-index (PI) was higher in JIA (Table 1). There was also significantly higher modified gingival bleeding index (GBI) in the group with JIA with median 22 (IQR 6-40) % compared to HC with median 6.0 (IQR 0-11) % but no association was found between

JIA and GBI when adjusting for OHI-S (**Supplementary Table 1**). Within the JIA group no significant differences in GBI were found between subjects without DMARDs, on methotrexate or on biologics, with GBI median 10 (IQR 10-30) %, median 20 (IQR 10-40) %, and median 30 (IQR 20-40) %, respectively. There was no difference in frequency of tooth brushing between participants with JIA and HC, in JIA 37 of 47 (79%) and in HC 23 of 32 (72%) brushed their teeth twice or more daily. Restrictions to food and drinks 2 hours prior to saliva sampling were reported in 41 of 93 study participants (44%). In 10 of 93 (11%) no restrictions were reported and in 42 of 93 (45%) information on restrictions were not available. Among the 93 participants 16 reported intake of no-DMARD medications, 3 methotrexate, and 6 biologics the same day or the day before saliva sampling.

Sequencing and data processing statistics

The raw data has been deposited and is publicly available from SRA (# PRJNA605805). A total of ~8.2 million sequences were obtained (range of 30,113-526,987 reads per sample), of which about 85% were successfully merged; however, only 35% were retained after quality filters and 20% after chimera removal. Of the high-quality, non-chimeric reads, 88% could be assigned species-level taxonomy (mean of 15,360± 18368 reads per sample). Details of the reads statistics before and after each quality control step are provided in **Supplementary dataset 1.**

Overall microbial profile

Using a minimum count of 100 reads per species as cutoff, a total of 216 bacterial species belonging to 58 genera and 8 phyla were identified across all samples; the relative abundances and detection frequencies of these taxa in each sample is provided in **Supplementary dataset 2**, **3** and **4** respectively. On average, 134 species (range 90-186) and 45 genera (range 32-58) were detected per subject. Fifty-seven species and 29 genera were identified in more than 90% of the samples and can be defined as core salivary taxa. The average relative abundances of all phyla, top genera and species (those present at an average abundance of ≥ 1% in the control group) in each of the study groups are

shown in **Figure 1**. Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Fusobacteria were the major phyla in order accounting for more than 98% of the reads. Thirteen genera accounted for 90% of the average microbiome, with *Prevotella, Streptococcus, Haemophilus, Actinomyces, Porphyromonas* and *Rothia* alone making up ~ 70%. At the species level, *Prevotella melaninogenica, Haemophilus parainfluenzae, Rothia mucilaginosa, Porphyromonas sp. oral taxon 279, Prevotella histicola, Actinomyces odontolyticus* were the most abundant species, constituting around 40% of the microbiome on average.

Bacterial diversity and differentially abundant species

There were no significant differences between children with JIA and the healthy group neither in species richness and alpha diversity, or in PCoA (beta diversity) as shown in **Figure 2**. However, differential abundance analysis did reveal significant differences (**Figure 3)**. At the phylum level JIA was associated with enrichment of Spirochaetes and Saccharibacteria and depletion of Proteobacteria. Genera *TM7-G1, Solobacterium* and *Mogibacterium* were associated with JIA, while *Haemophilus* and *Bacillus* were associated with healthy subjects (**Figure 3B**). *Haemophilus parainfluenzae, Leptotrichia species oral taxon 223, Haemophilus pittmanae*, *Prevotella denticola* and *Bacillus subtilis* were key bacterial species associated with the healthy group, whereas the JIA group showed higher abundance of 11 bacterial species of which *Leptotrichia species oral taxon 417, TM7 G1, Capnocytophaga species oral taxon 864, Veilonella atypica* and *Mogibacterium diversum* were most enriched (**Figure 3C**).

The relative abundances of the top six differentially abundant taxa (based on LDA score) are shown for individual samples in **Figure 4.** These microbial associations between the JIA and the healthy group were independent of the differences between the two groups in GBI. The microbial associations with the GBI are shown in **Supplementary Figure 1**. Notably, after adjustment of p-values for multiple comparisons with Benjamini-Hochberg method only genus *Bacillus* and *B.*

subtilis maintained a false discovery rate (FDR) of ≤ 0.1 and the per-sample relative abundance plot for *B. subtilis* is shown in **Supplementary Figure 2.**

Microbial association with disease activity

Correlation analysis revealed significant association between a group of bacteria species and disease activity (**Figure 5**). *Gemella morbillorum, Leptotrichia* sp. oral taxon 498 and *Alloprevotella* oral taxon 914 correlated positively with the JADAS10, primarily through their association with MDgloVAS. *G. morbillorum* also correlated with PRgloVAS. Several species correlated positively with the number of active joints but *Campylobacter* oral taxon 44 showed the strongest association and was the only species that maintained FDR ≤ 0.1 when *P*-values were adjusted for multiplicity with the Benjamini-Hockberg method.

JIA subjects with TMJ arthritis showed a different microbial association compared to JIA subjects without TMJ arthritis **(Figure 6**). *Haemophilus parainfluenzae, Prevotella pallens, actinomyces species oral taxon 180* were the top species differentially enriched in JIA with TMJ subjects. *Campylobacter* oral taxon 44 also showed an association with TMJ arthritis (**Supplementary Figure 3),** although opposed to its association with the number of active joints, it did not maintain FDR ≤ 0.1. *Rothia mucilaginosa, Atopobium parvulum* and *Oribacterium sinus* were significantly more abundant in children with JIA without TMJ arthritis.

DISCUSSION

This study is to our knowledge, the first to examine the salivary oral microbiome in subjects with JIA and healthy controls using the NGS method. We found no significant differences between children with JIA and HC in species richness or in PCoA, i.e. alpha or beta diversity. Differential abundance analysis, however, revealed that JIA was significantly associated with taxa associated with chronic inflammation, and that several of these species including *Campylobacter* oral taxon 44 correlated with disease activity in terms of increased number of active joints.

A strength of the study is that a majority of the children with JIA were females diagnosed with either oligoarthritis persistent or RF negative polyarthritis in accordance with most population-based studies, pointing to representability of our study cases. The oral environment is a complex environment that contains distinct microbial niches each with its distinct microbial inhabitant. One can argue that salivary microbiome represents oral microbiome but a limitation is that we did not sample multiple oral sites to study the full spectrum of the oral microbiome. In contrast to our study Grevich et al performed sampling from the dental plack when studying the oral microbiome in JIA (37). Additionally, our findings must be evaluated in the context of a limited sample size and being a cross-sectional study. In our study, saliva samples for collecting oral microbiota were directly frozen and aliquoted before further processing. However, other collection methods for sampling of oral microbiota, such as mouthwash sampling methods are available (38) and appear to be stable concerning bacterial diversity at ambient temperature after 4-7 days, thus making immediately freezing of microbial DNA not necessary. Some distinct differences in relative abundance of specific microbial taxa are seen between these methods compared to samples that are frozen immediately (38), thus indicating that directly freezing of samples is still the best choice. Other strengths with this study are the food and drinks restrictions prior to sampling taken in 41 of 93 children, and that a majority of the participants had no intake of systemic medication the same day or the day before saliva sampling. In our study between 90 and 186 different species were found in the salivary microbiome of the study subjects with fifty-seven species shared in more than 90% of the subjects. The core salivary microbiome in the study subjects comprised 22 species detected in all individuals. In other studies the core microbiome was found to be similar or even in a lower number (39, 40). The predominant bacterial genera found in the salivary microbiome in both JIA and healthy saliva in our study consisted of *Prevotella, Streptococcus, Haemophilus, Actinomyces, Porphyromonas* and *Rothia*, which is similar to other studies in both children with JIA and healthy (41). The microbial diversity and richness of the salivary oral microbiome between the JIA and healthy controls were comparable. This is in line with other studies that investigated the oral microbial diversity between

subjects with chronic inflammatory diseases, i.e. rheumatoid arthritis, and healthy controls (42, 43). Differential abundance analysis revealed several taxa to be associated with or depleted in JIA. At phylum level, we found an overabundance of Spirochaetes and Saccharibacteria and depletion of Proteobacteria. This is in line with Xu et al. showing Proteobacteria (*Neisseria*) and Firmicutes (*Selenomonas*) as a healthy core salivary microbiome, together with the phyla Bacteroidetes (*Porphyromonas*). They also showed that the salivary microbial composition shifts with aging in children, and a strength of our study is age-matching between children with JIA and healthy controls (44).

At the genus level, *Haemophilus, Bacillius* and *Olsenella* were depleted from the subjects with JIA while there were significant overabundance of bacteria known to be associated with chronic inflammation, such as *TM7-G1*, *Solobacterium* and *Mogibacterium* (45-47). The higher abundance of *Haemophilus parainfluenzae*, *Leptotrichia species oral taxon 223, Haemophilus pittmanae, Prevotella denticola* and *Bacillus subtilis* in the healthy group in our study could highlight the importance for health of sustaining a high proportion of these species in the oral microbiome. In fact, *Bacillus subtilis* species has been reported to have a role in limiting inflammatory response by down-regulation of the pro-inflammatory interleukin-8 production and up regulation of inducible nitric oxide synthase (iNOS) protein levels (48) . The depletion of *Haemophilus* species in salivary microbiome has also been reported in subjects with rheumatoid arthritis (49)**.** On the other hand *Leptotrichia species oral taxon 417, TM7 G1*, *Capnocytophaga species oral taxon 864*, *Veilonella atypica* and *Mogibacterium diversum* were found to be highly abundant in children with JIA. The oral taxon TM7 has been associated with chronic inflammation (50). In line with our study, Grevich et al found depletion of genera Prevotella (phylum Bacteroidetes) in JIA, but they report an overabundance of the genera Haemophilus and Kingella (phylum proteobacteria) in JIA, which was not found in our study (37).

The role of oral and gut microbiota in many inflammatory diseases has been suggested, and there is evidence for the role of molecular mimicry in such diseases. It has for example, been reported that a

molecular mimicry between a peptide from the von Willebrand factor type A from the oral microbe *Capnocytophaga ochracea* can be attributed to the activation of the Sjögrens syndrome antigen A/Ro60-Reactive T cells (51).

Interestingly, in our study *Campylobacter* oral taxon 44 showed a strong correlation with the number of joints affected in subjects with JIA. *Campylobacter* has a well-known association with reactive arthritis and other inflammatory diseases in both children and adults (52). Dong et al. found in the gut microbiota in 32 patients with JIA a positive correlation between disease activity and increased abundance of *Firmicutes, Bacteroidetes* and *Bacteroidaceae* at the phyla level (14). The same authors found a negative correlation between disease activity and decreased abundance of *Ruminococcaceae, Faecalibacterium, Proteobacteria* or *Enterobacteriaceae* (14).

The species found in our study on the salivary oral microbiome in JIA are not found in studies on the gut microbiome in JIA (7-14). However, disruption of microbial ecology was found and this dysbiosis may have community effects on the host more powerful than the actions of just one single microbe (53). This is in line with Dijkhuizen et al. reporting dysbiosis in subjects with JIA in gut microbiota compared to healthy controls. They also found that age and geographic origin were connected to microbiota profiles (13). In rheumatoid arthritis both oral and gut dysbiosis are well described and no consistent single bacterial species appears to be the causing agent (54), even if periodonto-pathogenic bacteria such as *Porphyromonas gingivalis* have been suggested to contribute to generation of anti-citrullinated protein antibodies (ACPAs) in rheumatoid arthritis (55-57). In addition, dysbiosis and periodontitis were found to be associated to increased severity of rheumatoid arthritis (18). Other factors reported to be associated with dysbiosis are diet, lifestyle and drug use, especially the use of antibiotics (58, 59). Early life antibiotic use is shown to increase the risk of developing JIA later in life, and may predispose due to a shift in microbiota composition (59, 60). In our study none of the participants were on any antibiotics prior to sampling, but previous history of antibiotic use were not recorded.

The significantly higher gingival inflammation found in patients with JIA compared to healthy controls is in line with other studies investigating JIA and oral health (20, 21, 37, 61, 62) but also in contrast with some studies finding no significant difference between JIA and healthy (63-69), depending on different study design and measurement of gingival inflammation (70). Despite higher GBI, no difference in frequency of tooth brushing was found between JIA and healthy controls in our study. After adjusting for dental plack and calculus (OHI-S), JIA was not found to be a predictor for gingival inflammation in terms of higher GBI. In line with other studies (65) we found OHI-S to be a predictor for gingival inflammation. There were no overlap between overabundant bacteria associated with GBI and those associated with JIA. This may be explained by the disruption of microbial taxa in JIA and not by specific bacteria, resulting in more gingival inflammation in JIA. Furthermore, we did not sample for microbiota in dental plack but in saliva.

There are some indications that the biologic agent etanercept might reduce periodontal inflammation in children with JIA (68). In our study 40% of the subjects with JIA were on biologic treatment either alone or in combination with methotrexate, but no significant differences were seen in GBI between the different medication groups. Instead, children with JIA had more gingival bleeding compared to healthy, despite immune-modulating medication.

CONCLUSION

Taxa associated with chronic inflammation was found to be enriched in the saliva of children with JIA and associated to disease activity. This disrupted microbial ecology may have triggered a local pathological immune response resulting in increased gingival bleeding in JIA. Prospective cohort-studies with treatment-naïve patients with new onset JIA are warranted to further elucidate the role of the oral microbiome in disease etiology and severity.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained by the Regional Committee for Medical and Health Research Ethics (REK Nord; approval no. 2015/318). Study participant gave their consent to participate in the study.

CONSENT FOR PUBLICATION

Not applicable

COMPETING INTERESTS

Nothing to declare

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Authors' contributions

P.F, E.N and M.Al-H design the study. P.F, J.H, V.R, N. T. S, A.R, J. R. B, B. Fl, E.G.G, and L. C collected the clinical data and saliva samples. D. B, N.N. Al-H, F. A, and T. C did the the sequencing analysis. P.F, E.N, N.N.Al-H and M.Al-H wrote the manuscript. All Authors critically reviewed the manuscript. The corresponding authors attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Disclaimer

The authors declare that they have no competing interests

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FIGURE LEGENDS

Figure 1. Microbiological profiles. DNA extracted from saliva was sequenced for the V1-V3 region of the 16S rRNA gene using paired-end chemistry. The generated reads were merged, quality-filtered and classified to the species level using a BLASTn-based algorithm. The stacked bars show the average relative abundances of all phyla and top genera and species (those with relative abundance ≥ 1%) identified in the study groups. OT: oral taxon.

Figure 2. Species richness and diversity. Taxonomic profiles were rarified and used to calculate observed richness, expected richness (Chao index), alpha diversity indices (Shannon's and Simpson's) and distance matrices employing standard QIIME scripts. Left: Box and whisker plots of species richness and aloha diversity in each group. Differences were not significant by Mann–Whitney U test. Right: Clustering of samples with PCoA based on abundance Jaccard distance matrix. Plots were generated with QIIME and R Package.

Figure 3. Differentially abundant taxa. (a) Phyla, **(**b) Genera and (c) species that showed significant differences in relative abundance between the two study groups as identified by linear discriminant analysis (LDA) effect size analysis (LEfSe) – 2.5 LDA score cutoff. OT: oral taxon. ** FDR ≤ 0.1 (Benjamini-Hochberg method).

Figure 4. Per sample abundance plots. Relative abundances of top six differentially abundant species (based on LDA score) in individual samples. OT: oral taxon. ** FDR ≤ 0.1 (Benjamini-Hochberg method).

Figure 5. Heatmap of the microbial association with disease activity. A Spearman correlation matrix was computed using R package. Correlations with P-value ≤ 0.01 were considered

significant. The r-value for nonsignificant correlations was set to zero (blue on the heatmap). OT: oral taxon. ** FDR ≤ 0.1 (Benjamini-Hochberg method).

Figure 6. Differentially abundant taxa by TMJ arthritis. (a) Phyla, **(**b) Genera and (c) species that showed significant differences in relative abundance between the JIA subjects with and without TMJ involvement, as identified by linear discriminant analysis (LDA) effect size analysis (LEfSe). 2.5 LDA score cutoff. OT: oral taxon. ** FDR ≤ 0.1 (Benjamini-Hochberg method).

SUPPLEMENTARY MATERIAL

Supplementary figure 1. Heatmap of the microbial association with GBI. A Spearman correlation matrix was computed using R package. Correlations with P-value ≤ 0.01 were considered significant.

Supplementary figure 2. Per sample abundance plots for *Bacillus subtilis*. Relative abundances of *Bacillus subtilis* in individual samples by disease status (left) and TMJ involvement status (right).

Supplementary figure 3. Per sample abundance plots for *Campylobacter sp.* oral taxon 44. Relative abundances of *Campylobacter sp.* oral taxon 44 in individual samples by TMJ involvement status.

Supplementary Dataset1. Sequencing and data processing statistics.

Supplementary Dataset 2. Relative abundances and detection frequencies of phyla identified in the individual samples.

Supplementary Dataset 3. Relative abundances and detection frequencies of genera identified in the individual samples.

Supplementary Dataset 4. Relative abundances and detection frequencies of species identified in the individual samples.

Supplementary table 1. Clinical characteristics associated with gingival bleeding (gingival bleeding index (GBI) ≥10%)*

	Gingival bleeding (n=41)			
	Crude OR (95% CI)	p-value	**Adjusted OR (95% CI)**	p-value
JIA	4.8 (1.7-14.0)	0.004	2.9 (0.9-9.5)	0.07
Age	0.9 (0.7-1.2)	0.651	0.9 (0.7-1.2)	0.578
Gender (female)	0.9 (0.3-3.1)	0.917	0.8 (0.2-2.8)	0.688

*Multivariable logistic regression analysis adjusted for simplified oral hygiene index score (OHI-S).

Table 1. Demographic and disease activity characteristics among children with juvenile idiopathic arthritis (JIA) and healthy controls (HC).

