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Orthodontic treatment in patients with juvenile idiopathic arthritis (JIA): a systematic review

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Orthodontic treatment in patients with juvenile idiopathic arthritis (JIA): a systematic review

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TABLE OF CONTENTS

ABSTRACT

Introduction: Juvenile idiopathic arthritis (JIA) represents the most common childhood rheumatic disease in the Western world. The etiology is not completely understood but it is considered as multifactorial. Different joints can be involved, including the temporomandibular joint (TMJ). TMJ arthritis remains one of the most underdiagnosed and undertreated conditions in JIA, and its delayed detection may lead to severe structural and functional abnormalities of the masticatory system, so it is important that clinicians are aware of the treatment possibilities for these patients.

Aim: The aim of this systematic review is to summarize the existing evidence concerning the orthodontic treatment in JIA patients.

Materials and methods: This review was conducted according to the PRISMA statement to answer the following focused question: “Which orthodontic treatments are most appropriate in patients with juvenile idiopathic arthritis?” Research has been done in four databases (PubMed, EBSCOhost, Web of Science and Cochrane). Seven articles were selected, including only clinical studies.

Results: The studies included in this systemic review show that the most affected gender is female. The age of the patients ranged from 6 to 15 years. The most prevalent JIA subtype was first the oligoarticular, and then the polyarticular. One criteria present in all studies is that patients with JIA could only had unilateral TMJ involvement. Regarding systemic medication, four articles addressed methotrexate. In respect on the administration of TMJ steroid injections, only two studies reported that there was no intervention of any type. The most used diagnostic methods were CBCT and orthopantomography. Concerning clinical approaches, two studies presented hyrax palatal expander, other two approached a distraction splint, one addressed a stabilization splint, another presented an activator and finally one study addressed an orthopedic appliance and distraction osteogenesis.

Conclusion: There is limited evidence that dentofacial orthopedic treatment using functional appliances can improve mandibular retrognathia and reduce pain in adolescent patients with JIA. Although, orthopedic treatment can prevent an approach that is much more complex and with greater morbidity than orthodontic and surgical treatment in adulthood. However, there is still no concordance about interceptive treatment effectiveness due to the rheumatic condition and differences between patients.

Keywords: arthritis juvenile, orthodontics, temporomandibular joint, child, malocclusion, treatment outcome

RESUMO

Introdução: A artrite idiopática juvenil (AIJ) representa a doença reumática infantil mais comum no mundo ocidental. A etiologia não é totalmente conhecida, mas é considerada multifatorial. Diferentes articulações podem estar envolvidas, incluindo a articulação temporomandibular (ATM). A artrite da ATM continua a ser uma das patologias mais subdiagnosticadas e subtratadas na AIJ, e a sua deteção tardia pode levar a graves anomalias estruturais e funcionais do sistema estomatognático por isso, é importante que os clínicos estejam cientes das possibilidades de tratamento para estes pacientes.

Objetivo: O objetivo desta revisão sistemática é resumir as evidências existentes sobre o do tratamento ortodôntico em pacientes com AIJ

Material e métodos: Esta revisão foi elaborada de acordo com as guidelines PRISMA para responder à seguinte questão: “Quais os tratamentos ortodônticos mais apropriados em pacientes com artrite idiopática juvenil?” A pesquisa foi feita em quatro bancos de dados (PubMed, EBSCOhost, Web of Science e Cochrane). Sete artigos foram selecionados incluindo apenas estudos clínicos.

Resultados: Os estudos incluídos nesta revisão sistemática mostram que o gênero mais afetado é o feminino. A idade dos pacientes variou entre os 6 e 15 anos. O subtipo de AIJ mais prevalente foi o oligoarticular e depois o poliarticular. Um critério presente em todos os estudos é que os pacientes com AIJ só poderiam ter envolvimento unilateral da ATM. Em relação à medicação sistêmica, quatro artigos abordaram o metotrexato. Sobre a administração de injeções de corticosteroides na ATM, apenas dois estudos relataram que não houve intervenção de qualquer tipo. Os métodos de diagnóstico mais utilizados foram o CBCT e a ortopantomografia. Em relação às abordagens clínicas, dois estudos apresentaram expansor palatino do tipo hyrax, outros dois abordaram um aparelho de distração osteogénica, um abordou um aparelho de estabilização, outro apresentou um ativador e por último um estudo abordou um aparelho funcional e distração osteogênica.

Conclusão: Há evidências limitadas de que o tratamento ortopédico dentofacial com aparelhos funcionais possa melhorar a retrognatia mandibular e reduzir a dor em pacientes adolescentes com AIJ. Contudo, o tratamento ortopédico pode impedir uma abordagem muito mais complexa e de maior morbilidade do que o tratamento ortodôntico e cirúrgico na idade adulta. No entanto, ainda não há concordância sobre a eficácia do tratamento intercetivo devido ao quadro reumático e às diferenças entre os pacientes.

Palavras-chave: artrite juvenil, ortodontia, articulação temporomandibular, criança, má oclusão, resultado do tratamento

INTRODUCTION

Juvenile idiopathic arthritis (JIA), also referred in literature as juvenile chronic arthritis and juvenile rheumatoid arthritis, represents the most common childhood rheumatic disease in the Western world, affecting approximately 1 per 1000 children, with girls more frequently affected than boys.(1–4)

The International League of Associations of Rheumatology (ILAR) defines JIA as arthritis of unknown etiology, starting before the age of 16 years and with a duration of at least 6 weeks. It is characterized by persistent inflammation of joints.(1,3,5,6)

The etiology is not completely understood but it is considered as multifactorial with an essential role of auto-immune, genetic and environmental factors. Strong evidence supports for the role of Human Leukocyte Antigen (HLA), class I and II alleles in the pathogenesis of different subtypes of JIA.(7) Several studies suggested pathophysiologic factors for bone destruction and erosion are stimulation of osteoclasts by interleukins, tumor necrosis factor, macrophage colony-stimulating factor, and inhibition of the functional capacity of osteoblasts in patients with rheumatoid arthritis.(2) There might be an inflammatory response to an unknown stimulus with a local accumulation of monocytes and macrophages producing cytokines. Macrophages contribute to the recruitment of the T lymphocytes, which in turn activate the B lymphocytes. The inflammatory tissue proliferates at the synovial level (pannus). Pannus is considered a chronic manifestation, and is often associated with other permanent features such as erosions/flattened condyle. (8) It tends to cover the articular cartilage by gradually inducing its destruction.(9) . This may lead to local growth disturbances that occur as a result of inflammation, increased vascularization and destruction of the growth sites in the mandibular condyle. The severity can range from condylar flattening, sometimes combined with minor lesions, to complete absence of the condylar head. (10,11)

The resultant abnormalities cause grow disturbances, which are present in up to 69% of subjects with JIA, include micrognathia, downward and posterior growth rotation of the mandible, facial asymmetry, limited mouth opening as well as various malocclusions, especially hyperdivergent class II, jaw pain, dysfunction, psychological disturbances and a reduced quality of life. (8,11)

TMJ arthritis has the potential to be severely destructive, since a major growth zone of the lower jaw located in the condyles affects the growth of the mandible, the dentition, and the facial skeleton .These symmetrically located growth centers are in direct proximity to the inflamed synovial membrane due to their superficial proliferative zone in the articular cartilage and are thus particularly susceptible to growth disturbances, as compared with the rather wide intervals between the synovial membrane and growth zones in peripheral joints. (12)

The best chance to minimize the sequelae and reaching an optimal treatment is to detect any involvement of the TMJs as early as possible and to initiate the necessary treatment. (13)

Further research is necessary to clarify the contributing role that genetics and environment play in the onset and disease course of JIA, in particular regarding the pathogenic mechanisms leading to the development of TMJ arthritis.(7)

Juvenile idiopathic arthritis can be divided into 7 subtypes based on clinical symptoms during the first 6 months of the disease. These different subtypes are systematic arthritis, oligoarticular arthritis (persistent and extended), polyarticular rheumatoid factor (RF)-positive arthritis, polyarticular RF-negative arthritis, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis.(2,10) Oligoarticular arthritis is the most frequent subtype of JIA, accounting for 27–56% of all cases.(14,15)

In juvenile idiopathic arthritis, different joints can be involved, including the temporomandibular joint (TMJ). The TMJ can be the first and/or the only affected joint, and it can be unilateral or bilateral.(2,14) The prevalence of clinically detectable temporomandibular joint involvement varies between 38 and 72%, depending on the diagnostic method used and the JIA subtype examined.(16)

The temporomandibular joint is a unique and highly complex joint in comparison with others joints of the body.(5) The TMJ is a synovial joint composed of 4 articulating surfaces: glenoid fossa of the temporal bone, the upper and lower surfaces of the articular disc, and the mandibular condyle. The disc divides the joint into the superior and inferior compartments. As it can move independently of the condyle, there is a potential for disc displacement, which results in joint sounds, and in some symptomatic cases can cause pain and limited range of motion. Specifically, motion at the inferior compartment consists of rotation and manifests as moving the chin, while motion at the superior compartment consists of sliding or translation and manifests as protrusion of the mandible. Both movements are very important for maximum mouth opening and function. A unique aspect of the joint is that both right and left must work in synchrony with partial dislocation. The TMJ is among the more challenging joints to evaluate clinically, due to the absence of visible joint swelling and lack of symptomatology early during arthritis.(17)The TMJ cannot work separately. Any movement within one of the TMJs requires a movement in the other TMJ.(9)

Temporomandibular joint arthritis remains one of the most underdiagnosed and undertreated conditions in JIA, and its delayed detection may lead to severe structural and functional abnormalities of the masticatory system. It is also clear that earlier onset, long

duration, and the degree of severity of the disease are directly related to the extent of the maxillofacial abnormalities.(11)

Temporomandibular joint involvement is diagnosed on clinical examination (including a subjective and objective assessment) and on imaging techniques, including panoramic radiograph, computed tomography (CT), magnetic resonance imaging (MRI), and ultra-sonography (US). The gold standard to verify TMJ inflammation is a contrast-enhanced MRI.(2,3) Clinical examination seems to be relatively specific, but has a poor sensitivity to detect inflammation and might therefore lead to either a delay or an overdiagnosis of TMJ arthritis.(8)

Juvenile idiopathic arthritis with TMJ involvement in children and adolescents will lead to a disturbance of mandibular growth and to the alteration of craniofacial morphology.(18) TMJ involvement in JIA children is often overlooked since temporomandibular joint problems are initially not a chief complaint.(4) If unrecognized, or left untreated, a TMJ involvement can lead to articular and mandibular temporomandibular disorder, with condylar destruction that may compromised mandibular growth to pain-impaired functional disorders, such as reduced mandibular mobility and bite force as well as tenderness of the masseter and temporalis muscles and headaches.(16,19) This can also result in severe mandibular growth disturbances, resulting in an open bite, increased anterior face height, skeletal class 2 appearance, steep occlusion plane, proinclination of lower incisor, short mandibular ramus height and a distinct retrognathic mandible (bird face) and, thus, functional, and esthetic impairment.(4,20) Patients with unilateral involvement mainly have unilateral underdevelopment of the mandible and show asymmetry of the mandible and the chin toward the affected side.(21)

The main sings and symptom’s reported by patients with TMJ involvement are reduced maximal opening capacity, pain during jaw movements, tiredness of the jaws, TMJ crepitus, chewing disabilities and neck pain.(3,22) Management is important because TMJ arthritis induced orofacial symptoms. These may be disability and interfere with daily life activities and because optimal TMJ and muscular function are crucial to normal craniofacial development in children and adolescents.(23) Treatment is complex and multidisciplinary, involving pediatric rheumatologists, maxillofacial surgeons, orthodontists, radiologists, pediatric dentists, occupational and physiotherapists, and orofacial pain specialists.(24) The objectives of TMJ arthritis management are to provide timely diagnosis, reduce TMJ inflammation, relieve orofacial symptoms, optimize orofacial function, normalize dentofacial growth, and correct dentofacial deformity.(10)

Orthodontic treatment in JIA patients should be integrated on a multidisciplinary approach with pharmacological and non-pharmacological interventions. Pharmacological interventions include systemic and local medications and those are often efficient in relieving symptoms and restricting the development of degenerative changes in the joints.(13) Orthodontic treatment can have an important role and contribution to the orthopedic stabilization of the stomatognathic system, the reduction of TMJ overload and the balance of sagittal and vertical mandibular growth. Medical literature on orthodontic treatment in patients suffering from this rheumatic condition is scarce. Recent literature reviews have affirmed the importance of orthodontic treatment in growing JIA patients.(9,11,12,24,25)