	JIA (n=59)	HC (n=34)	Cut-off	P-value*
Demographic characteristics				
Female, no. (%)	43 (73)	27 (79)		0.482[a]
Age at sampling, years	12.6 ± 2.7	12.3± 3.0		0.650[b]
Age at onset	6.0 (2.0-10.0)			-
Geographics, no (%)				
Troms county	34 (57.6)	34 (100)		-
Finnmark county	17 (28.8)			-
Nordland county	5 (8.5)			-
Eastcoast county	2 (3.4)			-
Westcoast county	1 (1.7)			-
				-
Disease duration, years	5.0 (3.0-10.0)			
JIA category, no. (%)				
Persistent oligoarthritis	11 (189)			-
Extended oligoarthritis	13 (22)			-
Polyarthrtitis RF pos	3 (5)			-
Polyarthrtitis RF neg	15 (25)			-
Systemic arthritis	0 (0)			-
Psoriatic arthritis	3 (5)			-
Enthesitis related arthritis	7 (12)			-
Undifferentiated arthritis	7 (12)			-
Gingival bleeding index, %	22 (6-44) (n=44)	6 (0-11) (n=25)	>10	0.000[b]
Simplified oral hygiene index (IQR)	0.5 (0.3-0.8) (n=43)	0.3 (0.0-0.4) (n=25)		0.002[b]
Plack-index, % (IQR)	0.5 (0.3-0.8) (n=43)	0.3 (0.0-0.3) n=25)		0.001[b]
Disease activity variables**				
JADAS10	12.8 (7.6-18.0) n=48			
Subjects with active disease, no. (%)	44 (74.6)			-
Subjects with active joints, no. (%)	23 (39.0)			-
Subjects with TMJ arthritis, no. (%)	15 (25.4)			-
Subjects with IACs to the TMJ, no. (%)	8 (13.6)			-
No.of active joints	0.0 (0.0-1.0)			
MDgloVAS	2.5 (1.0-5.0) (n=58)			
PRgloVAS	2.5 (0.5-4.0) (n=49)			
HLA-B27 positive, no (%)	20 (36.4) (n=55)			-
Rheumatoid factor positive, no (%)	1 (2.0) (n=51)			-
Type of Medication				
No DMARDs, no (%)***	15 (25)			
Methotrexate, no (%)	20 (34)			-
Biologics comb, no (%)****	24 (41)			-

Values are the median (IQR) unless indicated otherwise. [a]Chi-square test. [b]Wilcoxon-Mann-Whitney test. *P <0.05 for statistical significance. ** remission status according to the ACR provisional remission criteria (26); ***NSAIDs and/or IACs; ****current or previous use alone or in combination with other DMARDs; JIA, juvenile idiopathic arthritis; JADAS10, the composite juvenile arthritis10-joint disease activity score; TMJ, temporomandibular joint; MDgloVAS, medical doctor global assessment of well-being; PRgloVAS; patient reported global assessment of well-being; IACs, intraarticular corticosteroid injections; DMARDs, disease modifying antirheumatic drugs

Figure 1.

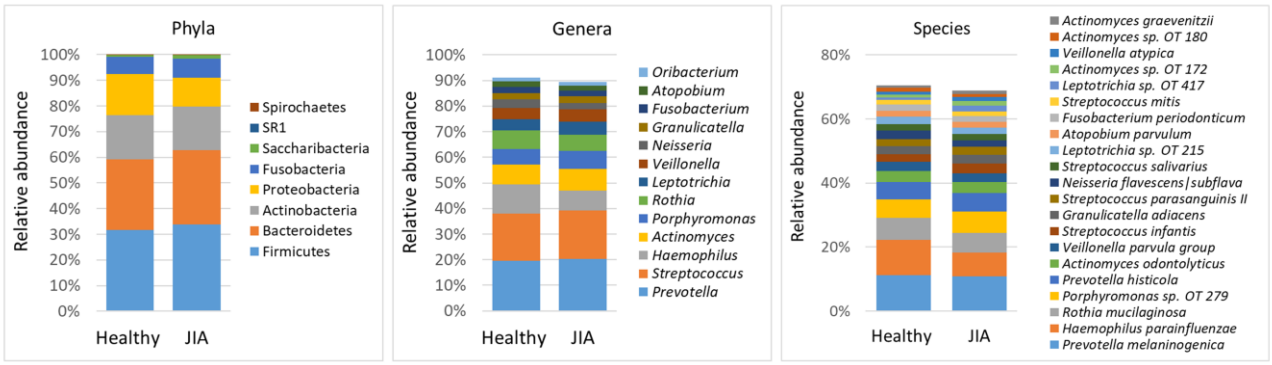


Figure 2.

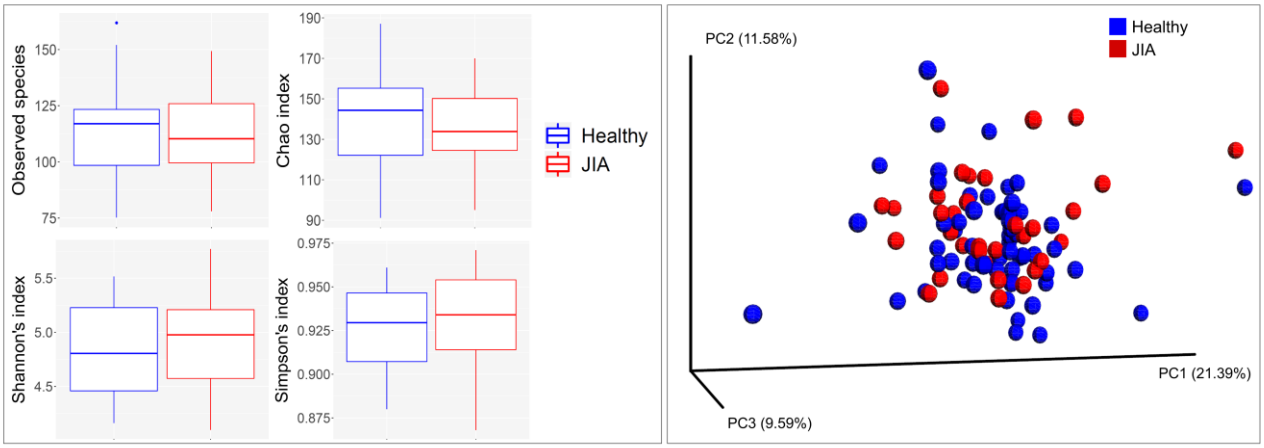
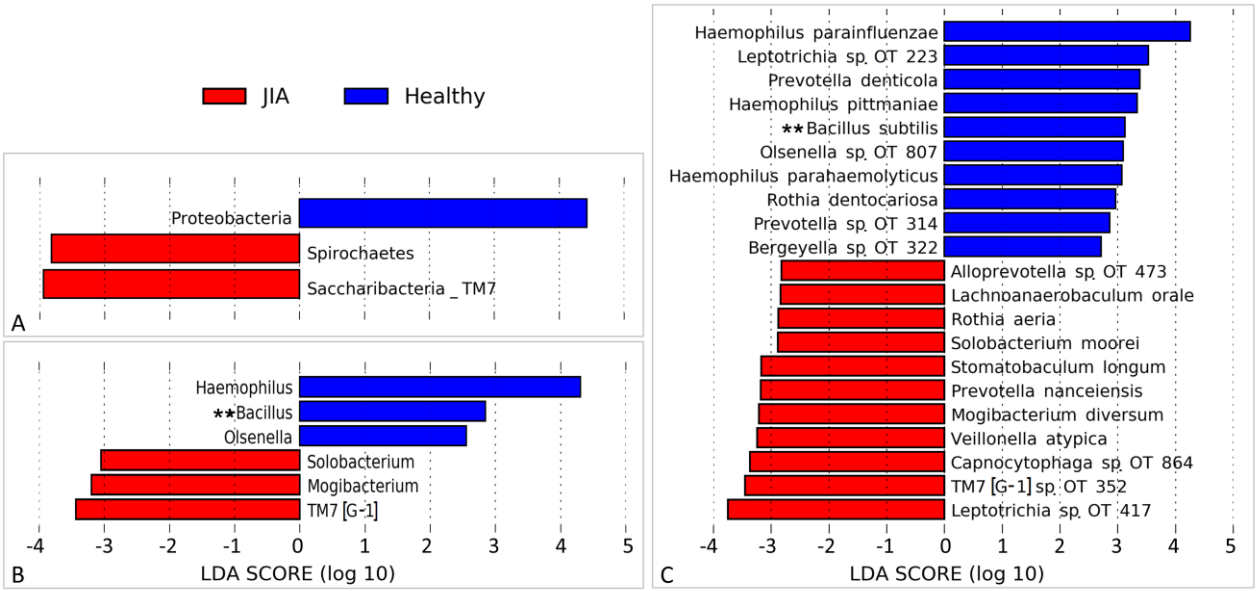


Figure 3.



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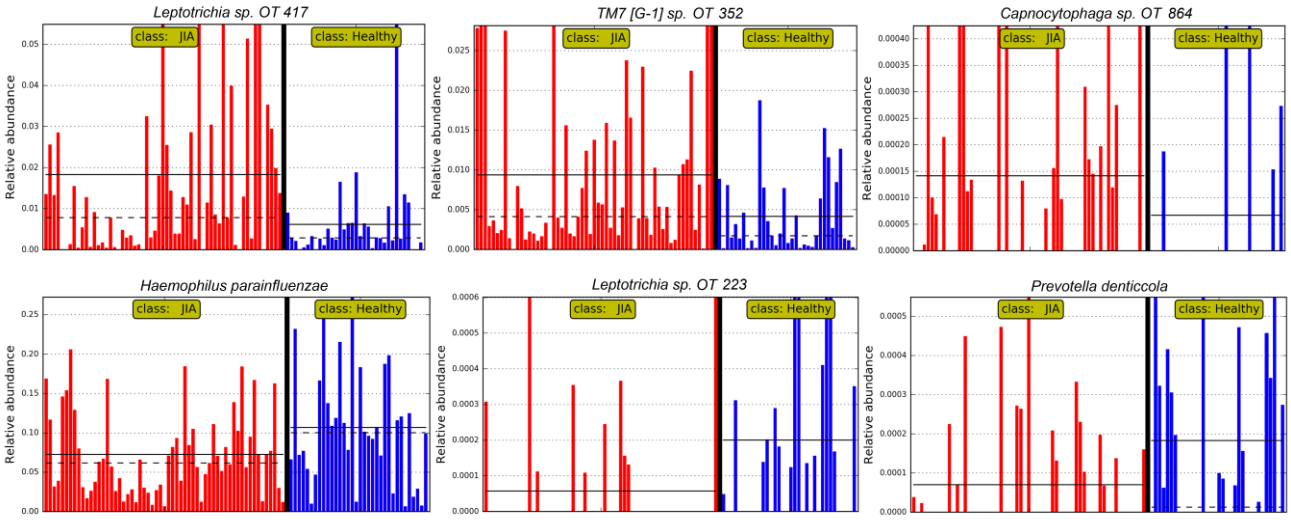

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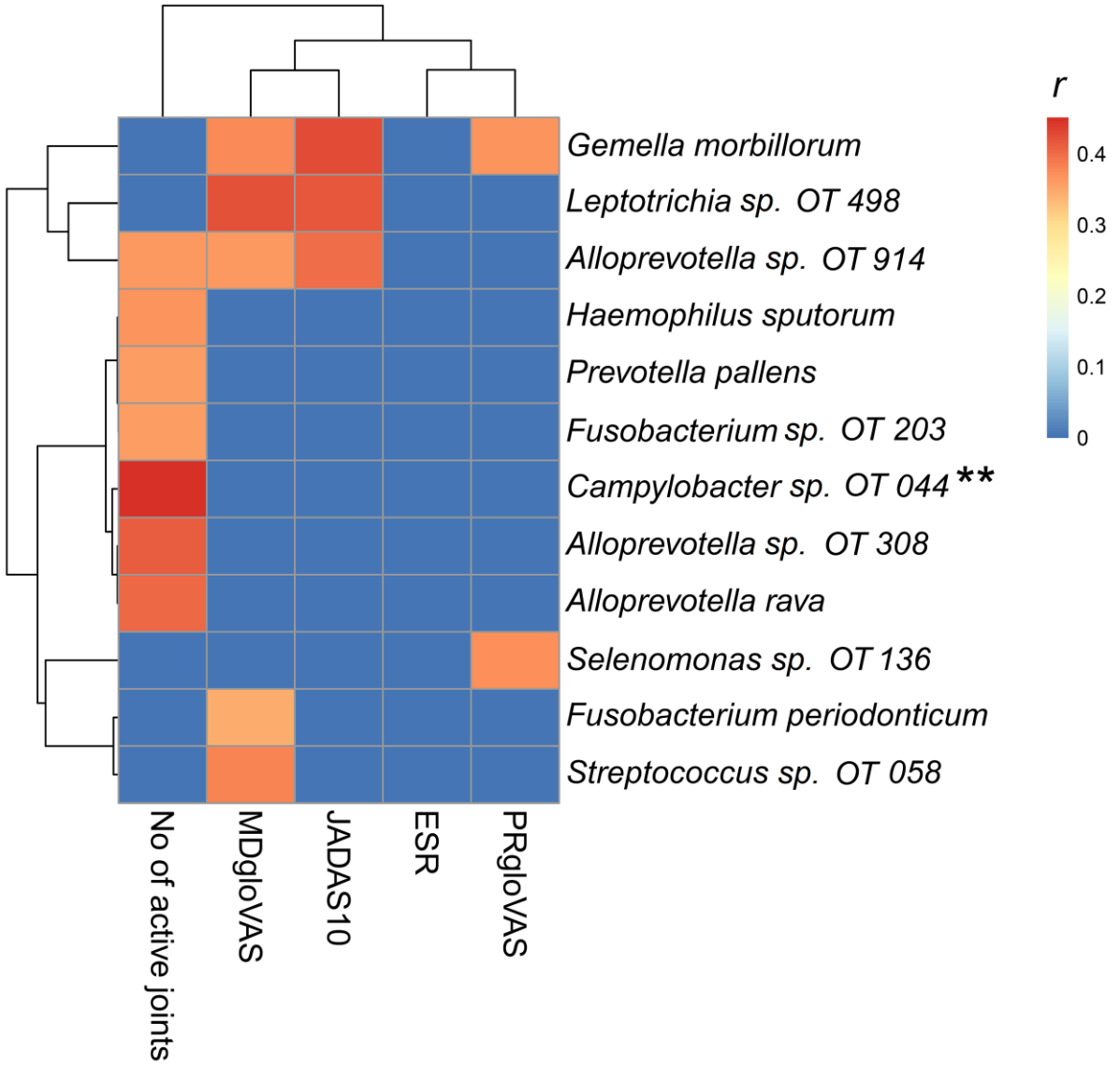
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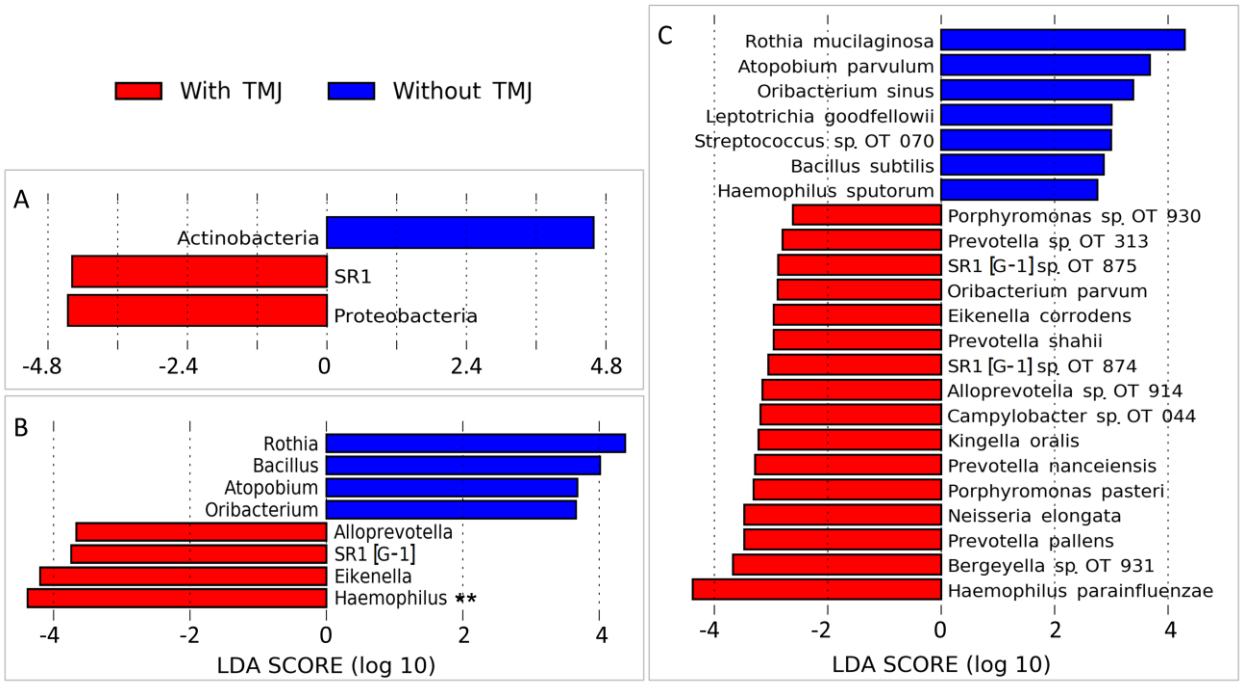
Gemella morbillorum
Leptotrichia sp. OT 498
Alloprevotella sp. OT 914
Haemophilus sputorum
Prevotella pallens
Fusobacterium sp. OT 203
Campylobacter sp. OT 044 **
Alloprevotella sp. OT 308
Alloprevotella rava
Selenomonas sp. OT 136
Fusobacterium periodonticum
Streptococcus sp. OT 058
No of active joints
MDgloVAS
JADAS10
ESR
PRgloVAS

Figure 6.