Functional orthopedic oral appliance (FOA) is routinely used to treat mandibular retrognathia, together with orthodontic-induced dentoalveolar compensations. FOA can be described as a removable appliance tooth or soft tissue borne, preventing a negative influence of soft tissue on mandibular growth, stretching muscles, training a favorable mandibular position, and introducing mechanical environmental forces to possibly influence bone formation.(17,26) Orthopedic treatment with a functional oral appliance to provide growth adaptation is often the first choice and this may correct or minimize the jaw deformity.(13)The general consensus is that they are optimally used when the disease is well-controlled medically and TMJ involvement starts altering the growth.(17,26)The purpose of an orthopedic appliance is to improve or normalize mandibular growth and development: posterior vertical mandibular dimension, mandibular length, and mandibular symmetry. Orthopedic treatment will avoid the need for later surgical treatment in some patients. Initiation of orthopedic treatment early in the development of the dentofacial deformity is crucial to a successful outcome with this management modality.(10,27)

After treatment with FOA, most patients will need an orthodontic treatment to establish a functional occlusion, a final settling of the occlusion to compensate for minor dental discrepancies. This will be achieved with fixed appliance therapy. (10,26)

Orthognathic surgery should be considered if orthopedic appliance treatment is insufficient to normalize the dentofacial deformity to an acceptable level. An important factor is the local and general disease activity and the need of medication for the arthritis. For the final treatment, mandibular growth should have ended and arthritic activity in the TMJs should preferably be low in order to give stability. The treatments of orthognathic surgery may comprise distraction osteogenesis, conventional orthognathic surgery and alloplastic joint prostheses.(13)Combined orthognathic surgery and orthodontic treatment should be postponed until skeletal maturity. Decision making depends on close collaboration between the orthodontist and oral maxillofacial surgeon.(10,28)

The evidence on orthodontic treatment principles for JIA children with temporomandibular joint involvement is very low. The aim of this systematic review is to summarize the existing evidence concerning the orthodontic treatment in JIA patients. There is a significant need to find the risks and benefits of orthodontic treatment, including different treatment approaches in JIA patients.

MATERIALS AND METHODS

The present systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement to answer the following focused question: “Which orthodontic treatments are most appropriate in patients with juvenile idiopathic arthritis?”

1. FOCUSED QUESTION

Initially, a PICO specialized framework was used to define the search strategy considering:

Population: Patients with juvenile idiopathic arthritis

Interventions: Orthodontic appliances

Comparison: Compare different orthodontic treatment options to assist the treatment of juvenile idiopathic arthritis

Outcomes: The impact of functional and non-functional orthodontic treatment on the improvement of clinical symptoms / signs of patients with JIA

2. PROTOCOL AND REGISTRATION

This systematic review was registered in the Prospero database and was performed according to PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines (http:// www.prisma-statement.org).

3. INCLUSION AND EXCLUSION CRITERIA

This systematic review considered as inclusion criteria:

- Age 8-16 years
- Juvenile idiopathic arthritis with TMJ involvement
- Diagnostic of temporomandibular disorders
- Systemic therapeutic
- Orthodontic treatment
- Clinical studies (randomized and non randomized controlled trials, controlled clinical trials, cohort studies, cross-sectional studies, case control studies) of patients without restriction of gender or sample size

The following items were considered as exclusion criteria:

- Editorial letters, in vitro and animal studies, case reports, series of case reports research based on secondary data (meta- analyses, systematic reviews)
- References with non-available abstract, abstracts of conferences
- Adult patients (more than 16 years)
- Patients without DTM
- Patients without orthodontic treatment
- Patients with other autoimmune diseases

4. SEARCH STRATEGY

For the identification of studies to be included in this review, an electronic search strategy was performed for MEDLINE via PubMed, Dentistry and Oral Sources Database via EBSCOhost, Web of science and the Cochrane Central Register of Controlled Trials up to 23 May 2021. Only publications until 2010 were included.

The search strategy was modified for each database.

PubMed: 84 records

("arthritis, juvenile"[MeSH Terms] OR "arthritis"[All Fields] AND "juvenile"[All Fields]) OR "juvenile arthritis"[All Fields] OR ("juvenile"[All Fields] AND "idiopathic"[All Fields] AND ("arthritis"[All Fields]) OR "juvenile idiopathic arthritis"[All Fields]) AND ("temporomandibular joint"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields]) OR "temporomandibular joint"[All Fields]) AND("orthodontal"[All Fields] OR "orthodontic"[All Fields] OR "orthodontical"[All Fields] OR "orthodontically"[All Fields] OR "orthodontics"[MeSH Terms] OR "orthodontics"[All Fields]) AND("2010/01/01"[PDAT] : "2021/05/23"[PDAT])

Using filters of language, only publications in english, portuguese or spanish

EBSCOhost:

#1- 45 records

TI= ("arthritis, juvenile" OR "juvenile arthritis" OR "juvenile idiopathic arthritis") AND (orthodontics) AND ("temporomandibular joint" OR "temporomandibular joint disorders")

#2- 6 records

TI= “juvenile idiopathic arthritis” AND orthodontics AB

#3- 3 records

TI= “juvenile idiopathic arthritis” AND orthodontics TI

Web of science:

#1- 10 records

TS= ("juvenile idiopathic arthritis" AND "temporomandibular joint" AND orthodontics)

#2- 12 records

TS= (arthritis, juvenile AND temporomandibular joint AND orthodontics)

Cochrane:

#1- 2 records

arthritis, juvenile AND orthodontics

#2 – 1 record

juvenile idiopathic arthritis AND orthodontics

#3- 3 records

arthritis, juvenile AND temporomandibular disorder

#4- 2 records

arthritis, juvenile AND temporomandibular joint AND orthodontics

5. STUDY SELECTION

The process of selection of the studies comprised several steps. After research, the articles were exported to a reference management program. At first, the duplicate studies were removed. Then, the titles and abstracts of all identified reports were independently screened by two review authors. When studies apparently met the inclusion criteria and when the abstract was not available or was insufficient to correctly assess validity, the full texts of this articles were obtained and independently analyzed by two authors. Inclusion ambiguities were discussed and resolved by consensus between the same two authors. The studies that did not

meet the inclusion criteria were excluded. When agreement was not obtained, a third author was consulted. Finally, the studies that did not meet the inclusion criteria were excluded.

6. DATA COLECTION AND ANALYSIS

After selecting the studies, data on the following parameters were extracted:
reference to author(s) and year of publication, study design, follow up, objectives, inclusion and exclusion criteria, number of participants and gender, participant's age, type of treatment/intervention, outcomes.

Data was extracted by two authors using specially designed data extraction forms. Disagreements and technical uncertainties were resolved by discussion.

Owing to the heterogeneity of the included articles (different JIA subtypes, unclear general medication, limited evidence about dentofacial orthopedic treatment) the results could not be statistically assessed and, therefore, a meta-analysis was not attempted.

7. ASSESSMENT OF RISK OF BIAS

To assess cohort, cross-sectional and case-control studies, the Newcastle–Ottawa Scale (NOS) tool was adapted and used. Three factors were considered to score the quality of included studies: (1) selection, (2) comparability, and (3) outcome or exposure (if the study was a case control study). The quality of the studies (poor, fair or good quality) was assessed by awarding stars in each domain following the guidelines of the NOS tool. If less than five stars were selected, the article has poor quality. If it was between five to six stars, fair quality was considered. If it was more than seven stars, the article had a good quality.

RESULTS

1. STUDY SELECTION

Electronic search resulted in a total of 168 studies. After removing duplicates, 111 articles remained. The titles and abstracts were screened and 100 irrelevant studies were excluded. Eleven full texts were assessed for eligibility and 4 studies were excluded from the review. In the end, 7 articles were included. **Figure 1** describes the selection process.

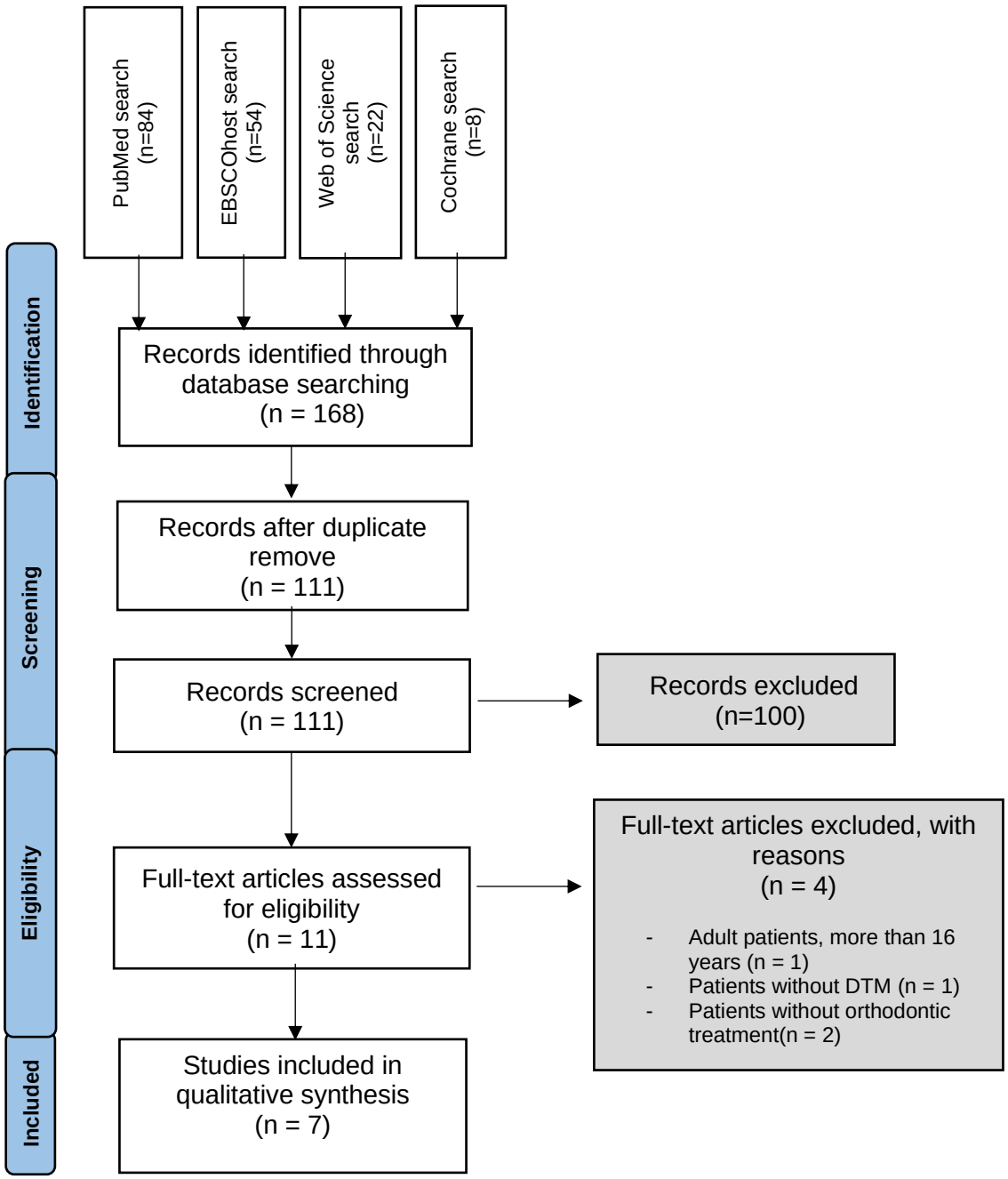

Fig. 1 - PRISMA flow diagram of systematic searching process

2. STUDY CHARACTERISTICS

The characteristics of the seven selected studies are presented in **Table 1**. (14,23,25,29–32)

Included studies were published between 2013 to 2021. Four of them were cohort studies two were prospective and two were restrospective. (14,23,29,31) Two case-control studies and one cross-sectional study. (25, 32,30) The number of participants ranged from 22 to 54. From all, only one did not mention the gender of participants. (29) Female gender was prevailing, except in one study.(14)

The types of treatment mentioned varied a lot, from hyrax palatal expander, distractions splint, functional appliance, stabilization splint and distraction osteogenesis.