With TMJ
Without TMJ
A
Actinobacteria
SR1
Proteobacteria
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Alloprevotella
SR1 [G-1]
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Haemophilus **
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LDA SCORE (log 10)
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Rothia mucilaginosa
Atopobium parvulum
Oribacterium sinus
Leptotrichia goodfellowii
Streptococcus sp. OT 070
Bacillus subtilis
Haemophilus sputorum
Porphyromonas sp. OT 930
Prevotella sp. OT 313
SR1 [G-1] sp. OT 875
Oribacterium parvum
Eikenella corrodens
Prevotella shahii
SR1 [G-1] sp. OT 874
Alloprevotella sp. OT 914
Campylobacter sp. OT 044
Kingella oralis
Prevotella nanceiensis
Porphyromonas pasteri
Neisseria elongata
Prevotella pallens
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Haemophilus parainfluenzae
-4
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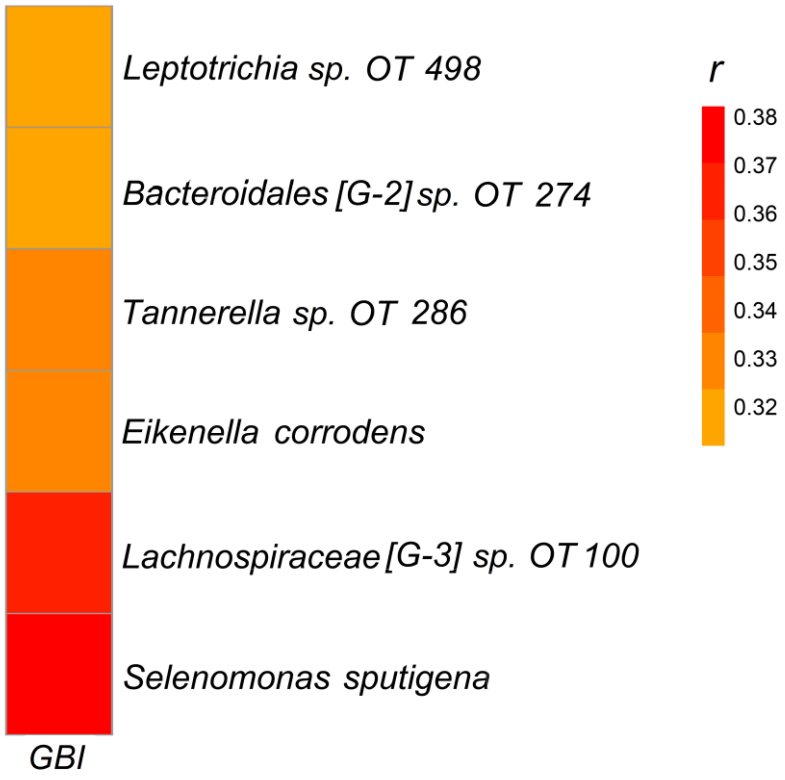
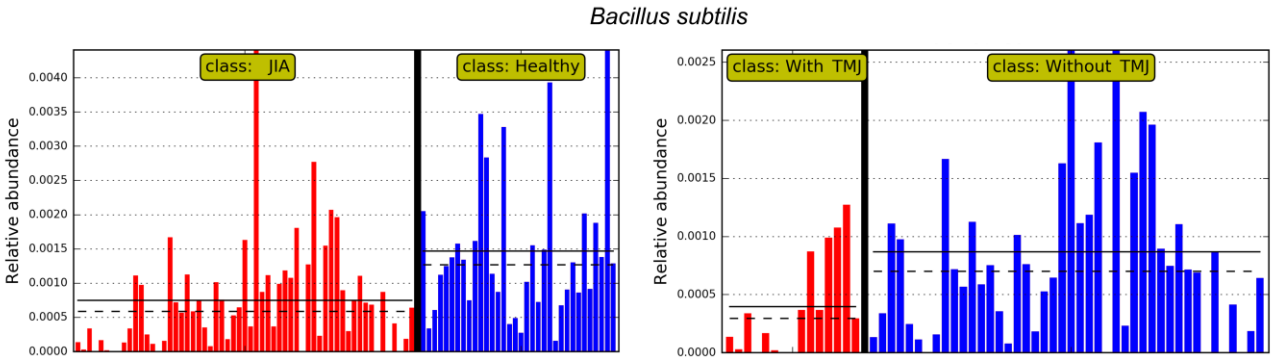
LDA SCORE (log 10)

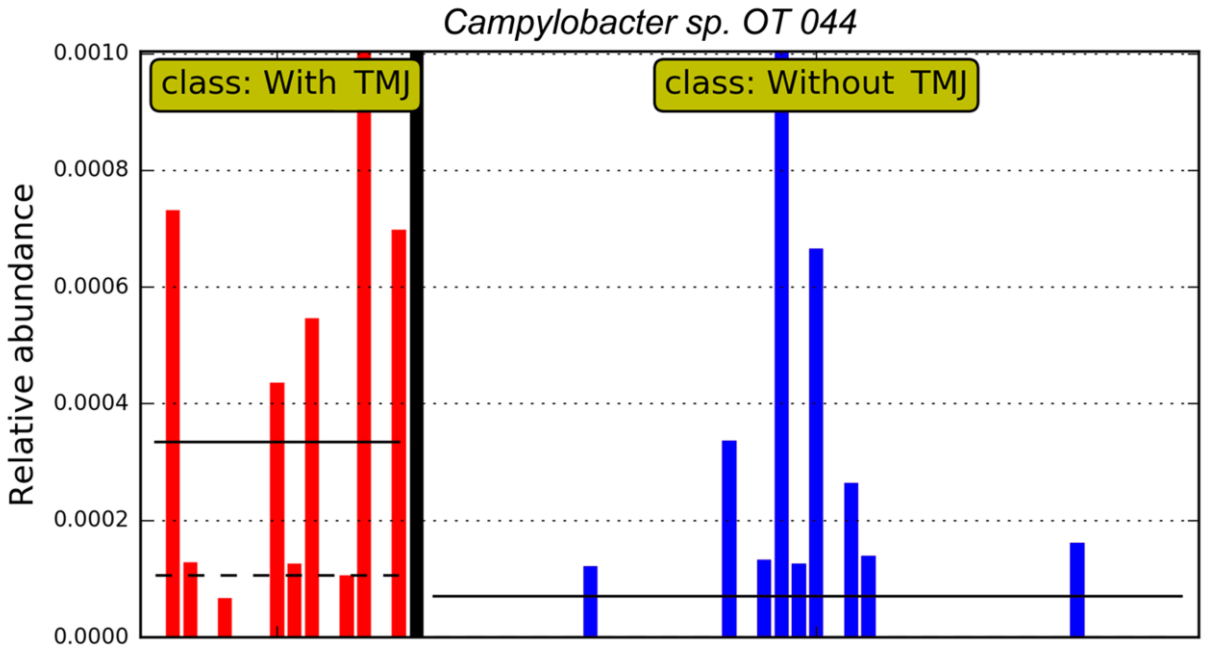
Supplementary Figure 1.



Supplementary figure 2.



Supplementary figure 3.



Paper III

Efficacy and safety of intraarticular corticosteroid injection in adolescents with juvenile idiopathic arthritis in the temporomandibular joint: A Norwegian 2-year prospective multicenter-study.

Frid P, Augdal T, Larheim T.A, Halbig J, Rypdal V, Songstad N-T, Rosen A, Tylleskär K.B, Berstad J.R, Flatø B, Stoustrup P, Rosendahl K, Kirkhus E, Nordal E.

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Efficacy and safety of intraarticular corticosteroid injections in adolescents with juvenile idiopathic arthritis in the temporomandibular joint: A Norwegian 2-year prospective multicenter pilot study.

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Abstract

Background. Intraarticular corticosteroids (IACs) have been used to treat temporomandibular joint (TMJ) arthritis. However, prospective clinical studies with magnetic resonance imaging (MRI) scoring are lacking. The aim of this study was to examine efficacy and safety of a single IAC in the TMJ in adolescents with juvenile idiopathic arthritis (JIA) in a clinical setting.

Methods. In this Norwegian prospective multicenter pilot study 15 patients with JIA (mostly persistent oligo-arthritis or RF negative polyarthritis categories) and a clinically and MRI-verified diagnosis of TMJ arthritis were treated with IACs and followed for two years. Demographics, systemic medication, general disease activity and outcome measures were recorded including a pain-index score and maximal incisal opening (MIO). Inflammation and bone damage scores were assessed, using two recently published MRI scoring systems with masked radiological evaluation.

Results. Among the 15 patients, 13 received a single IAC (5 bilateral), and 2 repeated IACs once unilaterally. Thus, the total number of IACs was 22. Median age was 15 years and the majority had an age not thought of as critical regarding mandibular growth retardation due to steroid injection. During the 2-year observation period systemic medication with disease modifying antirheumatic drugs (DMARDs) including biologics was initiated or adjusted in 10/15 (67%) patients. At the 2-months study visit after injection we observed a minimal improvement in MIO from median 44 (1^{st}, 3^{rd} quartiles; 36, 48) mm to 45 (43, 47) mm, p= 0.045 and decreased MRI mean additive inflammatory score from 4.4±1.8 standard deviations (SD) to 3.4±2.0, p= 0.040. From baseline to the 2-months follow-up pain improved in 6/11 patients but pain scores were not significantly improved. MRI-assessed damage increased in two patients with repeated IACs, and decreased in 3 patients but most of the patients were stable over the 2-year follow-up. Intra-rater repeatability of the MRI scoring system domains varied from poor to excellent.

Conclusions. In this pilot study of predominately single IACs to the TMJ in combination with

systemic treatment we observed improvement in MRI-assessed inflammation, mostly stable condylar bone conditions and minimal clinical improvement in adolescents with JIA and TMJ arthritis. No side effects were seen.

Keywords: Juvenile idiopathic arthritis, Temporomandibular joint, Intraarticular corticosteroids, Temporomandibular arthritis, Magnetic resonance imaging, efficacy, adverse events

Background

The temporomandibular joint (TMJ) is one of the most commonly involved joints in children with juvenile idiopathic arthritis (JIA), and may lead to impaired joint function, pain, growth impairment with dentofacial deformities (1-4), a reduced posterior airway space with related comorbidities (5, 6), and impaired quality of life (7). The rate of TMJ arthritis varies significantly (40-90%) in different JIA-cohorts using magnetic resonance imaging (MRI) (8-10), as reviewed by Larheim et al (11). TMJ arthritis may be clinically silent with symptoms and signs seen only late in the disease course (3). The diagnostic assessment is therefore a particular challenge (12).

Both systemic and local treatments have been used in patients with TMJ arthritis (13, 14). Several observational studies report short-term effect of intraarticular corticosteroid injections (IACs) to the TMJ on pain and maximal incisal opening (MIO) (15-20). It has also been shown that the IACs can be safely performed by trained specialists with or without imaging guidance (16, 18). However, treatment with IACs has been suspected to inflict rather than improve mandibular growth impairment (21, 22).

Retrospective studies with observation periods ranging from mean 2 to 23 months show a highly variable rate of improvement in MRI-assessed inflammation (18-83%) in TMJs receiving IACs, most often with stable condylar status on MRI (15, 16, 23-25). However, according to Stoustrup et al. (26) and Stoll et al. (27) studies on IACs have a low level of evidence due to methodological issues. The

studies are mostly retrospective and single center case-series, and the outcome assessors are not masked regarding pre- or post-treatment assessments. Randomized controlled trials are lacking, and systematic prospective follow-up studies with validated clinical assessments tools and imaging scoring systems are also missing. To our knowledge, there are no prospective studies with masked standardized MRI assessment addressing safety and efficacy of IACs in the TMJ in JIA. Therefore, the aim of this Norwegian 2-year prospective multicenter pilot study of adolescents with JIA and TMJ arthritis was, by using validated clinical outcome measures and two newly published MRI scoring systems, to assess efficacy and safety of single IACs in the TMJ in terms of (i) reducing pain and improving maximal mouth opening capacity, and (ii) reducing joint inflammation and bone damage.

MATERIAL AND METHODS

Study design and patients

This 2-year prospective multicenter-study of IACs in adolescents with JIA and TMJ arthritis, is part of a larger Norwegian prospective multicenter cohort on JIA (www.norjia.com). The terminology adheres to TMJaw (earlier EuroTMJoint) consensus-based standardized terminology (28). Clinical and demographic data were collected between November 2015 and September 2019 at the Department of Pediatrics, University Hospital North Norway Tromsø, Public Dental Service Competence Centre of North Norway, Tromsø, Haukeland University Hospital Bergen, and Oslo University Hospital, Rikshospitalet, Oslo.

Fifteen adolescents with JIA were consecutively recruited and a total of 22 TMJ injections with corticosteroids were performed. No control group was included due to ethical reasons. TMJ arthritis was defined as "clinical signs of pain on jaw movement, limitation of MIO, limitation of laterotrusive- or protrusive jaw movements or dentofacial growth disturbances and MRI signs of TMJ-arthritis (i.e. active inflammation in the TMJ based on increased contrast enhancement, bone marrow edema and/or effusion). Inclusion criteria were patients fulfilling the JIA diagnosis according to the classification criteria defined by the International League of Associations for

Rheumatology (ILAR) (12), age <18 years, and arthritis in one or both TMJs. Exclusion criteria were contraindications to MRI such as cardiac pacemaker, metallic clips, contrast allergy etc. or previous TMJ IACs within the last 3 years. The included patients had a clinical examination and a MRI at baseline before the TMJ IACs were performed, and at follow-up visits after 1-3 months, 1 year and 2 years.

Clinical variables, TMJ examination, and assessment of disease activity

Demographics, systemic medication, JIA category, disease onset and course type of JIA, medication, and a general clinical examination including number of joints with active arthritis, were registered by specialists in pediatric rheumatology at each study visit. The physician global evaluation of overall disease activity on a 10-cm visual analogue scale (VAS) (MDgloVAS) was also assessed at the visit. The specialists were calibrated by thorough discussions of all study variables assessed in the NorJIA study and the present NorJIA TMJ injection substudy. Patient-reported global assessment of overall well-being (PRgloVAS) and patient-reported pain (PRpainVAS) within the last week on a 10-cm VAS were also collected. On these scales, 0 indicates no disease activity/no pain/best overall well-being, and 10 indicate the maximum disease activity/worst pain/poorest overall well-being, respectively (29). Number of active joints other than the TMJ was defined according to the clinical definition of arthritis: swelling within a joint or limitation in the range of joint movement with joint pain or tenderness (30).

Clinical TMJ examination was performed by either a specialist in oral and maxillofacial surgery or a specialist in pediatric dentistry (PF, AR, JRB, JH) according to the DC / TMD examination and diagnostics protocol (31) and EuroTMJoint Clinical Recommendations protocol (32). The two examiners were calibrated repeatedly during the study period (33). The TMJ clinical outcomes for this study were: 1, Pain-index score (i.e. pain frequency last 2 weeks x pain intensity last 2 weeks (VAS 0-10)) scored by the patient, 2, Maximal incisal opening (MIO) in mm scored by the clinical TMJ examiner and 3, jaw function the last 2 weeks (VAS 0-10) scored by the

patient was registered.

A routine complete blood cell count, erythrocyte sedimentation rate (ESR) (mm/hour), and C-reactive protein (CRP) (<5mg/l was set as 0) was obtained. Rheumatoid factor (RF) immunoglobulin M was analyzed twice more than three months apart. The composite juvenile arthritis disease activity score (JADAS10, range from 0 to 40) was assessed, based on the MDgloVAS (range 0–10), PRgloVAS (range 0–10), active joint count (maximum 10 joints), and the ESR (normalized to 0–10, <10 mm/h was set as 0)) (29, 34). Disease status was defined as either active disease, inactive disease, clinical remission on medication, or clinical remission off medication according to the ACR provisional criteria (35); inactive disease requiring all the following: 1) no active joints; 2) no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA 3) no active uveitis; 4) normal ESR or CRP; 5) MDgloVAS =0; and 6) duration of morning stiffness of ≤15 minutes. Side effects were assessed and registered as per protocol at each study visit, including any signs of infection, bleeding, skin atrophy, facial palsy, or intraarticular calcifications on MRI.

MRI method and outcomes

Fifty-seven examinations were obtained on either 3-T-units (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany) using a 64-channel head/neck coil (n=50) or a 1.5-T-unit (Magnetom Aera or Avanto, Siemens Healthcare, Erlangen, Germany) using 4-channel special purpose coils (n=7), according to protocol A or B, respectively. As a minimum the protocols included water-sensitive images, pre- and post-contrast T1-weighted images and one sequence with the mouth in the open position. Details are provided in Supplementary table 2. One examination had susceptibility artefact-reducing sequences (WARP). The contrast medium given was 0.2 mL/kg (0.1 mmol/kg) body weight gadoterate meglumine (Dotarem, Guerbet, Paris, France). None of the patients needed sedation. All examinations were reviewed on a PACS workstation (IDS7, Sectra Medical Systems, Linköping, Sweden) in consensus between

two experienced specialists in radiology (TAL, TAA) at random order, masked for personal data, injection laterality and time point. One examination from each subject was randomly selected for a second reading after an interval of approximately three months.

The image outcomes were based on inflammation and bone damage according to the two newly published MRI scoring systems for evaluating TMJ arthritis as described by Tolend et al. (36, 37) and Kellenberger and Lochbuhler et al. (38, 39). The scoring systems were thoroughly discussed between the radiologists before the reading session. Total scores ranged from 0-8 for the Additive inflammatory domain (bone marrow edema (absent/present 0/1), bone marrow enhancement (absent/present 0/1), joint effusion (absent/small/large 0/1/2), synovial thickening (absent/mild/moderate, severe 0/1/2), joint enhancement (absent/mild/moderate, severe 0/1/2)) and 0-5 in the Additive damage domain (condylar flattening (absent/mild/moderate, severe 0/1/2), erosions (absent/mild/moderate, severe 0/1/2), disc abnormalities (absent/present 0/1)), and 0-4 in the Progressive scoring system: Progressive inflammation (no inflammation/mild/ moderate/severe/pannus 0/1/2/3/4) and Progressive osseous deformity (normal/mild/moderate/ severe/destruction 0/1/2/3/4). The scores were set as missing if the images were not of sufficient quality due to braces or other artefacts. In case of bilateral injection, the joint with the most severe inflammation/bone damage was chosen for statistical analysis.