Tab.1 - Description of the characteristics of the studies

AUTHOR AND YEAR	TYPE OF STUDY	NUMBER OF PARTICIPANTS	GENDER	MEAN AGE (years)	FOLLOW UP	TYPE OF TREATMENT
Abate et al.,2021 (32)	retrospective case-control	25	F- 68%, M-32%	8.6 ± 1.8	6 ± 3 months	Hyrax palatal expander
Maspero et al., 2020 (25)	retrospective case-control	25	F- 56%, M-44%	10.3 ± 1.6	6 months	Hyrax palatal expander
Stoustrup et al., 2018 (30)	cross-sectional	47	F-68.1%, M-31.9%	12.5 ± 2.6	-	Distraction splint
Isola et al., 2017 (14)	cohort retrospective	54	F-40.7%, M- 59.3%	13.2±3.7	24 months	Functional appliance
Stoustrup et al., 2014 (23)	cohort prospective	28	F- 92.9%, M- 7.1%	15.5	8 weeks	Stabilization splint
Nørholt et al., 2013 (31)	cohort prospective	23	F- 60.9%, M- 39.1%	6.4±3.9	1-6 years	orthopaedic appliances and distraction osteogenesis
Stoustrup et al., 2013 (29)	cohort retrospective	22	-	7.5	57 months	Distraction splint

3. RISK OF BIAS WITHIN STUDIES

The assessment of the risk of bias of the selected studies are presented in **Tables 2-4**.

Regarding to the case control studies, the selection of controls were patients without JIA from a dental school, so this parameter was considered 0, since they were hospital controls.(25,32)The main factor compared in both studies was the effects and safety of rapid

maxillary expansion (RME) in growing patients affected by JIA and non JIA patients. There were not any additional factors to compare. Both studies acquired good quality.

In respect of cross-sectional study the representativeness of the sample was 0 because it was a selected group, patients with JIA and at least 1 TMJ with radiologic normal or healthy osseous appearance. (30) The main factor compared with the control group was associate radiologic TMJ abnormalities with the degree of dentofacial asymmetry.

In relation to the cohort studies, all of them had 0 in the representativeness of the sample because it was a selected group (JIA patients). (14,23,29,31) Only one study, achieved good quality because it had a control group (non exposed cohort). (23) The main parameter that caused most bias between the studies was “selection”.

To sum up, four studies had good quality. (23,25,30,32) Three had fair quality.(14,29,31)

Tab. 2 - Author's assessment of risk of bias of case-control studies

STUDY	SELECTION				COMPARABILITY OF COHORTS		EXPOSURE			TOTAL (9/9)	Overall Bias
	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls	Main factor	Additional factor	Ascertainment of exposure	Ascertainment for cases and controls	Non response rate		
Abate et al.,2021 (32)	★	★	0	★	★	NA	★	★	★	7/9	Good quality
Maspero et al., 2020 (25)	★	★	0	★	★	NA	★	★	★	7/9	Good quality

Tab. 3 - Author's assessment of risk of bias of cross-sectional study

STUDY	SELECTION					COMPARABILITY OF COHORTS		OUTCOME			TOTAL (10/10)	Overall Bias
	Repre-sentati-veness of the sample	Sample size	Non-respon dents	Ascertain ment of the exposure (risk factor)		Main factor	Additio-nal factor	Assess-ment of outcome		Statisti-cal test		
Stoustrup et al., 2018 (30)	0	★	★	★	★	★	NA	★	★	★	8/10	Good quality

Tab. 4- Author's assessment of risk of bias of cohort studies

STUDY	SELECTION				COMPARABILITY OF COHORTS		OUTCOME			TOTAL (9/9)	Overall Bias
	Repre-sentati-veness of the exposed cohort	Selec-tion of non-expo-sed cohort	Ascertain ment of exposure	Outcom e of interest not present at start	Main factor	Additio nal factor	Assess-ment of outcome	Foll-ow up long enou-gh	Ade-quacy of follow up		
Isola et al., 2017 (14)	0	NA	★	★	NA	NA	★	★	★	5/9	Fair quality
Stoustrup et al., 2014 (23)	0	★	★	★	★	NA	★	★	★	7/9	Good quality
Nørholt et al., 2013 (31)	0	NA	★	★	NA	NA	★	★	★	5/9	Fair quality
Stoustrup et al., 2013 (29)	0	NA	★	★	NA	★	★	★	★	6/9	Fair quality

4. PATIENTS DEMOGRAPHIC

The results of this review presented large heterogeneity.

The studies included in this systemic review show that the most affected gender is female, except in the study of *Isola et al.(2017)*, in which the predominant gender is male and another of *Stroustrup et al.(2013)* does not refer to gender.(14,29) The age of the patients ranged from 6 to 15 years.

All articles include several types of JIA, the most prevalent is the oligoarticular, and then the polyarticular. One criteria present in all studies is that patients with JIA could only had unilateral TMJ involvement.

Regarding systemic medication, the articles of *Nørholt et al. (2013), Maspero et al.(2020)* and *Abate et al.(2021)***,** reveal that methotrexate was taken 12 months before any intervention and the article of *Nørholt et al.(2013)* suspended at the time of surgery.(25,31,32) In respect on the administration of TMJ steroid injections, only the studies of *Stoustrup et al.(2013)* and *Stoustrup et al.(2014)* reported that there was no intervention of any type. (23,29) The other 5 studies did not address TMJ steroid injections.(14,25,30-32)

5. DIAGNOSTIC

All the patients were diagnosed with JIA, according to the International League of Associations for Rheumatology criteria.

The most used diagnostic methods were CBCT and orthopantomography. Both methods allow to observe flattening, erosive changes, sclerosis, and made bilateral measurements on panoramic pictures of condylar height, ramus height, and total mandibular vertical heigh to compare the affected and the non-affected side. In addition, none of the studies make reference to the diagnosis of temporomandibular disorder, only the diagnosis of JIA with unilateral TMJ involvement.

Only in the article of *Abate et al.(2021),* MRI was also made to observe the severity of inflammation.(32)

6. CLINICAL APPROACH AND ITS EFFECTS

I. Hyrax palatal expander

Two studies evaluate sagittal and transversal effects on maxillofacial structures of a rapid maxillary expander (RME) in JIA patients with no disease activity at the TMJ for at least one year and only one TMJ was affected. They also compare the results with a control group, comprising non JIA patients with maxillary hypoplasia. (25,32)

A Hyrax-type rapid maxillary expander was bonded to the maxillary second primary molar. On the first day two activations of the hyrax screw were performed by the orthodontist, and two by the patient's parents (0.25 mm per activation). On the following days, activations were prescribed twice a day (0.50 mm) until the next follow-up appointment after 7 days when patients were re-evaluated, and the clinician would decide whether to end or continue the activations. The active treatment lasted between 15 and 21 days. After that, the screw was fixed and was kept in place for at least 6 months to allow mineralization of the midpalate sutures.

In both studies, none of the patients reported experiencing any spontaneous pain at the level of either joint during lateral excursion, protrusive excursion, unassisted maximum opening, or function during all follow-up visits.

A statistically significant augmentation in maxillary transverse dimensions (maxillary width, upper intermolar width and width of the nasal cavity) after RME was found both in JIA and in control subjects. In the study of *Abate et al.(2021)*, the average mean maxillary width increase was 3.07 mm in JIA group and of 2.94 in the control group, and the average upper intermolar width increased 6.08 mm in JIA group and of 5.67 mm in the controls.(32) The width of nasal cavity increased in average 2.92 mm in JIA group and 3.29 mm in control group.

No relevant difference was noted between cases and controls on values regarding maxillary expansion in both studies.

Concerning mandibular asymmetry, both studies reveal improvement in this parameter, since RME could also have positive effect on TMJ health of JIA patients, as the increase in condylar space and the promotion of forward repositioning of mandibular posture could reduce condylar functional stress and promote mandibular growth. Palatal expansion also releases the mandible to move forward, thus promoting the mandible to grow, helping in Class II correction.

In these studies, RME promoted the mandibular asymmetry reduction, palatal expansion, nasal breathing and nasal resistances reduction and helped Class II correction.

II. Distraction splint

The studies *of Stoustrup et al.(2013)* and *Stoustrup et al.(2018)*, used a distraction splint, which is an acrylic orthopedic functional device worn full time that covers the occlusal surfaces of the teeth in the mandible.(29,30) Its posterior height is gradually increased with 0.25 – 1 mm every 6th – 10th week in the arthritic side. This detail controls the development of the upper occlusal plane by maintaining the distance between the upper and the lower jaw and thereby creating space for normalized vertical dentoalveolar development, which leads to an increased posterior face height development in the affected side, with the reduced vertical dimension.

The study of *Stoustrup et al.(2013)* aimed to evaluate the effect of distraction splint treatment used to reduce asymmetry of mandibular growth between the affected and the non-affected side in terms of condylar height, ramus height, and total vertical mandibular height.(29) The result in this study was that a significant mandibular asymmetry was seen in all three variables examined when compared to a hypothetical symmetrical group. However, among the 22 JIA patients referred in this study, three were directed to surgical correction due to insufficient response to the functional treatment.

The study of *Stoustrup et al.(2018)* associated radiologic TMJ abnormalities with the degree of dentofacial asymmetry in patients with unilateral TMJ involvement and compared these features with a control group, non JIA patients without diagnosis of temporomandibular dysfunction.(30) The radiologic evaluation was carried out on the joint level, giving each subject 1 score for the affected joint. Three definitions of condylar scores were determined based on categorization of the condylar radiologic appearance:

- First: normal shape with smooth and intact outline and surface (score 0);

- Second- deformed: marked flattening or other changes in shape with smooth and intact outline and surface (score A);

- Third- erosive: disruption of outline or uneven surface due to cysts or erosion (score B).

Forty-seven JIA patients were grouped into 3 subgroups based on the radiologic findings: JIA 0-0 (n=17), JIA 0-A (n=20), and JIA 0-B (n=10). Forty-one of the forty-seven JIA patients were currently being treated or had previously been treated with a functional orthopedic appliance. In this study, the JIA patients with unilateral TMJ abnormalities exhibited significantly more severe dentofacial asymmetries than did the JIA patients without TMJ abnormalities and the control subjects. Mandibular dysmorphic development was affected to the same extent in patients with either unilateral condylar deformations (score A) or unilateral erosions (score B).The study demonstrated that the site of the asymmetry is related to a short

condyle on the affected side, since significant differences were found for mandibular posterior height in the JIA 0-A and JIA 0-B groups when compared with the control and JIA 0-0 groups; however, there were no significant differences for ramus height, indicating that a shorter condyle was responsible for the decreased posterior face height in the patient group. No further morphologic differences were found. The reason for a lack of other deformities, could be explained through an orthopedic treatment that forty-one patients had received after a diagnosis of TMJ arthritis. The included JIA patients represented a group of well-treated patients with an orthopedic distraction splint. In five of the remaining six patients, an orthopedic distraction splint was fabricated immediately after the CBCT scan, and functional treatment began.

III. Stabilization splint

The study of *Stoustrup et al.(2014)* did not used an orthodontic therapy but used a stabilization splint to evaluated changes in sensory-discriminative components of self-reported orofacial symptoms (pain frequency, intensity, and localization, and main complaints).(23)

The stabilization splint was fabricated and positioned in the mandibular dentition. Patients were instructed to use the splint during sleeping hours, at a minimum; further use was recommended in some patients based on individual clinical assessment. Splint treatment was planned to continue until noticeable reduction or resolution of the orofacial pain was seen.

Before initiating the splint treatment, the included patients reported the following values for pain: a pain frequency mean score of 3.1 (median score 3 equivalent to pain 4–6 times a week), a VAS (average pain intensity- the patients were asked to assess the average pain intensity on a non-verbal VAS of 100 mm, where the left extreme represents ‘no pain’ and the right extreme represents the ‘worst imaginable pain) pain mean intensity of 55.2mm. Eight weeks after splint therapy, all of these variables were statistically significantly reduced to a pain frequency score of 2.5 (median score 2 equivalent to pain 1–3 times a week) and a VAS pain intensity of 40.5 mm.

To sum up, a significant symptomatic relief was reported in terms of reduced orofacial pain frequency and intensity without substantially changing the pain locations or the nature of the self-reported complaints. However, total resolution of orofacial pain was rare.