Injection procedure

The preauricular skin was disinfected with 70% ethanol and 5% chlorhexidine, before local anesthesia with an auriculotemporal nerve block was applied. The push-pull technique, and the amount of recovered synovial fluid in each sample was quantified with the hydroxocobalamin method, as described by Alstergren et al (40, 41). A washing solution consisting of 22% hydroxocobalamin (Behepan® 1mg/ml) in physiological saline (sodium chloride 9 mg/ml) was used. The TMJ was injected with a total of 4 ml washing solution through a stop-cock syringe. One milliliter of washing solution was injected slowly, the valve was turned and then as much

fluid as possible was aspirated back. This procedure was repeated a total of three times for each joint leaving the same cannula inside the joint. If aspiration of the washing solution was possible and the resistance in the syringe was minor during injection, then the needle tip was considered to be placed within the joint space. After sampling of synovial fluid from the upper joint compartment, steroids were injected according to the landmark guiding or ultrasound guiding technique. Two different types of steroids were used: methylprednisolone acetate (Depomedrol®) and triamcinolone hexacetonide (Lederspan®). The following dosages were set: patients >30kg: 0.4ml triamcinolone hexacetonide 20mg/ml and children <30kg: individual dosage. In 15 TMJs a syringe of 25G 0.5 x 25mm and in 7 TMJs a syringe of 23G 0.6 x 30mm was used for the injection. The injection procedure was performed by experienced specialists in oral and maxillofacial surgery at all centers (PF, AR, JRB). The results of the synovial fluid analyses will be published in a separate paper.

Statistical analyses

For description of clinical and demographic data, median (1^{st}, 3^{rd} quartiles), mean (standard deviations (SD)) and frequencies (percentage) were used as appropriate. For the not normally distributed data of MRI-scoring mean (SD) was used for more informative description of the values. Multiple testing of four time-points and Bonferroni correction for 6 comparisons with a p-value <0.008 was analyzed and considered, but found to be less informative than testing for two time-points; with differences between baseline and 2-months, and 2-year follow-up because of some missing data at different follow-up time-points, varying number of follow-up visits from 2-4, together with the low number of participants. Based on previous studies (15, 16, 23-25) and clinical experience we chose to assess change in clinical parameters (MIO and pain index) and change in the MRI inflammatory scores mainly between baseline and 2-months, while change in MRI osseous deformities and damage scores was assessed between baseline and 2-year follow-up.

When testing continuous data for differences between baseline and 2-months, and 2-year follow-up, the Wilcoxon Signed Ranks Test was used for not normally distributed data. For nominal data tested for differences between baseline and 2-months, and 2-year follow-up McNemar Chi-square test was used, and for ordinal data Wilcoxon signed rank test. A p-value <0.05 was considered statistically significant. For description of outcome after receiving IACs at the different time-points in Figure 1, percentage of patients were used for absolute improvement of the variables pain, MIO and MRI. For the MRI assessment, the intra-observer consensus agreement for the MRI-scoring was assessed with Cohen's kappa: poor (0.01-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80) and almost perfect (0.81-1.00) agreement. Statistical analysis was performed using SPSS software, versions 25 or 26.

RESULTS

Demographic and disease activity parameters

Demographic and disease activity characteristics at baseline are given in Table 1. In total 15 adolescents were included and 22 TMJ injections were performed in this study. Among the 15, 80% were female and the median (quartiles) age at baseline was 15 (1^{st}, 3^{rd} quartiles 11, 16) years. The majority of adolescents belonged to the persistent oligoarthritis (6/15; 40%) or the RF negative polyarthritis (5/15; 33%) JIA categories. Five patients (33%) received bilateral TMJ IACs. Two patients (13%) had repeated injections once unilaterally 11 and 13 months after baseline, on indication pain and ongoing MRI-assessed inflammation. Ten of 22 TMJs were sampled with the push-pull technique (46%). Follow-up visits were performed at a median of 2.0 (1.8, 3.3) months (n=14), 12.0 (11.0, 13.0) months (n=15), and 22.0 (22.0, 23.0) months (n=11) after TMJ injections at baseline. All patients had active disease at baseline. At the 2-year follow-up five of 11 (46%) patients were in remission either on or off medication. During the 2-year follow-up period 10/15 (67%) changed or increased their systemic medication with DMARDs and biologics. From participant centers, two patients were included

Table 1. Characteristics at baseline in adolescents with juvenile idiopathic arthritis (JIA) (n=15) receiving intraarticular corticosteroids (IACs) to the temporomandibular joints (TMJs) (n=22).

Baseline characteristic	**Value**
Female, no. (%)	12 (80)
Age at injections, yrs	15 (11, 16)
Age at JIA onset, yrs	11 (8, 14)
Disease duration, yrs	1 (0, 5)
JIA-category, no (%)	
Oligoarthritis persistent	6 (40.0)
Polyarthritis RF negative	5 (33.3)
Oligoarthritis extended	3 (20)
Enthesitis related arthritis	1 (6.7)
Disease activity, no (%)*	
Active	15 (100)
Remission on medication	-
Remission off medication	-
Medication baseline, no (%)	
No DMARDs	6 (40.0)
DMARDs (MTX)	3 (20.0)
Biologics combination	6 (40.0)
Disease activity variables	
JADAS10 baseline (n=8)	15.8 (12.9, 49.1)
No.of active joints (n=14)	2.0 (1.0, 3.0)
PRpainVAS (n=10)	4.8 (3.3, 7.6)
PRgloVAS (n=10)	5.5 (3.3, 7.1)
MDgloVAS (n=12)	2.5 (1.6, 4.5)
ESR (mm/h) (n=12)	6.5 (3.5, 10.5)
TMJ-examination to injection, days	14.0 (1.0, 68.0)
Follow-up, months	22.0 (16.0, 23.0)
Injection to 2-months follow-up, (n=14)	2.0 (1.8, 3.3)
Injection to 1-year follow-up, months (n=15)	12.0 (11.0, 13.0)
Injection to 2-year follow-up, months (n=11)	22.0 (22.0, 23.0)
Triamcinolone hexacetonide, dose, mg (n=14)	20.0 (9.5, 20.0)
Methylprednisolone acetate, dose, mg (n=1)	40.0 (n=1)
Push-pull technique / No. TMJs (%)	10/22 (46%)
Needle length, mm/ No. TMJs	25mm/15, 30mm/7

Data are median (1st, 3rd quartile) unless otherwise indicated. Two patients received repeated injection on the same side, five patients received bilateral injection; JIA, juvenile idiopathic arthritis; TMJ, temporomandibular joint; PRpainVAS, patient reported pain visual analogue scale; PRgloVAS; patient reported global assessment of well-being; MDgloVAS, medical doctor global assessment of well-being; JADAS10, the composite juvenile arthritis10-joint disease activity score; ESR, erythrocyte sedimentation rate; MTX, methotrexate; DMARDs, disease modifying antirheumatic drugs; *disease activity status according to the ACR provisional remission criteria (35)

in Oslo, one patient in Bergen and twelve patients in Tromsø.

Clinical outcomes

Among the clinical TMJ parameters pain-index score changed from median 6.0 (0.0-13.0) at baseline to 2.0 (0.0-10.0) at 2-months follow-up, this was not a statistically significant improvement (p=0.263). There was a minimal, but statistically significant increase in MIO during the same observation period (p=0.045) (Table 2). At 2-year follow-up, scores for pain and jaw function improved from baseline in terms of pain frequency (p=0.016), pain intensity (p=0.012), VAS jaw function (p=0.034), and pain-index score (p=0.012) (Table 2). Absolute improvement in pain-index was seen in 6/11 (55%) of the patients at 2-months follow-up, 9/13 (69%) of the patients at 1-year follow-up and 8/10 (80%) of the patients at 2-year follow-up (Figure 1). Two of 11 patients (18%) had increased pain and 3 (27%) unchanged pain from baseline to 2-months follow-up. At 2-year follow-up 2 of 10 patients (20%) had a stable pain-index score of zero, and none of the patients had increased pain-index compared to baseline. Absolute improvements in MIO at the three follow-up visits were 9 of 13 (69%), 10 of 13 (77%) and 9 of 11 (82%) respectively (Figure 1). In 3 of 13 patients (23%) MIO decreased at 2-months follow-up (48 to 42 mm, 46 to 45 mm, 45 to 44 mm respectively). In 2 of 11 patients (18%) MIO decreased (40 to 37 mm, 49 to 45 mm respectively) between baseline and 2-year follow-up. Improvements in MIO ≥5 mm at the three follow-up visits were 4 of 13 (31%), 6 of 13 (46%) and 5 of 11 (46%) respectively.

Table 2. Disease activity and temporomandibular joint (TMJ) clinical measures during 2-year follow-up in 15 adolescents with juvenile idiopathic arthritis (JIA) and TMJ-arthritis receiving intraarticular corticosteroids (IACs).

	Pre- injection (T0)	2-months FU (T1)	1-year FU (T2)	2-year FU (T3)	p-value T0-T1
Median months after IACs (1st, 3rd quartile)	0 n=15	2.0 (1.8, 3.3) n=14	12.0 (11.0, 13.0) n=15	22.0 (22.0, 23.0) n=11	
Disease activity, no (%)**					
Active	15 (100.0)	7 (54) n=13	10 (77) n=13	6 (55)	
Remission on medication	-	2 (15) n=13	2 (15) n=13	2 (18)	
Remission off medication	-	4 (31) n=13	1 (8) n=13	3 (27)	
Medication * **					
No DMARDs, no (%)	6 (40)	5 (39) (n=13)	4 (27)	3 (27)	0.317 [a]
DMARDs (MTX), no (%)	3 (20)	2 (15) (n=13)	3 (20)	3 (27)	
Biologics comb, no (%)	6 (40)	6 (46) (n=13)	8 (53)	5 (46)	
Disease activity measures					
JADAS10	15.8 (12.9, 49.1) n=8	11.0 (6.0, 20.0) n=7	12.5 (6.8, 14.5) n=9	8.5 (3.3, 15.3) n=4	0.273[b]
No.of active joints	2.0 (1.0, 3.0) n=14	0.0 (0.0, 2.0) n=13	1.0 (0.0, 1.5) n=13	0.0 (0.0, 1.0) n=10	0.076[b]
ESR (mm/h)	6.5 (3.5, 10.5) n=12	6.0 (3.8, 11.0) n=10	5.0 (3.0, 7.0) n=11	5.5 (3.8, 7.3) n=10	0.445[b]
PRpainVAS	4.8 (3.3, 7.6) n=10	3.5 (0.0, 5.8) n=8	3.8 (1.6, 6.3) n=10	1.5 (0.0, 4.5) n=4	0.500[b]
PRgloVAS	5.5 (3.3, 7.1) n=10	3.5 (0.1, 5.8) n=8	4.0 (1.6, 5.1) n=10	0.5 (0.0, 4.0) n=4	0.345[b]
MDgloVAS	2.5 (1.6, 4.5) n=12	0.5 (0.0, 4.0) n=10	1.5 (0.1, 2.8) n=12	0.0 (0.0, 1.0) n=7	0.207[b]
TMJ activity measures					
Pain frequency	2.0 (0.0, 4.0)	1.0 (0.0, 2.0) n=11	1.0 (0.0, 2.0) n=13	0.0 (0.0, 2.0) n=10	0.245[b]
VAS pain intensity	3.0 (0.0, 6.5) n=15	2.0 (0.0, 4.5) n=11	2.0 (0.0, 3.5) n=13	0.0 (0.0, 2.1) n=10	0.292[b]
VAS jaw function	3.0 (0.0, 4.3) n=13	0.0 (0.0, 2.4) n=10	0.0 (0.0, 0.0) n=13	0.0 (0.0, 2.8) n=9	0.201[b]
Pain indexγ	6.0 (0.0, 13.0) n=15	2.0 (0.0, 10.0) n=11	2.0 (0.0, 8.5) n=13	0.0 (0.0, 5.3) n=10	0.263[b]
MIO (mm)	44 (36, 48) n=15	45 (43, 47) n=13	45 (42, 49) n= 13	46 (45, 48) n=11	0.045[b]

Data are median (1st, 3rd quartiles) unless indicated otherwise. [a]McNemar chi square test, [b]Wilcoxon rank test, *p ≤0.05 for statistical significance ** remission, status according to the ACR provisional remission criteria (35)***No DMARDs, Current us of NSAIDs and/or IACs; DMARDs, current use alone of MTX; Biologics comb, current use of Biologics alone or in combination with MTX; γ Pain index= Pain frequency last 2 weeks x Pain intensity last 2 weeks (VAS 0-10); JIA, juvenile idiopathic arthritis; TMJ, temporo-mandibular joint; LOM, limited range on motion; VAS, visual analogue scale; MTX, methotrexate; DMARDs, disease modifying antirheumatic drugs; PRpainVAS, patient reported pain visual analogue scale; PRgloVAS; Patient reported global assessment of well-being; MDgloVAS, medical doctor global assessment of well-being; JADAS10, The composite juvenile arthritis 10-joint disease activity score; IACs, intraarticular corticosteroid injections; ESR, erythrocyte sedimentation rate; MIO, maximal incisal opening; FU, follow-up

MRI outcomes

There was a statistically significant reduction in the additive inflammatory domain from baseline to the 2-months- and from baseline to the 2-year follow-up, (p= 0.040, p=0.017 respectively) (Table 3) (Figure 1). At the 2-months follow-up, 6 of 13 patients (46%) had lower score as shown in Figure 1, while 6 (46%) had unchanged and 1 (8%) had higher score in the additive inflammatory score. Among the 10 patients at 2-year follow-up, 7 (70%) had lower score, while 3 (30%) remained unchanged. The MRIs at baseline and at follow-up 2 months after IAC in one of the patients with improvement of temporomandibular joint enhancement is shown in Figure 2.

There was no statistically significant change in the mean progressive inflammation score between baseline and 2-months follow-up; 4 of 13 (31%) had lower score, and 9 of 13 (46%) had unchanged score. At the 2-year follow-up; 5 of 11 patients (46%) had lower score and 6 (55%) was unchanged compared to baseline.

No statistically significant change was seen in the two bone damage scores. In the mean additive damage domain, 2 of 14 (14%) had lower score, 9 (64%) unchanged and 3 (21%) had increased score at 2-months follow-up. At 2-year follow-up 2 of 10 (20%) had lower score, 6 (60%) was unchanged and 2 (20%) had higher score. The MRIs at baseline and at follow-up 2 years after IAC and systemic treatment show aggravation of bone damage in one patient (Case 10) and improvement in case 9 as shown in Figure 3. In the mean progressive osseous deformity score at the 2-months follow-up, 2 of 14 (14%) had a lower score, 11 (79%) had unchanged score, and 1 (7%) had higher score. At the 2-year follow-up 1 of 11 (9%) had lower score, 9 (82%) was unchanged, 1 (9%) had higher score.

MRI score intra-observer agreement

For the additive inflammatory domain, the intra-observer agreement between the readings was poor for bone marrow edema and bone marrow enhancement (negative kappa values), fair and

moderate for joint effusion (kappa values 0.38 and 0.46), substantial and almost perfect for synovial thickening (0.63 and 0.90) and moderate and poor for joint enhancement (0.41 and 0.00) for the right and left side, respectively. The corresponding value for the progressive inflammation and progressive osseous deformity score was moderate and poor (0.49 and 0.20) and moderate (0.52 and 0.58). For the additive osseous domain, the intra-observer agreement was moderate to substantial for flattening (0.48 and 0.74), fair and moderate for erosions (0.36 and 0.44) and fair and almost perfect for disc abnormalities (0.36 and 0.84).

Side effects

No adverse events that could be related to the IACs were reported, and there was no finding of intraarticular calcifications on MRI. However, 2/10 (20%) had increased additive damage domain score and 1/11 (9%) had increased progressive osseous deformity score in the TMJ between baseline and 2-year follow-up. Both patients had ongoing MRI-assessed inflammation at 2-year follow-up and repeated IACs 11 and 13 months respectively after baseline. Among these one had lower pain index and the other one unchanged (=0), and both patients had increased MIO at the 2-year follow-up. Furthermore, two patients with only 1-year follow-up (cases 1 and 5) had increased scores according to additive damage domain and progressive osseous deformity, together with ongoing inflammation (Table 4). Also, case 1 had a trauma to the mandible, a blow against one of the condyles, in between the 2-month and the 1-year follow-ups. One of the patients, case 7, improved according to the progressive osseous deformity from score 1 at the 2-months follow-up to score 0 at the 2-year follow-up. Mandibular growth was not evaluated because the adolescents in this study had mostly finished their growth at time for TMJ injection: median age 15.0 (11.0, 16.0) years.

Table 3. Additive and progressive scoring system for assessment of inflammation and damage in the temporomandibular joint (TMJ) by magnetic resonance imaging (MRI) in 15 adolescents with juvenile idiopathic arthritis (JIA) and TMJ-arthritis receiving intraarticular corticosteroids (IACs).

	Pre- injection (T0)	2- months FU (T1)	1-year FU (T2)	2-year FU (T3)	p-value
Mean months after IACs (SD)	0 n=15	2.4±1.6 n=14	12.3±1.5 n=15	21.5±2.6 n=11	
Additive Inflammatory domain: (Bone marrow edema, bone marrow enhancement, Joint effusion, Synovial thickening, Joint enhancement)	4.4±1.8	3.4±2.0 n=13	3.6±1.7 n=14	2.3±1.7 n=10	0.040* a
Bone marrow edema	0.3±0.5	0.1±0.3	0.1±0.4 n=14	0.0±0.0 n=10	0.500* b
Bone marrow enhancement	0.4 ±0.5	0.2±0.4 n=13	0.1±0.4 n=14	0.0±0.0 n=11	0.250* b
Joint effusion	0.8±0.9	0.7±0.8 n=14	0.6±0.9 n=14	0.3±0.7 n=10	0.705* a
Synovial thickening	1.0±0.8	1.0±0.8 n=14	1.0±0.8 n=14	0.7±0.8 n=10	1.000* a
Joint enhancement	1.9±0.3	1.5±0.7 n=13	1.8±0.4 n=14	1.3±0.6 n=11	0.059* a
Additive Damage domain: (Condylar flattening, erosions, disc abnormalities)	2.6±1.5	2.8±1.5 n=14	2.7±1.6	2.5±1.7 n=10	1.000** a
Condylar flattening	1.3±0.9	1.6±0.8 n=14	1.5±0.9	1.5±0.9 n=11	0.157** a
Erosions	0.6±0.7	0.6±0.8 n=14	0.5±0.8	0.4±0.7 n=10	0.655** a
Disc abnormalities	0.7±0.5	0.6±0.5 n=14	0.7±0.5	0.7±0.5 n=11	1.000** b
Progressive inflammation	2.6±0.8	2.0±1.1 n=13	2.5±1.0 n=14	1.5±0.9 n=11	0.066* a
Progressive osseous deformity	2.0±1.3	2.1±1.1 n=14	2.0±1.4	2.0±1.3 n=11	1.000** a

Values are the mean±SD unless indicated otherwise. N=15 unless indicated otherwise. [a]Wilcoxon rank test. [b]McNemar chi square test. *P ≤0.05 considered statistically significant between T0-T1 and ** between T0-T3. Each joint is scored independently (the worst joint is chosen when bilateral injection), with possible total scores ranging from 0-8 in the Additive inflammatory scoring system and 0-5 in the Additative damage domain, and 0-4 in the Progressive scoring system according to (Tolend et al.) (36) and (Kellenberger et al.) (37);
2 patients received repeated injection on the same side, 5 patients received bilateral injection.

DISCUSSION

To our knowledge, this is the first prospective study validating and using two recently published MRI scoring systems to assess the efficacy and safety of IACs in the TMJ in adolescents with JIA. We found that a single IAC in combination with systemic therapy may improve short-term and long-term MRI-assessed inflammation and MIO, even though pain and MRI-assessed damage did not improve significantly.

Clinical outcomes: Pain and MIO

In our study the pain-index score improved in 6/11 patients at 2-months follow-up and 8/10 patients at the 2-year follow-up median 22 months after IACs to the TMJs. Pain was one of the main indications for performing the IACs in our study, and the pain-index score is reported to be a valid and sensitive outcome measure in TMJ arthritis (17). Improvement in pain is reported in most retrospective studies in JIA children based on medical chart information or the patients' self-assessment of pain, where improvement in orofacial symptoms is seen in 67–100%, follow-up ranging from mean 3 to 52 months after TMJ-IACs (15, 24, 42-44). However, none of these studies used quantified pain reports. Stoustrup et al. used the validated pain-index score in 13 JIA children receiving IACs to the TMJs in a prospective pilot study (17). They found significant short-term pain reduction, but remitting pain at long-term follow-up, indicating a loss of the initial effect of the IACs (17). Our study shows a trend for improvement in pain at the 2-month follow-up which is sustained during the observation period over two years (not statistically significant). The sustained tendency of reduced pain may be due to the systemic medication (DMARDs and biologics), which was changed in 10/15 patients in our study. Five of the 11 patients were in remission at the 2-year follow-up, indicating an effect of the treatment, which included IACs and the systemic medication. The sampling procedure with lavage may also induce improvement, Olsen-Bergem et al found that arthrocentesis with lavage in patients with TMJ arthritis and JIA might be beneficial for the treatment outcome, and that

steroids did not add additional effect to the outcome (45). The natural fluctuation with waxing and waning disease activity over time often seen in JIA must also be considered (46).

We found that MIO improved in 9 of 13 patients at 2-months follow-up, and in 9 of 11 patients between baseline and 2-year follow-up after IACs to the TMJs. This is similar to retrospective studies where improvements in MIO are reported between 2.7 and 6.6 mm (15-18, 24, 42-44). However, measurements of MIO are associated with much variation (47, 48), increase with age, and show a wide normal range in children of the same age (49). In our study we used standardized protocols and calibration of the examiners in order to avoid measurement bias (31) (32). Stoustrup et al. found the smallest detectable difference in repeated MIO measurements in patients with JIA to be 5 mm when a strict and standardized measurement protocol with repeated measurements were applied (48). A clinically relevant improvement ≥5 mm was found in our study in 4 of 13 patients between baseline and 2-months follow-up and in 5 of 11 between baseline and 2-year follow-up after IACs. Our median improvement in MIO may be influenced by random error within the measurement procedure. Moreover, MIO at baseline was not severely reduced, and we doubt that this small change in MIO is a clinically relevant effect on jaw function even if statistically significant.

MRI outcomes

MRI-verified TMJ-arthritis is not always accompanied by clinical symptoms from the TMJ. A systematic review concluded that no single clinical finding could accurately predict MRI findings consistent with arthritis (50). The measurements in our study therefore included both standardized clinical assessment tools with pain reports, MIO, and MRI to verify TMJ-arthritis both at both baseline and follow-up.

A problem in evaluating outcome after IACs has been the use of qualitative assessments and lack of consistent definitions and MRI-scoring systems (36, 37). In the assessment of inflammation in our study, the additive inflammatory domain improved significantly

between baseline and the 2-months follow-up. Improvement was seen in 6/13 patients as compared to 4/13 patients in the progressive inflammation score. At the 2-year follow-up, 7 of the 10 patients improved significantly in the additive inflammatory domain and 3 were stable, whereas in the progressive inflammation score 5 of 11 patients improved at 2-year follow-up, but no overall significant improvement was seen.

The improvement in MRI-assessed inflammation is in accordance with Resnick et al. who found reduced synovial enhancement in their retrospective study of 29 JIA patients with 50 TMJs, even if only 18% of their TMJs experienced complete resolution of synovitis (18). Most studies of IACs to the TMJs in patients with JIA report an MRI improvement of 48-83% regarding inflammation (15, 16, 23, 24). However, these studies used different definitions of MRI improvement than the MRI scoring systems used in our study (36, 37).

We found no improvement in the additive damage domain comprising condylar flattening, erosions and disc abnormalities or in the progressive osseous deformity score. Importantly, increased damage was not found at the group level, even if 2 of the 10 patients with 2-year follow-up in our study worsened in the additive damage domain and 1 of 11 patients worsened in the progressive score for osseous deformity. Furthermore, two patients with only 1-year follow-up worsened. We cannot discern the effect of IACs from the effect of ongoing arthritis, even if both patients with 2-year follow-up had repeated IACs once unilaterally. MRI showed persistent inflammation at 2-year follow-up in both these patients. Three patients improved from baseline to 2-year follow-up and one patient improved at 1-year follow-up. Furthermore, another patient who worsened in bone damage between injection and 2-months follow-up, improved at the 2-year follow-up.

Stoll et al. (16) found in 15/47 (32%) of the TMJs injected with IACs, evidence of new-onset erosion and flattening. Arabshahi et al.(15) also reported post-therapeutic progression with bony resorption in three (16%) of 19 TMJs. Ringold et al. (42) reported that 10/15 (67%) of the patients receiving IACs therapy showed signs of worsening. Lochbuhler et al. (22) reported

progressive osseous deformation in 45 of 66 TMJs in their cohort of children with JIA and TMJ arthritis receiving repeated injections (mean 2.4±1.4 IACs per joint, range 0-7).

The additive inflammatory MRI score consists of five domains. The fact that this additive inflammatory scoring system have scores 0 to 2 (maximum 2) for joint effusion, joint enhancement and synovial thickening, while bone marrow edema, bone marrow enhancement scores maximum 1, place less emphasis on the two latter domains. The same applies to the additive damage MRI score consisting of three domains, where condylar flattening and erosions score 0 to 2, and disc abnormalities score maximum 1 if present. It is also unclear how the progressive system was constructed with regard to relative weighting of findings. Whether this emphasis is based on data analyses or constructed for simplicity is not stated in the publications of the scores.

The progressive inflammation and osseous deformity scores incorporate several features into one score in a progressive manner. In one of the four papers (36) where the system has been presented it is stated that the most severe change is the deciding feature, however, in the three others (37-39) this statement is not included. Deciding the most severe change can be challenging, and our interpretation of the system was that a given score was reliant on fulfillment of the previous level of pathology. This may have lowered the progressive osseous deformity score if erosions were present without co-occurrence of flattening, and the progressive inflammation score if bone marrow oedema was present without increased synovial enhancement. There was some variation in the kappa coefficients, both between right and left side in both systems and between the different variables of the additive system. The best intra-observer agreement was found for disc abnormalities and synovial thickening, in the latter with substantial and almost perfect agreement. The repeatability varied somewhat more in our study compared to the report by Tolend et al. (36). Assessment variations may have influenced the outcome, particularly because of the small study sample. Furthermore, the scoring systems have not previously been clinically validated and their ability to detect change has not been

examined.

Whether MRI should be performed to assess the effect of interventions in TMJ remains unanswered. In Table 4 there is no uniform pattern, but a trend that the MRI changes in inflammatory scores parallell the clinical improvement. Based on our data, clinical experience and the literature, repeated MRI might be indicated primarily if clinical symptoms and signs do not improve.

Side effects

In our study no severe side effects occurred in terms of infection, bleeding or intraarticular calcifications, even if a computed tomography (CT) scan may better show calcifications. However, 2 patients had worsening in bone damage at 2-year follow-up. In addition two patients had worsened score for bone damage at 1-year follow-up but have not yet reached 2-year follow-up. However, these patients had all ongoing inflammation and one of them a trauma to the mandible that may explain the damage. Another patient worsened in bone damage between injection and 2-months follow-up but improved at the 2-year follow-up. Furthermore, three patients improved in bone damage from baseline to 2-year follow-up and 1 patient improved at 1-year follow-up.

Other studies have reported short-term adverse effects such as facial swelling, skin atrophy, pain, TMJ stiffness, chewing dysfunction, fever and TMJ calcifications/ossifications (15, 16, 42-44, 51). A chart review by Ringold et al. (51) described heterotopic ossification in the TMJ in children receiving 1–5 TMJ IACs, but the authors were unable to say whether these ossifications were the result of the IACs treatment or due to severe, long-standing TMJ inflammation. Also Lochbuhler et al. (22) reported severe side effects such as ossifications in the TMJs after repeated IACs. Rate of osseous deformities increased from 51% at baseline to 62% at the end of their study, with progression to severe condylar destruction in 26% of joints including 24% with development of intraarticular calcifications / ossifications. Importantly,

mandibular growth rate was reduced compared to the normal age- and sex-matched mean growth rate. In that study injections were however performed repeatedly. It is unclear whether the adverse effect of ossifications and reduced mandibular growth is a problem mainly of repeated steroid injections. We could not evaluate the effects on mandibular growth since the patients were mostly fully grown at the time the injection was performed. Our study may point to a single steroid injection as a treatment option for severe symptoms of TMJ-arthritis unresponsive to systemic treatment in skeletally mature individuals.

Study strengths and limitations

A strength of the present study is the prospective study design with standardized examination and MRI protocols in a clinical setting. MRI scoring assessments were performed by two experienced specialists and masked regarding whether the images were pre- or post-treatment. In addition, the clinical examiners used standardized examination protocols and were repeatedly calibrated, even if recalibration not necessary always change the inter-examiner reliability (33). Our study sample is comparable to population-based JIA cohorts and case-control studies regarding gender and JIA category distribution (7, 8, 16). A limitation is that clinical examiners and the patients were not masked before and after treatment, when assessing clinical variables such as MIO and pain. It must be emphasized that the patient group is small, and therefore the statistical analyses of the main clinical and imaging outcomes, and the discrepancies between the two scoring systems must be interpreted with caution. Furthermore, we found considerable intra-observer variability for some domains of the MRI scores, and our interpretation of the scoring systems may differ from that of the original authors.

CONCLUSION

We found that a single IAC in JIA-patients with TMJ arthritis may reduce MRI-assessed

inflammation, and improve mouth-opening capacity minimally. At the 2-months follow-up the pain-index score had improved in 6/11 patients but the change in pain-index score did not reach significance. Condylar bone damage was mostly stable but worsened during 2-year follow-up in two patients with repeated IACs and improved in 3 patients but no overall significant improvement was seen. There were no side effects. This is the first prospective clinical study validating and using two recently published MRI scoring systems. The combined effects of naturally fluctuating JIA disease activity, systemic medication changes, and TMJ lavage versus IACs must be considered in the assessment of the present findings. Further prospective clinical studies on adolescents with an age not critical for mandibular growth retardation due to steroid injection, including a control group, are needed in order to fully elucidate the effect of IACs on TMJ arthritis.

Availability of data and material:

Data can be obtained from the corresponding author, Paula Frid:

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Abbreviations:

ACR	American College of Rheumatology
Biologic comb	Current use of Biologics alone or in combination with MTX
CRP	C-reactive protein
CT	Computed Tomography
DC/TMD	Diagnostic criteria for temporomandibular dysfunction
DMARDs	Disease-modifying anti-rheumatic drugs
ESR	Erythrocyte sedimentation rate
IACs	Intraarticular corticosteroids
ILAR	International League of Associations for Rheumatology
JADAS	The composite juvenile arthritis10-joint disease activity score
JIA	Juvenile idiopathic arthritis
MDgloVAS	Physician global evaluation of overall disease activity on a 10-cm visual analogue scale
MIO	Maximal incisal opening
MRI	Magnetic Resonance Imaging
MTX	Methotreaxthe
NorJIA	The Norwegian JIA Study
NSAIDs	Non-steroidal anti-inflammatory drugs
PAS	Posterior airway space
PRgloVAS	Patient reported global assesment of well-being
PRpainVAS	Patient reported pain VAS
RF	Rheumatoid factor
SD	Standard deviations
TMJ	Temporomandibular joint
US	Ultrasound
VAS	Visual analogue scale

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Authors´contributions

Planning of the study, data collection, analysis of the data and interpretation of the results as well as writing of the manuscript: PF, EN.

Collection of data: PF, EN, JRB, BF, AR, KBT, TAA, VR, NTS, JH.

Critical review and editing of manuscript: AR, EK, BF, PS, TAL, KBT, NTS, VR, EN, JH, TAA, KR, JRB.

All authors read and approved the final manuscript.

Ethics approval and consent to participate

The authors assert that this work comply with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008. Informed consent was collected from all study participants and the study was approved by the Regional committees for medical and health research ethics in Norway (2015/318).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

FIGURE LEGENDS

Figure 1. Percentage of patients with improvement. Percentage of adolescents with juvenile idiopathic arthritis (JIA) and temporomandibular joint (TMJ) arthritis with improvement in Pain index, maximal incisal opening (MIO) and magnetic resonance imaging (MRI) inflammatory additive domain score, damage additive domain score, progressive inflammation score, progressive osseous deformity score, in the time interval between baseline and follow-up visits (FU) after receiving intraarticular corticosteroids (IACs).

Figure 2. MRI improvement of the inflammation. Oblique sagittal contrast enhanced T1 TSE images with fat suppression of a 16-year-old girl (case 8) (a) at baseline with increased temporomandibular joint enhancement and (b) at 2 months follow-up after IAC and no DMARDs with complete regression of joint enhancement. Note also the disrupted disc and flattened condyle in both images.

Figure 3. MRI changes of the bone condition.

Oblique sagittal pre- and postcontrast T1 TSE images with fat suppression of the left TMJ of a 16-year-old girl (case 10) without improvement in inflammation: joint enhancement is only minimally reduced from baseline (a, b) to 2-months after IAC (c, d). She was under MTX treatment. At 2-year follow up, with a repeated injection 11 months after baseline, there is some reduction in joint enhancement, but the disc has become perforated and the condylar surface discretely more flattened and irregular (e, f).

Oblique sagittal T1 TSE images with fat suppression of the right TMJ of a 15-year-old girl (case 9) with improved bone condition: discretely flattened and irregular condyle at baseline (g) has become smooth and more rounded at 2-year follow-up after IAC and systemic treatment with biologics and MTX (h).

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Magnetic resonance imaging (MRI) protocol for adolescents with juvenile idiopathic arthrtitis (JIA) and temporomandibular joint (TMJ) arthritis receiving intraarticular corticosteroids (IACs).

Table 4. Summary characteristics, use of medication at baseline and outcome-response during 2-year follow-up in adolescents with juvenile idiopathic arthritis (JIA) (n=15) receiving intraarticular corticosteroids (IACs) to the temporomandibular joints (TMJs) (n=22).