IV. Activator

The study of *Isola et al.(2017)*, evaluated the clinical effectiveness of functional therapy used to reduce asymmetry of mandibular growth and TMJ disorder in patients with JIA.(14)

All the appliances were individually customized and manufactured with acrylic resin and resilient stainless steel, with posterior and anterior metallic bite planes preventing the teeth

from intercuspal contact. The participants were instructed to use the appliance 12-14 hours per day. Initial checks were performed after 6 weeks, with the final follow-up at 24 months.

The use of a functional appliance, before (T0) and after (T1) active therapy of the JIA patients, determined a statistically significant difference of the following variables: pain during jaw movement (T0, 55.9±1.9%; T1, 21.6±2.4%); maximal mouth opening (T0, 34.45±2.3mm; T1, 45.32±3.2mm); TMJ sounds (T0, 44.8±3.4%; T1, 15.9±2.5%); TMJ click (T0, 25.2±2.7%; T1, 16.3%±5.3%), and TMJ crepitations (T0, 26.4±2.9%; T1, 18.2±3.5%). Condilar width, transverse and distal displacement increased significantly too during treatment in the study group.

V. Orthopedic appliance and distractions osteogenesis

The study of *Nørholt et al.(2013), combined* orthodontic and surgical treatment approaches.(31)

Twenty patients with JIA were treated with orthopedic appliances. If their growth restriction produced marked asymmetry, they were referred for orthognathic surgery planning. Three patients were fully grown at the time surgery was decided.

The criterion for proceeding with the corrective surgery was a TMJ with clinical and subjective good function. If there was any active disease of the TMJ at this evaluation distraction osteogenesis (DO) was precluded.

The distraction device was applied on the lateral surface of the ramus and fixed with one cortical screw activate the distraction device. The distraction rate was 0.8 or 1.2 mm per day. The device was removed under general anesthesia and any other corrective surgery was performed if indicated. The patients continued further orthopedic or orthodontic treatment as required to normalize their occlusion.

The results of the DO were reduced asymmetry of the vertical ramus when measured immediately after operation and until the last follow-up, the occlusal plane was corrected and improved during the post-surgical treatment and the chin shifted significantly to the midline. No swelling of the TMJ was observed at any time. TMJ pain when palpated, click and crepitation were rare and significant changes were not seen. Translation of the condylar head in the affected side was decreased in one- third of the patients. A small and insignificant variation in muscular tenderness (masseter and temporal muscle) on palpation was observed. Malocclusion clearly became less prominent. The horizontal overjet decreased significantly. The open-bite tendency was aggravated after distraction but returned significantly to normal in the post-distraction phase.

DISCUSSION

The aim of this systematic review is to summarize the existing evidence concerning the orthodontic treatment in JIA patients and compare the different options that are available.

Throughout this review, it was possible to notice that there are different options to approach an improvement of symptoms / clinical signs of patients with JIA and with involvement of the TMJ. However, there is still a lot of disinformation, since it is difficult to produce studies with a high level of evidence because of the heterogeneity of the subject material (different JIA subtypes, unclear general medication, different diagnostic methods, TMD diagnostic classification system not used).

Intervention in patients with JIA and including TMJ specifically aims to maintain optimal joint function and reduce orofacial symptoms, avoid permanent damage to the cartilaginous and osseous components of the TMJ and reduce unfavorable mandibular and craniofacial growth alterations. (33) Management is important because TMJ arthritis induced orofacial symptoms that may be disabling and interfere with daily life activities and an optimal TMJ and muscular function are crucial to a normal craniofacial development in children and adolescents. (26)

Almost all the studies have reinforced the importance that the best chance of reaching an optimal treatment is to detect any involvement of the TMJs as early as possible and to initiate the necessary treatment. So particular attention should be paid to the diagnosis and correct treatment planning. Observation by multidisciplinary teams, consisting of orthodontists, maxillofacial surgeons, rheumatologists, radiologists, and pediatricians, is required for the comprehensive clinical management of these patients. (3,6) In most of the papers included in this review, the female gender is the most affected. Therefore, we must pay attention to the growth peak of this gender, which is generally earlier than in male gender, and we must act at the appropriate time.

Regarding systemic medication, non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen or ibuprofen are the most used drugs in children with JIA. Generally, they are well tolerated and have few side effects. NSAIDs were used as maintenance medication and were not beneficial for reducing TMJ complaints, so more aggressive interventions were necessary. (2,5) Intra-articular corticosteroid injections (IACIs) are used in the TMJ, to reduce the inflammation and pain, and to improve jaw mobility. (2) Negative effects on mandibular growth following the use of IACIs have been reported; however, this issue is a consequence since the disease itself can also cause mandibular growth disturbances.(34) This is problematic especially because repeated injections may be necessary. For the patient and family, the mandibular growth controversy may be secondary as the patient may wish to rapidly eliminate

pain and be able to return to a normal with a normal mouth opening and without the avoidance of hard foods. The advantage of using IACIs in children with TMJ involvement in JIA is questionable because possible risks may outweigh the benefits and, as such, protocols vary across centers. (5) The current level of evidence on the effect of intra-articular steroid injection treatment is very limited and the knowledge of the long- term impact on growth is still not available. (2,27) Another medication used in the included studies was Methotrexate (MTX). MTX is a disease-modifying anti-rheumatic drug (DMARD). It has been found to be effective in minimizing TMJ destruction and infections, and craniofacial dysmorphology in patients with JIA. (2,17) In the included papers of this review, only four articles reveal that methotrexate was taken and only two studies reported that there were not TMJ steroid injections. As there are papers that do not refer to medication, we do not know if some improvements like pain reduction or greater mouth opening it is due to the use of systemic medication, orthodontic appliances, or both.

Management of dentofacial deformities in JIA patients involves several options. First, interceptive treatment, growth-adaptive initiatives in skeletally immature subjects with a dentofacial deformity, using nonsurgical orthopedic appliance treatment. However, a combination of orthopedic appliance and distraction osteogenesis (DO) can be considered in severe cases. If functional treatment does not work, it is necessary corrective surgical interventions in skeletally mature patients for an existing advanced dentofacial deformity or a TMJ replacement.