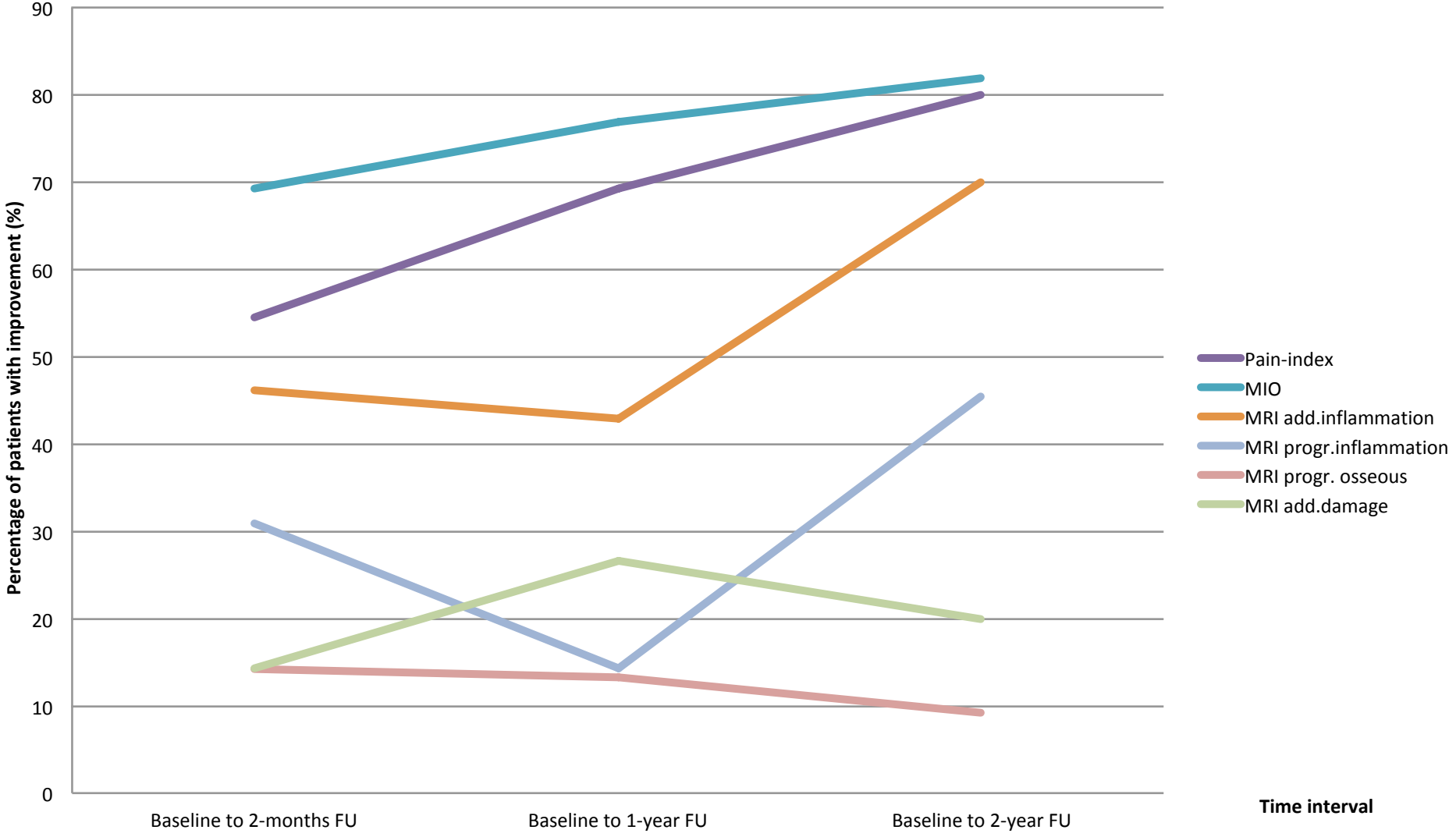
Case	**M/F**	Age Onset	Age Inj	Dose inj (mg)	Medic (T0)	Medic (T1)	Medic (T2)	Medic (T3)	MIO	Pain index	MRI additive inflammatory domain*	MRI Progressive inflammation*	MRI additive damage domain*	MRI progressive osseous deformity*	Comments
1	M	10	10	6	MTX	MTX	MTX		T0: 48 T1: 42 T2: 48 T3: -	T0: 6 T1 T2: 2 T3: -	T0: 6 T1: 4 T2: 6 T3: -	T0: 3 T1: 3 T2: 4 T3: -	T0: 3 T1: 4 T2: 4 T3: -	T0: 3 T1: 3 T2: 4 T3: -	Bilateral IACs Mandibular trauma between T1 and T2
2	F	17	17	8	MTX	BioCo	BioCo	BioCo	T0: 40 T1: - T2: 37 T3: -	T0: 0 T1: - T2: - T3: -	T0: 3 T1: 2 T2: 5 T3: 1	T0: 3 T1: 2 T2: 3 T3: 1	T0: 4 T1: 4 T2: 3 T3: 3	T0: 3 T1: 3 T2: 3 T3: 3	Unilateral IACs
3	F	11	11	8	MTX	MTX	BioCo		T0: 32 T1: 35 T2: 30 T3: -	T0: 9 T1: 0 T2: 0 T3: -	T0: 5 T1: 5 T2: 5 T3: -	T0: 3 T1: 3 T2: 3 T3: -	T0: 3 T1: 3 T2: 2 T3: -	T0: 3 T1: 2 T2: 0 T3: -	Unilateral IACs
4	F	13	14	20	No DMARD	No DMARD	No DMARD	No DMARD	T0: 44 T1: 48 T2: 41 T3: 47	T0: 0 T1: 0 T2: 9 T3: 0	T0: 4 T1: 2 T2: - T3: - T4: -	T0: 4 T1: 1 T2: - T3: 1 T4: 2	T0: 2 T1: 4 T2: 5 T3: 4 T4: 4	T0: 2 T1: 2 T2: 3 T3: 3 T4: 3	Unilateral repeated IACs (13 months interval)
5	F	9	15	20	BioCo		BioCo		T0: 48 T1: - T2: - T3: -	T0: 3 T1: - T2: - T3: 0	T0: 6 T1: - T2: 6 T3: -	T0: 3 T1: - T2: 3 T3: -	T0: 1 T1: - T2: 4 T3: -	T0: 0 T1: - T2: 2 T3: -	Unilateral IACs
6	F	9	14	10	BioCo	BioCo	BioCo	BioCo	T0: 46 T1: 45 T2: 47 T3: 47	T0: 5.5 T1: 2 T2: 0 T3: 0	T0: 1 T1: 1 T2: 1 T3: 1	T0: 1 T1: 1 T2: 1 T3: 1	T0: 0 T1: 0 T2: 0 T3: 0	T0: 0 T1: 0 T2: 0 T3: 0	Bilateral IACs
7	F	2	15	20	No DMARD	No DMARD	No DMARD	MTX	T0: 36 T1: 44 T2: 44 T3: 44	T0: 36 T1: 10 T2: 6 T3: 0	T0: 3 T1: 3 T2: 3 T3: 1	T0: 1 T1: 1 T2: 2 T3: 1	T0: 1 T1: 2 T2: 1 T3: 1	T0: 0 T1: 1 T2: 0 T3: 0	Bilateral IACs
8	F	15	16	40**	No DMARD	No DMARD	MTX		T0: 45 T1: 46 T2: 50 T3: -	T0: 0 T1: 0 T2: 12 T3: -	T0: 2 T1: 2 T2: 2 T3: -	T0: 2 T1: 2 T2: 2 T3: -	T0: 4 T1: 4 T2: 4 T3: -	T0: 2 T1: 2 T2: 2 T3: -	Unilateral IACs
9	F	0	15	20	BioCo	BioCo	BioCo	No DMARD	T0: 49 T1: 54 T2: 54 T3: 45	T0: 0 T1: 5 T2: 0 T3: -	T0: 2 T1: 0 T2: 2 T3: 2	T0: 2 T1: 0 T2: 2 T3: 2	T0: 4 T1: 2 T2: 2 T3: 2	T0: 2 T1: 2 T2: 2 T3: 2	Unilateral IACs
10	F	15	16	20	No	No	MTX	MTX	T0: 45	T0: 12	T0: 5	T0: 3	T0: 3	T0: 3	Unilateral

					DMARD	DMARD			T1: 44 T2: 49 T3: 48	T1: 22.5 T2: 0 T3: 6	T1: 6 T2: 4 T3: 2 T4: 3	T1: 3 T2: 3 T3: 1 T4: 3	T1: 3 T2: 3 T3: 4 T4: 3	T1: 3 T2: 3 T3: 3 T4: 3	repeated IACs (11 months interval)
11	M	11	16	20	No DMARD	No DMARD	No DMARD	No DMARD	T0: 55 T1: 55 T2: 62 T3: 63	T0: 0 T1: 0 T2: 0 T3: 0	T0: 5 T1: 4 T2: 2 T3: 5	T0: 2 T1: 1 T2: 1 T3: 2	T0: 3 T1: 3 T2: 3 T3: 3	T0: 3 T1: 2 T2: 2 T3: 2	Unilateral injection
12	M	8	9	10	BioCo	BioCo	BioCo	BioCo	T0: 34 T1: 40 T2: 41 T3: 45	T0: 7.5 T1: 0 T2: 0 T3: 0	T0: 7 T1: 3 T2: 1 T3: 0	T0: 3 T1: 3 T2: 1 T3: 0	T0: 0 T1: 0 T2: 0 T3: 0	T0: 0 T1: 0 T2: 0 T3: 0	Bilateral IACs
13	F	14	15	16	BioCo	BioCo	BioCo	BioCo	T0: 42 T1: 44 T2: 45 T3: 46	T0: 21 T1: 14 T2: 2.5 T3: 5	T0: 6 T1: 6 T2: 5 T3: 5	T0: 3 T1: 3 T2: 3 T3: 3	T0: 5 T1: 5 T2: 5 T3: 5	T0: 3 T1: 3 T2: 3 T3: 3	Unilateral IACs
14	F	5	11	20	BioCo	BioCo	BioCo	BioCo	T0: 43 T1: 45 T2: 44 T3: 48	T0: 13 T1: 9 T2: 9 T3: 12	T0: 5 T1: - T2: 4 T3: 3	T0: 3 T1: - T2: 3 T3: 3	T0: 3 T1: 2 T2: 2 T3: -	T0: 3 T1: 3 T2: 3 T3: 3	Unilateral IACs
15	F	13	15	20	No DMARD		No DMARD	MTX	T0: 35 T1: 45 T2: 45 T3: 45	T0: 32 T1: - T2: 8 T3: 3	T0: 6 T1: 6 T2: 4 T3: 3	T0: 3 T1: 3 T2: 4 T3: 2	T0: 3 T1: 3 T2: 3 T3: 3	T0: 3 T1: 3 T2: 3 T3: 3	Bilateral IACs

*Additive and progressive MRI score (36, 37) ** Metylprednisolone acetate; Inj, injection; Medic, medication; MIO, maximal incisal opening; MRI, magnetic resonance imaging; FU, follow-up; MTX, methotrexate; BioCo, biologics alone or in combination with other DMARDs; disease modifying antirheumatic drugs; JIA, juvenile idiopathic arthritis; TMJ, temporomandibular joint; IACs, intraarticular corticosteroid injections; T0=Pre-injection, T1= 2-months follow-up, T2= 1-year follow-up, T3= 2-year follow-up; - missing data

Figure 1.

Click here to access/download;Figure;Figure 1.pdf



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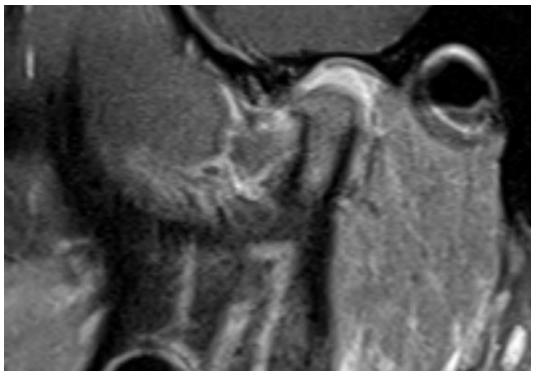

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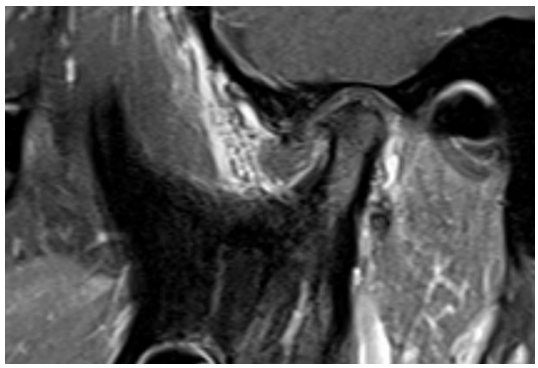

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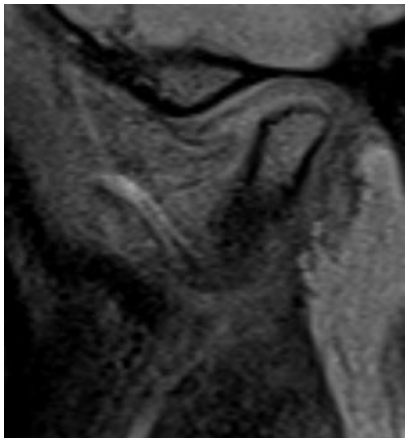

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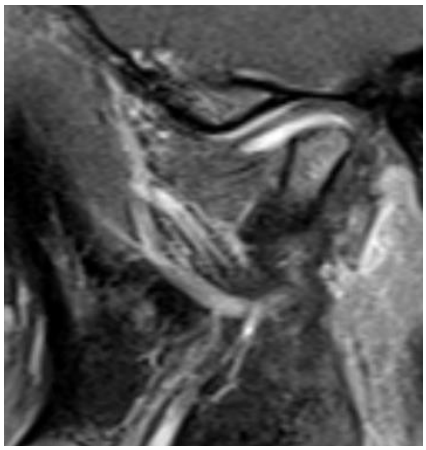

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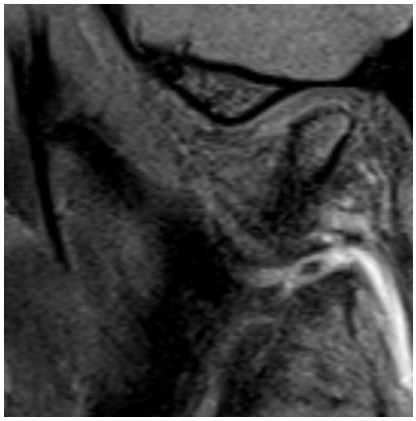

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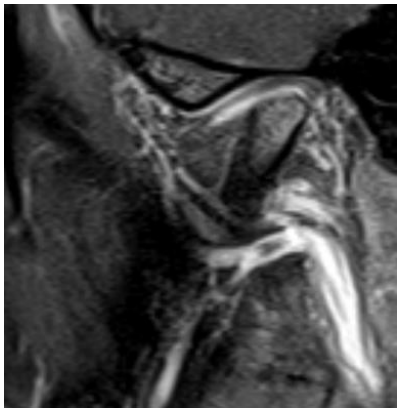

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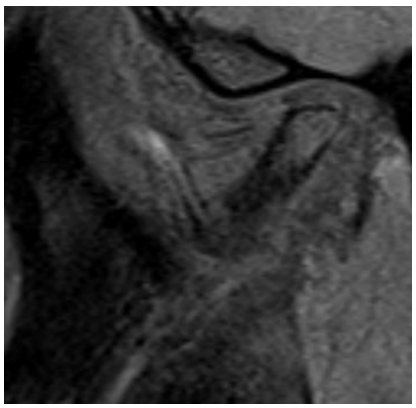

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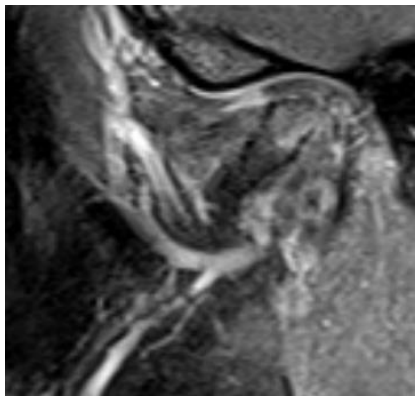

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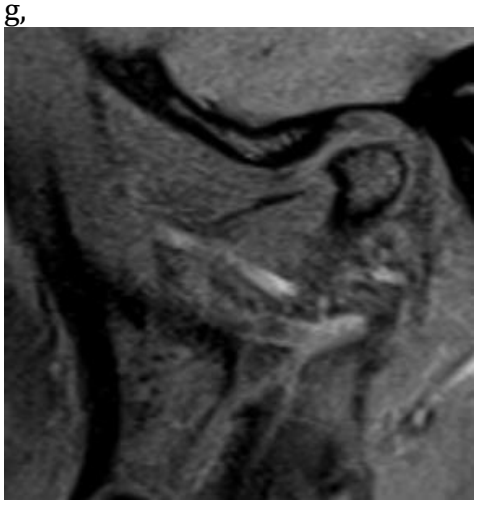

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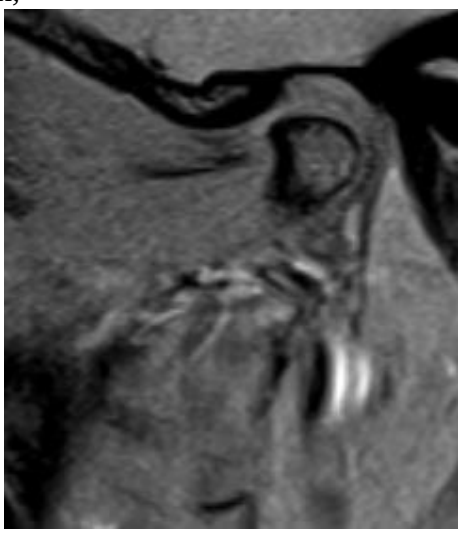

Paper IV

Surgical correction of dentofacial deformities in juvenile idiopathic arthritis: a systematic review; Temporomandibular Joint Juvenile Arthritis Work Group TMJaw.

Frid P, Resnick C, Abramowicz S, Stoustrup P, Nørholt SE.

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Systematic Review
Orthognathic Surgery

Surgical correction of dentofacial deformities in juvenile idiopathic arthritis: a systematic literature review

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P. Frid, C. Resnick, S. Abramowicz, P. Stoustrup, S.E. Nørholt: Surgical correction of dentofacial deformities in juvenile idiopathic arthritis: a systematic literature review. Int. J. Oral Maxillofac. Surg. 2019; 48: 1032–1042.

Abstract. The aim of this study was to assess current evidence for the surgical correction of dentofacial deformities in patients with temporomandibular joint (TMJ) involvement from juvenile idiopathic arthritis (JIA). A systematic literature review, according to the PRISMA guidelines, was conducted. Meta-analyses, randomized controlled trials, cohort studies, observational studies, and case reports were eligible for inclusion. Exclusion criteria were no JIA diagnosis, no clearly defined outcomes, dual publications (except meta-analyses), non peer-reviewed studies, non English language publications, and animal studies. The outcome measures assessed were TMJ function, skeletal alignment, and morbidity. The database search identified 255 citations, of which 28 met the eligibility criteria. Of these, 24 were case reports or case series with a low level of evidence that did not allow for meta-analysis. Extrapolated evidence supports orthognathic surgery in skeletally mature patients with controlled or quiescent JIA and a stable dentofacial deformity. Distraction osteogenesis was recommended for severe deformities. Some authors demonstrated unpredictable postoperative mandibular growth with costochondral grafts. Alloplastic TMJ reconstruction was efficacious, but should be used cautiously in skeletally immature patients. TMJ function and skeletal alignment was improved with reconstruction by any technique and morbidity was low. The surgical correction of arthritis-induced dentofacial deformities is indicated but the level of evidence is low. Prospective multicenter studies are needed.

Key words: juvenile idiopathic arthritis; temporomandibular joint arthritis; juvenile chronic arthritis; orthognathic surgery; Le Fort I; bilateral sagittal split osteotomy; vertical ramus osteotomy; bimaxillary surgery; genioplasty; reconstructive surgery; TMJ prosthesis; costochondral graft; distraction osteogenesis.

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Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children, with an annual incidence of 1.3 to 22.6 per 100,000[1–7]. The temporomandibular joint (TMJ) is involved in 11.6–80% of cases[8–11]. TMJ arthritis can lead to reduced mouth opening, impaired mastication, pain, disruption of condylar growth, and dentofacial deformities[12]. Unilateral TMJ arthritis may cause facial asymmetry and/or an occlusal cant[13]. Bilateral involvement may lead to clockwise rotation of the mandible, resulting in micrognathia, anterior open bite, and a reduction in posterior airway space (PAS)[14,15]. A small PAS is associated with obstructive sleep apnea (OSA) and related comorbidities[16].

TMJ arthritis is difficult to diagnose and control[14]. Uncontrolled arthritis may lead to severe dentofacial deformities. In some patients, growth deviation resulting from TMJ arthritis can be improved with orthopedic/orthodontic treatment during growth[17]. Indications for reconstructive surgery include the following: improvement in TMJ function and/or occlusion, skeletal alignment, desire for facial esthetic improvement, and/or improvement of OSA.

There are two strategies for the surgical correction of JIA-induced dentofacial deformities: (1) TMJ preservation (i.e., orthognathic surgery, distraction osteogenesis (DO)), and (2) TMJ reconstruction (i.e., resection of the remaining condyle, synovial lining, and disc, and reconstruction with an autologous graft[18] or an alloplastic prosthesis[19]). The choice of operational strategy depends on the patient's age, disease activity, extent of the skeletal deformity, and surgeon preference and experience.

The aim of this study was to assess the level of evidence for surgical correction of dentofacial deformities in patients with JIA-related TMJ involvement.

Materials and methods

This study was conducted by the TMJaw Surgical Task Force. TMJaw is an international, multidisciplinary research network founded in Oslo, Norway in 2010, which focuses on research of TMJ arthritis related to JIA. The terminology of the present systematic review adheres to the TMJaw consensus-based standardized terminology[20].

Search strategy

An electronic database search strategy was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[21]. References were archived in a RefWorks database (ProQuest LLC, Ann Arbor, MI, USA). The search strategy was developed for MEDLINE and modified for Embase. The search was limited to these two databases because they are the most inclusive. The primary search was conducted in June 2017 and updated in February 2018. Search terms included the following: juvenile idiopathic arthritis OR juvenile chronic arthritis AND orthognathic surgery OR Le Fort 1 OR bilateral sagittal split OR vertical ramus osteotomy OR bimaxillary surgery OR genioplasty OR distraction osteogenesis OR temporomandibular joint surgery.

Outcome variables

The PICO criteria (patients, intervention, comparison, and outcome) for the study are presented in Table 1. Outcome variables included: (1) TMJ function (i.e., maximum mouth opening measured between the incisal edges of the central incisor teeth, in millimeters), (2) pain, (3) occlusion and skeletal alignment, and (4) operation-related morbidity.

Meta-analyses, randomized controlled trials (RCTs), cohort studies, observational studies, case series, and case reports were eligible for inclusion. Case reports were also included due to the limited number of publications with a high level of evidence identified with the predefined terms. Studies were excluded if they did not include information on JIA diagnosis, had poorly defined outcomes measures, or were dual publications (except meta-analysis), non peer-reviewed studies (e.g., conference abstracts), animal studies, or written in a language other than English.

Study selection and bias

Two authors (PF, SEN) independently assessed the studies identified in the literature search on three occasions. The first selection was based on titles only. The second selection included an assessment of the abstracts. The third and final assessment involved full text review (Fig. 1). Any disagreement between the reviewers was resolved through discussion and the involvement of a third reviewer, until consensus was reached.

The following data were collected from the eligible studies: study design, level of evidence, patient selection criteria, number of subjects, patient sex, mean patient age, surgical procedure, outcomes, adverse effects, and other relevant findings.

The selected studies were assessed for risk of bias on the basis of the following variables: prospective study design, sufficient description of the outcome variable, uniform inclusion criteria, standardized examination protocol, outcome assessor blinded to imaging findings, and information on outcome variable variation. Risk of bias was classified as 'high' if a 'no' was obtained in three or more criteria. The level of evidence was scored according to the Oxford Centre for Evidence-based Medicine (OCEBM) level of evidence guide (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/), as follows: 1a: systematic review with homogeneity of RCTs; 1b: individual RCT with narrow confidence interval; 1c: all or none case series; 2a: systematic review with homogeneity of cohort studies; 2b: individual cohort study including low quality RCT; e.g., <80% follow-up; 2c: 'outcomes' research and ecological studies; 3a: systematic review (with homogeneity) of case–control studies; 3b: individual case–control study; 4: case series (and poor cohort and case–control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research, or 'first principles'.

Results

Two hundred and fifty-five articles were identified in the first search; 85 remained

Table 1. PICO criteria.

PICO	
Patients	Patients with a JIA diagnosis and involvement of the TMJ
Intervention	Receiving a reconstructive or orthognathic surgical intervention
Comparison	Efficacy and safety of various reconstructive or orthognathic surgical modalities in JIA
Outcome	Assessment of treatment outcomes and safety profile
Databases included: MEDLINE via PubMed and Embase. Search terms were constructed for MEDLINE and modified for Embase[a]	

JIA, juvenile idiopathic arthritis; TMJ, temporomandibular joint.

[a] The MEDLINE search terms: ((juvenile idiopathic arthritis) OR (juvenile chronic arthritis)) AND ((orthognathic surgery) OR (Le Fort I) OR (bilateral sagittal split) OR (vertical ramus osteotomy) OR (bimaxillary surgery) OR (genioplasty)).

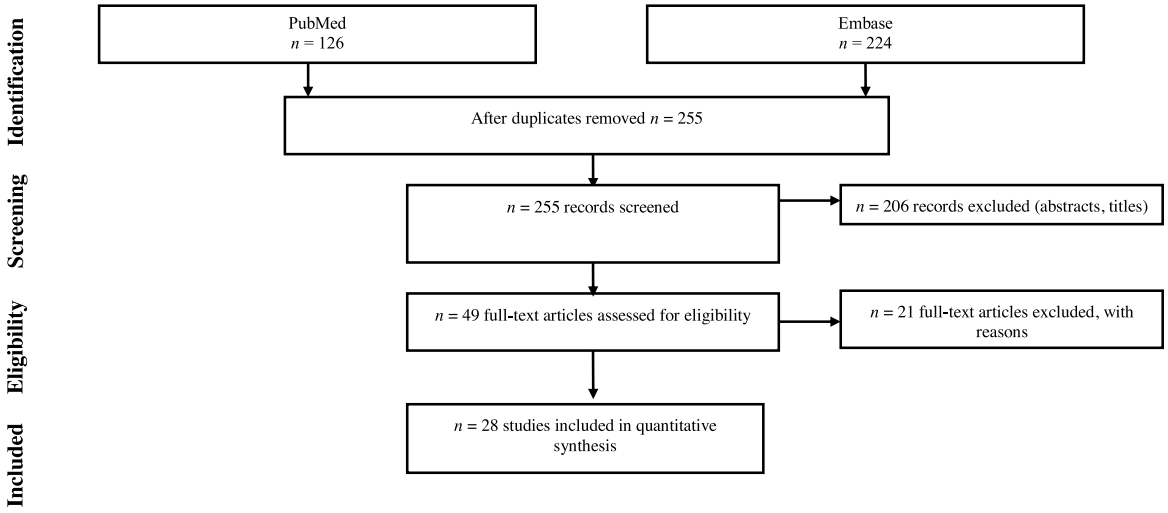

Fig. 1. PRISMA flow diagram of the study selection process.

after title screening. Abstract evaluation resulted in 49 articles. Articles were excluded during full-text assessment for the following reasons: animal studies ($n = 1$), studies not in English ($n = 3$), meta-analysis ($n = 1$), or lack of clearly defined outcome variables ($n = 16$). The final sample included 28 papers for full text evaluation (Fig. 1, Tables 2 and 3)[18,22–48]. The inter-rater agreement for study selection was 100% for all of the variables (Supplementary Material, Table S1). Of the 28 articles included, 24 were case reports or case series[18,22–44], three were retrospective chart reviews[45–47], and one was a prospective cohort study[48]. Many of the included articles described surgical procedures in a mixed group of patients. The included studies described a total of 172 subjects with JIA who underwent a reconstructive surgical procedure.

The risk of bias was rated 'high' in 26 (93%) of the included studies; two (7%) articles had a 'medium' risk of bias30,48 (Supplementary Material, Table S1).

No study included a control group. Four studies did not have uniform inclusion criteria, i.e. not all study subjects had a JIA diagnosis[24,29,30,32]. Various methods were used for the evaluation of outcomes, such as cephalometric analysis and clinical photographs when evaluating skeletal alignment, polysomnography when evaluating OSA, and mouth opening (in millimeters) to evaluate function. The examination protocol was unclear in two studies[26,28]. No outcome assessors in the studies were blinded to imaging findings. Detailed information on outcome variables, such as mean jaw advancement, mean relapse, and mean mouth opening in millimeters, were presented in 23 studies[18,23–25,27,29–32,34,35,37–48]. According to the OCEBM level of evidence, all included articles were grouped in category four (i.e., case series and poor cohort and case–control studies).

Surgical intervention and outcomes

TMJ preservation—orthognathic surgery

Nine case reports and case series discussed orthognathic surgery in 80 patients (43 with JIA)[30–32,34,36,37,42,45,46]. Age at operation ranged from 15 years to 53 years. Follow-up varied from <1 year to 10 years. All studies reported improved function, occlusion, and skeletal alignment. All studies reported few complications; these included infection, wound dehiscence, skeletal relapse, and continued TMJ pain.

Kahnberg and Holmstrom described maxillary and mandibular orthognathic surgery with chin augmentation (implant) in 19 of 34 analyzed patients (37 in total, three with JIA). In 15 patients, a chin implant was the only procedure. All patients reported high postoperative satisfaction[30]. Two patients had postoperative dehiscence and one patient had infection of the implant. Pagnoni et al. described Le Fort I osteotomy and genioplasty in five patients with quiescent JIA[37]. Occlusion and skeletal movements were stable 8 months postoperatively. All patients reported relief of TMJ pain, increased bite strength, and a reduction of headache and sleep respiratory distress postoperatively. These authors advocated for Le Fort I osteotomy with autorotation of the mandible and genioplasty, without a mandibular osteotomy, theorizing that a mandibular operation exacerbates condylar resorption, TMJ pain and dysfunction. According to the same authors, postoperative exacerbation of TMJ arthritis did not occur.

Leshem et al. reported skeletal relapse of 2.1 mm after a mean 9.6 mm mandibular advancement at 1 year postoperatively in eight patients with JIA[45]. They also reported an improvement in quality of life for all patients. These authors recommended a surgical splint with a small posterior open bite and edge-to-edge incisor relationship to compensate for expected relapse. One patient in their series continued to suffer from TMJ pain postoperatively.

Kreiborg et al. described a 15-year old patient with ''some relapse'' 1 year after bimaxillary surgery[34]. They hypothesized that dysplastic mandibular growth leads to occlusal instability and poor masticatory muscle function. Therefore, they recommended early orthognathic surgery (i.e., prior to skeletal maturity) to maintain occlusal stability throughout growth.

One of seven subjects (age 10–24 years) described by Myall et al. required a reoperation at age 18 years due to relapse after sagittal ramus osteotomy and genioplasty at age 10 years[36]. Oye et al. described mean skeletal relapse of 2.3 mm after average mandibular advancement of 5.3 mm in 16 patients[46]. Half of these patients had TMJ pain before surgery (mean visual analog scale (VAS) score 2.4), and 38% reported pain postoperatively (mean VAS score 1.3). These authors therefore concluded that orthognathic surgery reduces pain.

TMJ preservation—distraction osteogenesis

Seven studies described DO in 40 patients with JIA[23,25,33,35,39,47,48]. One study was a prospective cohort study[48] and one was a

Table 2. Summary table of articles on TMJ preservation surgery (i.e., orthognathic surgery and distraction osteogenesis) included in the review.

Source	Study design	LOE[a]	Patient selection criteria	Number of patients	Sex Age (years)[b]	Surgical procedure	Outcome[c]	Adverse effects	Follow-up Other relevant findings
Orthognathic surgery									
Kahnberg and Holmstrom[30]	CS	4	Consec.	37 (3 JIA)	20 F, 17 M 25 (16–43)	Chin augmentation: acrylic implant combined with orthognathic surgery	Stable position of chin, high patient satisfaction	2 dehiscences, 1 infection	FU: <1 year for 3 pts, min 1 year for 34 pts; 5 years for 17 pts
Kasfikis et al.[31]	CR	4	Consec.	1 (mandibular hypoplasia, OSA, Crohn's disease)	F 18	BSSO + genioplasty	Stable function and esthetics at 2 years postop.	No	FU: 2 years
Kennett and Curran[32]	CS	4	Selected	4 (1 JIA)	3 F, 1 M 16 (12–18)	JIA pt: VRO with iliac BG, onlay BG to the chin, 6 weeks of MMF; other pts: BSSO, condylectomy + rib graft, sliding genioplasty	Improved occlusion and profile	Resorption of the onlay BG to the chin	FU JIA pt: 1 year (3–18 months) The need for postop. jaw exercises is stressed
Kreiborg et al.[34]	CR	4	Consec.	1 (9–17 years, baseline to FU)	F 15	LFI + BSSO + genioplasty	Facial growth/facial appearance and oral function improvement	Some relapse 1 year postop., but it did not affect the soft tissue profile	FU: 1 year postop.
Leshem et al.[45]	Retrosp. CS	4	Consec.	8	5 F, 3 M 18 (17–22)	BSSO (8), LFI (6/8), genioplasty (4/8)	Improved occlusion, facial esthetics, QOL; continued TMJ pain (1 pt) Mean MA 9.6 mm: Co–Gn; mean mandible relapse 2.1 mm (did not significantly affect the clinical outcome)	Some relapse 1 year postop., but it did not affect the soft tissue profile	FU: min 8 months (mean 36 months)
Myall et al.[36]	CS	4	Consec.	7	5 F, 2 M Age at onset of JIA 1–11 Age at surgery 10–24	All: BSSO and genioplasty; 2 pts LFI; MMF 6 weeks and wire/screws	6 patients with satisfactory function and esthetic results; all 7 had normal sensitivity and TMJ function	1 pt underwent reoperation (1 st surgery at age 10, 2nd at age 18)	FU: 6 months No patients had ankylosis Not the authors experience that children with JRA are predisposed to this condition Prefer to delay surgery until growth has finished
Oye et al.[46]	Retrosp. CS (1991–2000)	4	Consec.[d]	16	12 F, 4 M 24.25 (16–53)	BSSO + genioplasty	Improved profile, all patients satisfied; may reduce TMJ pain Mean relapse 2.3 mm of MA 5.3 mm (48%) (Pog–Co); 50% of pts (8) relapsed ≥2 mm	Safe treatment; reoperation for 4 pts, infection in 2 pts; negative tooth sensitivity in 3 pts, scar in 3 pts; plates removed from 3 pts; extraoral changes in 5 pts	FU: 1–10 years

Table 2 (*Continued*)

Source	Study design	LOE[a]	Patient selection criteria	Number of patients	Sex Age (years)[b]	Surgical procedure	Outcome[c]	Adverse effects	Follow-up Other relevant findings
Pagnoni et al.[37]	CS	4	Consec.	5	4 F 21.75 (17–29)	LFI + genioplasty	Improved occlusion and facial profile Mean MA rotation 5.6 mm Mean posterior–anterior face height ratio 63.9 (S–Go/N–Me)	None	FU: min 8 months (8 months–8 years) ''Mandibular procedures may evoke further condylar resorption with pain and functional impairment of the TMJ''
Turpin and West[42]	CR	4	Consec.	1	F 9	BSSO + alloplastic chin implant	Improved facial esthetics and occlusion	Good function Some relapse; chin implant migration, some increased overjet	FU: 30 months postop., 14 months after removal of orthodontic appliances
Distraction osteogenesis									
Cattaneo et al.[23]	CR	4	Consec.	1 (unilateral hypoplasia of right mandibular ramus, JIA)	M 12.5	Unilateral MDO	Evaluation of load transfer mechanism to the TMJs before, under, and after DO	No long-term FU	Before DO: high peak stresses to the affected TMJ After DO: more symmetrical loading to the TMJs Under DO: the reaction forces in the TMJs were low
de Zee et al.[25]	CR			simulation model CBCT/MRI	4	Consec.	1 pt with JIA	M 12.5	Unilateral MDO
Shape of articular eminence (load, remodeling fossa): reduced load after DO	No	FU: 6.5 years							
Mackool et al.[35]	CR	4	Selected	1	F 26	Bilateral extraoral ramus DO, 24 mm, consolidation 85 days	Improved esthetics, sleep apnea; MIO: 10 mm to 12 mm	Scar tissue in skin	FU: not stated Cephalometric measures reported
Kofod et al.[33]	CR	4	Selected	1 (asymmetry secondary to JIA)	M Young	Unilateral vertical ramus DO 16 mm	Skeletal deformity corrected Stress load is higher on distracted side during distraction	NR	No FU data
Nørholt et al.[48]	Prosp. cohort study	4/3	Consec.	23	9 M, 14 F Age at onset 6.4 $\pm$ 3.9 Age at surgery 15.8 $\pm$ 4.7	Unilateral ramus DO 18 mm At removal of DO device: 7 LFI, 1 genioplasty Later surgery: 2 LFI and 1 genioplasty	No aggravating symptoms from TMJ, predictable correction of asymmetry, good function	Minor problem with pain and activation of the device, 2 pts mild dysesthesia, 2 pts trismus	FU: min 12 months

Singer et al.[39]	CR	4	Consec.	1	F 18	BMDO + LFI + genioplasty	Improved esthetics, overjet (remained positive),chin, occlusal plane	Stable results 1 year postop., MIO 32 mm, unchanged postop.; no TMJ pain or muscle pain postop.	FU: 1 year
Stoor et al.[47]	Retrosp.	4	Consec.	12	9 F, 3 M 27.4 (at 1 st surgery)	MA (11) and additional DO (3), or additional AJR, unilateral/bilateral (3); bilateral AJR (1)	TMJ function and healing good, stable occlusion, improved facial appearance	Mean MA 10.1 mm and mean relapse 2.1 mm (pogonion)	FU: mean 2.3 years

AJR, alloplastic joint reconstruction; BG, bone graft; BMDO, bilateral mandibular distraction osteogenesis; BSSO, bilateral sagittal split osteotomy; CBCT, cone beam computed tomography; Consec., consecutive; CR, case report; CS, case series; DO, distraction osteogenesis; F, female; FU, follow-up; JIA, juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis; LFI, Le Fort I; LOE, level of evidence; M, male; MA, mandibular advancement; MDO, mandibular distraction osteogenesis; MIO, maximum incisal opening; MMF, maxillomandibular fixation; MRI, magnetic resonance imaging; NR, not reported; OSA, obstructive sleep apnea; postop., postoperative; Prosp., prospective; pts, patients; QOL, quality of life; Retrosp., retrospective; TMJ, temporomandibular joint; VRO, vertical ramus osteotomy.

[a] Level of evidence was scored according to the Oxford Centre for Evidence-based Medicine level of evidence guide (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/).

[b] Presented as the mean (range) for case series studies; presented as the mean ± standard deviation for the prospective cohort study.

[c] S–Go, sella–gonion; N–Me, nasion–menton; Pog–Co, pogonion–condylion; Co–Gn, condylion–gnathion.

[d] Patients referred from Rheumatology Department, Rikshospitalet.

retrospective study[47]. Five of the studies were case reports[23,25,33,35,39]. Three of the included studies evaluated load transfer to the TMJs before, during, and after DO[23,25,33].

Nørholt et al. prospectively followed a cohort of 23 patients with JIA after unilateral DO, with or without a maxillary osteotomy or genioplasty, for at least 12 months postoperatively[48]. They found predictable correction of asymmetry, improved function, and decreased TMJ pain after DO. Two patients developed dysesthesia in the lower lip. A significant improvement in condylar translation was observed during distraction, but postoperatively this was not significantly improved when compared to the preoperative conditions.

In the retrospective study of Stoor et al., 11 patients with JIA and severe TMJ degeneration had mandibular advancements with orthognathic surgery, of whom three had additional mandibular DO and three had a unilateral or bilateral TMJ prosthetic reconstruction[47]. An additional patient underwent only bilateral TMJ prosthetic reconstruction. The mean mandibular advancement was 10.1 mm. Mean follow-up was 2.3 years. There was a mean relapse at pogonion of 2.1 mm. The occlusion was stable in 11/12 patients. The TMJ function was good and the facial esthetics improved in all patients.

Singer et al. reported an 18-year-old female who had bilateral mandibular DO, Le Fort I osteotomy, and a genioplasty[39]. At the 1-year follow-up, she had improved skeletal relationships and good function. Preoperative bilateral masseter pain resolved postoperatively.

Mackool et al. described a 26-year-old woman with JIA who had relief of OSA and an improved facial profile after bilateral mandibular DO[35]. However, MIO only improved from 10 mm to 12 mm.

Cattaneo et al. and Kofod et al. presented the case of a 12-year-old boy with JIA, unilateral mandibular hypoplasia, and condylar erosion[23,33]. Using a simulation model, the authors showed high peak stresses to the affected resorbed condyles before operation with DO. During active distraction, forces in the TMJs were low. After DO, load sharing was more symmetric to the condyles compared to the preoperative measurement. de Zee et al. also found reduced load to the affected TMJ 6 years after DO[25].

TMJ reconstruction—autologous TMJ reconstruction

Seven case reports and case series ($n = 48$ patients, 29 with JIA) discussed TMJ reconstruction using costochondral grafts

Table 3. Summary table of articles on TMJ reconstruction surgery (i.e. costochondral grafts and alloplastic joint reconstruction) included in the review.

Source	Study design	LOE[a]	Patient selection criteria	Number of patients	Sex Age (years)[b]	Surgical procedure	Outcome[c]	Adverse effects	Follow-up Other relevant findings
Costochondral grafts									
Bowler[22]	CS	4	Consec.	2	2 F 14	Bilateral CCG + dermis graft	Excellent functional and esthetic results, self-confidence improved	No	FU: 4 years (1 case)
Cohen et al.[24]	CS (OSA)	4	Consec.	20 OSA (1 JIA)	M 16 (6 days–18 years, total sample)	Skeletal expansion/ osteotomies: orthognathic surgery, CCG, DO, TMJ arthroplasty, segmental Le Fort I osteotomy and soft tissue surgery	Improved respiration, increased volume of naso-oropharynx	No	FU: 6–12 months ''Tracheostomy leads to social isolation for these children''
Felix et al.[27]	CR and review	4	Consec.	1 bilateral ankylosis	F 13	Bilateral TMJ reconstruction with CCG	MIO 40 mm = good function; good esthetics	No	FU: 24 months
Guyuron[28]	CR	4	Referred	1	F 35	Ankylosis age 10 LFI osteotomy with anterior rotation, BSSO 8 mm advancement, genioplasty 7 mm, bilateral CCG; after 6 months, lipectomy and removal of submaxillary glands	Relapse 1–2 mm first year, stable following 5 years; psychological improvement; TMJ function good, 40 mm MIO	No	FU: 5 years Diagnosis 9 years, prednisolone
Stringer et al.[18]	CS	4	Consec.	5	5 F 14–18	Orthognathic surgery + CCG (inverted L-osteotomy + LFI + iliac graft + genioplasty) = 1 surgery	Gn–N–Ba, 4 of 5 pts class I occlusion on FU, 1 pt a 3 mm open bite postop. Mean increase anterior–posterior 22.7 mm T1–T2	Relapse average 1.5 mm T2–T3 Infection ($n = 1$)	FU: mean 9.6 years (range 4–14 years)
Svensson and Adell[41]	CS, Retrosp.	4	Selected	12 (=7 pts from Svensson 1993)	11 F, 1 M 10–17	CCG 9 bilateral, 3 unilateral; disc removed in 12 joints, preserved in 9 joints	Good function: 11/12 had no pain or symptoms from TMJ; MIO 35.6 mm preop., 41.3 mm at FU; 5 pts class I, 7 pts class III at FU; 7 pts further orthognathic surgery	Overgrowth of CCG (8/12)	Mean FU: 5.3 years (age 18.9 years) Considerable risk of unilateral overgrowth of CCG ($n = 8$)
Svensson et al.[40]	CS	4	Selected	7	All F Mean age at onset 4.5 Mean age at surgery 12.5 (range 10–14)	5 bilateral, 2 unilateral, resection of condyle (disc preserved) and coronoid process; CCG from C5 or C6; fixation with screws; 6 weeks of MMF Functional treatment after 8 weeks	5/7 no functional problems or pain; MIO after 2–4.5 years: 39 mm (range 30–43 mm); good symmetry in bilateral cases; slight asymmetry in unilateral cases	No complications to CCG	FU: 2–4.5 years Extensive mandible growth from 8 weeks postop. to latest FU No report of excessive overgrowth or resorption of CCG – longer FU needed
Alloplastic joint reconstruction									
Fanaras et al.[26]	CR	4	Consec.	1	F 42	Bilateral AJR, custom-made (Biomet)	Full range of hinge movement, good function	No	FU: MIO 31 mm 6 months later

Haq et al.[29]	CS	4	Selected	5 (1 JIA)	F 43 (16-year history of trismus/ ankylosis)	Bilateral custom-made AJR	MIO increased to 25 mm	No	FU: 18 months
Paul et al.[38]	CR	4	Selected	1	M 29	Absence of both condyles; 1 st surgery AJR, 2nd surgery BSSO with BG and 10-mm plate	Improved sleep and esthetics; AHI decreased from 48 to 7	Not reported	FU: 10 months No fossa component!
Webster et al.[43]	CR	4	Consec.	1	F 18 (= time at surgery)	Bilateral custom-made AJR (Biomet) + mandibular advancement and genioplasty	Improved facial and dental esthetics	None	FU: 3 years
Wolford et al.[44]	CS	4	Consec.	56	55 F 1 M 39 (15–61)	Bilateral TMJ AJR Techmedica	Outcome groups based on clinical assessment: one or no previous TMJ surgery: good 86%, fair 14%, poor 0%	5 AJR removed; 17 pts (30%) reoperated due to heterotopic bone formation, fibrosis, calcification, inflammation	FU: 30 months (range 16–46 months)

AHI, apnea–hypopnea index; AJR, alloplastic joint reconstruction; BG, bone graft; BSSO, bilateral sagittal split osteotomy; CCG, costochondral graft; Consec., consecutive; CR, case report; CS, case series; DO, distraction osteogenesis; F, female; FU, follow-up; JIA, juvenile idiopathic arthritis; LFI, Le Fort I; LOE, level of evidence; M, male; MIO, maximum incisal opening; MMF, maxillomandibular fixation; OSA, obstructive sleep apnea; postop., postoperative; preop., preoperative; Retrosp., retrospective; TMJ, temporomandibular joint.

[a] Level of evidence was scored according to the Oxford Centre for Evidence-based Medicine level of evidence guide (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/).

[b] Presented as the mean (range) for case series studies.

[c] Gn–N–Ba, gnathion–nasion–basion.

(CCG) in both skeletally mature and immature subjects[18,22,24,27,28,40,41]. Age at operation varied from 10 years to 35 years. Follow-up ranged from 6 months to 14 years. Following CCG, six studies reported improved functional outcomes (defined as increased mouth opening) and improved skeletal profiles[18,22,27,28,40,41]. Two studies reported improved self-confidence[22,28] and two case reports found improvement in OSA[24,28]. One paper suggested synovectomy in conjunction with CCG to prevent progression of TMJ destruction[22]. Morbidity at both the donor and recipient sites was low. All seven case reports and case series discussing autologous TMJ reconstruction reported no or few TMJ symptoms or muscle symptoms after surgery. Two studies discussed the risk of overgrowth of the CCG, resorption of the graft, and donor site morbidity[40,41]. Svensson et al. followed 12 patients with JIA for a mean of 5.3 years after CCG and demonstrated asymmetric mandibular overgrowth in eight[41]. Resorption of the graft was seen when bone screws were removed 1–2 years after CCG reconstruction.

Guyuron reported skeletal relapse of 1–2 mm at 1 year after CCG reconstruction and BSSO advancement of the mandible and genioplasty, but no further change over the subsequent 5 years[28]. Stringer et al. reported a skeletal relapse of 1.5 mm at a mean of 9.6 years following CCG and concomitant Le Fort I osteotomy[18].

TMJ reconstruction—alloplastic TMJ reconstruction (AJR)

There were five case reports and case series on reconstruction with alloplastic TMJ prostheses in patients with JIA[26,29,38,43,44]. In total, these studies included 64 subjects, 60 of whom had a diagnosis of JIA. Age at the time of operation ranged from 15 years to 61 years. Follow-up ranged from 6 months to 46 months. TMJ replacement was either by stock joint ($n = 1$)[38] or custom joint prosthesis by Biomet or TMJ Concepts ($n = 4$)[26,29,43,44]. All reported improved functional and skeletal outcomes. One manuscript reported improved OSA[38]. All five case reports and series discussing alloplastic TMJ reconstruction reported low morbidity with no or few TMJ symptoms or muscle symptoms after surgery.

Webster et al. recommended AJR as the most suitable treatment for patients with JIA, condylar degeneration, and dentofacial deformity[43]. They performed AJR

with a simultaneous mandibular advancement and genioplasty due to the extent of condylar destruction and clockwise mandibular rotation.

Wolford et al. reported good treatment results after AJR in patients who had undergone ''no or one previous TMJ surgery'' before joint replacement, based on clinical assessment of stability, function, and residual pain[44]. Paul et al. reported improved OSA and esthetics at 10 months of follow-up, after ''dual stage surgery'' using first an alloplastic TMJ prosthesis followed later by mandibular advancement with a body osteotomy fixed with a titanium reconstruction plate with an inter-positioning iliac graft bilaterally[38].

Discussion

The aim of this study was to assess the level of evidence for surgical correction of dentofacial deformities in patients with TMJ degeneration from JIA. Currently, there is no consensus regarding the most appropriate reconstructive approach for this patient population. The choice of operation may be influenced by the degree of skeletal maturity, level of TMJ arthritis activity, extent of TMJ and dentofacial deformity, and surgeon preference and experience.

The findings of this systematic review suggest that all available reconstructive surgical interventions (orthognathic surgery, DO, CCG, AJR) improve TMJ function and skeletal relationships in this patient population. Only minor to moderate complications have been reported, such as temporary nerve damage, infection, and mandibular overgrowth. However, these reports must be evaluated in the context of the low level of evidence.

The management of TMJ dysfunction and pain is important for activities of daily living such as mastication, speech, and oral hygiene. Improvements in mouth opening and micrognathia are critical for airway management under general anesthesia[50]. Also, improvements in occlusion, skeletal alignment, facial esthetics, and self-confidence are considered important for patient well-being, since facial attractiveness has been shown to influence education, relationships, and employment[51].

All of the included case reports and case series on orthognathic surgery in JIA reported improved functional outcomes, occlusion, and skeletal alignment[30–32,34,36,37,42,45,46]. Orthognathic surgery is traditionally performed after skeletal maturity to maximize stability. A major concern in this context are the high-angle cases, i.e. cases with a steep mandibular plane angle, undergoing a large mandibular advancement, with skeletal relapse secondary to soft tissue forces[52]. Children with JIA often are high-angle cases due to TMJ arthritis with a TMJ deformity causing posterior rotation of the mandible resulting in an anterior open bite. Mandibular advancement has been reported to show relapse even in non-JIA patients[14,53]. Thus, some authors recommend early surgical intervention in order to provide better conditions for normal development of the facial skeleton[34,53].

Other investigators recommend anti-inflammatory medications and stabilizing splints until the TMJs are 'stable' before orthognathic surgery, with minimal postoperative loading of the TMJs[17,54]. The rationale for this approach is to avoid or minimize the mandibular advancement in order to avoid overloading the TMJs. However, these treatment approaches may also result in significantly compromised function and esthetics, continued restriction of the oropharyngeal airway, and continued or worsening of pain.

Morbidity was low for orthognathic surgery compared to TMJ reconstruction (CCG or alloplastic prosthesis) or DO. Surgical exposure when performing CCG, AJR, or DO with an extraoral approach is usually via a combined preauricular and submandibular incision. Therefore, there is a risk of facial nerve damage during surgery[55].

In this review, improvements in functional outcome and skeletal alignment[39,47,48], OSA[35], and load transfer to the TMJs[23,25,33] were reported after DO. For patients with significant dentofacial deformities, DO may be a suitable option. DO is widely used to improve the morphology of the facial skeleton in patients with congenital or acquired deformities[56]. DO may be more stable over time with less skeletal and dental relapse compared to conventional orthognathic surgery[48,57]. However, DO requires careful vector planning and patient collaboration during device activation. In asymmetric cases, JIA patients will have a period with potential overloading of the TMJ on the affected side. Therefore, it is argued that DO performed during adolescence reduces the time period of load to the affected TMJ, limits the risk of nerve damage to one side compared to both when performing the BSSO osteotomy, and reduces the need for a maxillary osteotomy by allowing normal growth of the maxilla concomitantly with the mandible[48]. However, a second operation is required to remove the distraction device.

In skeletally immature patients, autologous reconstruction may be preferred because the graft has the potential to grow with the child. This review of available articles found an improvement in functional outcome and esthetics[18,22,27,28,40,41], self-confidence[22,28], and OSA[24,28], after CCG. However, there is controversy in the literature regarding the use of CCG, primarily due to the potential for overgrowth[40,41]. Additionally, the CCG surgical procedure carries the risk of graft resorption and ankylosis, and is associated with donor site morbidity[55,58]. Nevertheless, other authors found no difference in outcomes of TMJ reconstruction with CCG or alloplastic graft in rheumatoid arthritis patients, except that the alloplastic graft group had fewer additional operations[55].

Some authors favored AJR in adult patients, advocating that this approach provides stable long-term results and facilitates early mobilization. However, long-term outcomes of AJR beyond 15 years are unknown[19]. Patients who have not reached skeletal maturity are expected to have a long life span, and thus there is a risk of mechanical failure requiring reoperation or replacement of the AJR. The included articles reported improved OSA and esthetics[38] and good functional outcomes[26,29,38,43,44], with the longest follow-up of 46 months[44].

Some authors suggested staged surgical procedures with AJR first, followed by BSSO with bone graft and plate osteosynthesis[38]. Others recommended a single AJR procedure[43]. The authors claimed that failure is likely to result when performing mandibular advancement surgery alone without TMJ surgery in patients with active TMJ arthritis disease, because of mandibular relapse from continued condylar resorption and/or increased pain levels. In cases of disease remission, maxillary surgery can be performed for closure of open bites; however, the esthetic results are often suboptimal[59,60].

This systematic review had some limitations. First, the studies included had a low level of evidence and a high risk of bias. Most of the studies had a small patient sample, and no study had a control group. Additionally, the mixture of JIA and non-JIA patients in many publications introduces confusion for the reader. Only some of the included patients had JIA (232 patients, 172 with JIA). Thus, it is difficult to ascertain that the results are specific to JIA and not to another condition. Also, the majority of the outcome assessors were not blinded in the included studies. Furthermore, only two databases were used for the literature search and this may have

been a bias at the review level. Therefore, the study heterogeneity did not allow for meta-analysis. The strength of this review is that it includes all manuscripts on JIA and dentofacial reconstruction.

The research and treatment of JIA-induced TMJ and dentofacial deformities requires multidisciplinary collaboration between rheumatologists, orthodontists, and oral and maxillofacial surgeons, and many other healthcare providers (e.g., radiologists, general dentists, physical therapists, etc.). There is a significant need for prospective studies with standardized variables in patients with JIA and dentofacial growth deviations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2019.01.007.

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