Functional or orthopedic appliance is routinely used to treat mandibular retrognathia, together with orthodontic-induced dentoalveolar compensations.(26) Two types of functional oral orthopedic appliance are available: active treatment like activator and distraction splints and stabilization splints. The general consensus is that they are optimally used when the JIA is well-controlled medically.(35)

Occlusal stabilization splints are used to help support and balance both TMJs and to prevent further pain and discomfort to the TMJ complex. They can be used in growing as well as in skeletally mature patients. They allow the patient to have even contacts when the teeth occlude in all ranges of motion including biting and side to side jaw movements, which can result in decreased pain.(17) Stabilization splint has a palliative (not curative) effect on the orofacial symptoms. This appliance is not a treatment against TMJ inflammation but a way to relieve the orofacial pain issues that are seen in some patients with JIA and TMJ arthritis by reducing the overload in the TMJ. Stabilization splint intervention is reversible, conservative, safe, familiar and low cost. The stabilization splint has been important in the management of temporomandibular disorder and orofacial symptoms for decades, even though its mode of

action while positioned on the teeth in the upper or lower jaw remains incompletely understood. Suggested mechanisms include repositioning of the condylar head in the TMJ, preventing high pressure on the joint surfaces, transient decrease in masticatory muscle activity, reduced bruxism, balanced occlusion, awareness of the cognitive-behavioral aspect of orofacial pain, and a placebo effect.(23) Stabilization splint therapy may reduce the intensity and frequency of TMJ arthritis-related symptoms and improve mandibular function.

In contrast, active treatment splints are only used in the growing phases of a child, typically ages 8–16 years of age, and are intended to add incremental height to the splint platform on the affected side of the arthritic joint, thus potentially reducing asymmetry and need for surgical correction of skeletal deformity. They can also result in more even distribution of muscular forces within the jaw.(17)

The distraction splint effects a slight, gradual change in the mandibular position, guiding the mandible to a symmetric position, promotes anterior mandibular advancement, enables control of tooth eruption and relative intrusion of teeth in specific regions, and limits unwanted dentoalveolar compensation. This is achieved by a continuous, gradual increase in the posterior height of the splint in the affected side, aiming a change in the inclination of the occlusal plane and preventing posterior bite collapse.(10,29) The treatment with a distraction splint is therefore not focused on sagittal advancement of the mandible, but rather on the reestablishment of the vertical support. The splint allows the clinicians to guide eruption of the molars and is replaced approximately every second year due to the eruption of new teeth and general wear of the splint and it can be placed in the upper as well as in the lower. The splint placement is decided based on convenience in relation to changes in the dentition and is continued until an acceptable mandibular skeletal symmetry is achieved. Also, the distraction splint may have a protective effect against overloading of the involved TMJ in periods with acute arthritis, thereby relieving symptoms and reducing joint contraction and stiffness. The activator promotes anterior mandibular advancement to correct the sagittal intermaxillary discrepancy and enables control of tooth eruption. Patient compliance is an issue to this modality because of the considerable size of the appliance.(10)

Another orthodontic appliance used in the included studies was Hyrax-type rapid maxillary. This RME is a fast option for solving premature contacts and cross-bite within 15 to 21 days. Even though it is perceived as more traumatic because of its rapidity of action, RME has been proven not to cause any damage to TMJs.(17) Positive effects of RME include repositioning of the mandible forward and an increase in condylar space, thus improving skeletal class II and reducing condylar functional stresses. The positive effects are allegedly partly due to mandible repositioning after premature contact removal and partly due to skeletal

growth at the level of the condyle that will continue during the residual growth period following the restoration of a correct occlusion. (10,17,32) Palatal expansion releases the mandible to move forward, thus promoting the mandible to grow, which reduces mandibular asymmetry, helping in Class II correction, that are the common maxillofacial problems of JIA patients.

In what concerns to orthognathic surgery, it should be performed if functional orthopedic treatment is insufficient to regularize the dentofacial deformity and it is indicated in skeletally mature patients. Before initiation the surgical treatment, specific information is necessary regarding general disease activity and TMJ stability, progressing deformity of the facial skeleton over the past 12 months, age and skeletal maturity of the patient, and the severity of the skeletal deformity. The activity of the arthritis is assessed in collaboration with a pediatric rheumatologist; and in case of surgical treatment, any adjustments in medication are planned.(10) Surgical treatment strategies have included costochondral graft reconstruction, total TMJ prosthesis, conventional orthognathic surgery and distraction osteogenesis (DO). DO is indicated in growing or skeletally mature patients with moderate to severe deformity and quiescent TMJ arthritis. The aim is to compensate for the lack of posterior vertical growth through a partial osteotomy that is performed in the cortex of the ramus, and slow mechanical forces are created daily increasing the desired length. New bone is slowly generated similar to growth.(10,13) Although, DO requires careful vector planning and patient collaboration during device activation a second operation is required to remove the distraction device.(28) Orthognathic surgery is a common procedure to reconstruct the dentoskeletal deformity with precise masticatory function, and TMJ articulation, usually performed in young adults. This may involve a bilateral sagittal osteotomy of the ramus and/or a Lefort 1 of the maxilla for alignment of the masticatory system with proper plane of occlusion to the TMJ.(17) However orthognathic surgery in JIA patients is known to have tendency for relapse. The relapse is mainly due to two factors; firstly, extensive surgical movements of the bone segments in patients with micrognathia might challenge the soft tissue limits; secondly, instability of the TMJ. Although only a small group of JIA patients will need orthognathic surgical correction, it is recommendable to elaborate individual treatment plans taking into account the disease activity, joint stability, risk of relapse and burden of treatment.(13)

Despite being one of the most consensual approaches to TMD at the moment, none of the papers included in this systematic review addresses functional therapy through physiotherapy. However, it is an option that should be considered by the demonstrated capacities to minimize symptoms and effectiveness in controlling the consequences on the TMJ and joints in general, as a more conservative and functional option.

Strengths and limitations

The greatest strength of this systematic review is a correct methodology, involving two reviewers in searching/evaluation process.

Since the study designs are so different, there is a greater heterogeneity that might be expected. There are few studies that address orthodontic treatment in patients with JIA and involving TMJ, and in these studies the sample is small and there is scarce information about medication, method of diagnosis and specific TMD diagnostic.

Implications for clinical practice

Since TMJ arthritis remains one of the most underdiagnosed and undertreated conditions in JIA, and its delayed detection may lead to severe structural and functional abnormalities of the masticatory system, it is important that dentists, pediatricians and parents are aware about the main signs and symptoms for a proper diagnosis. The clinicians must recognize the main orthodontic treatments and when to intervene to improve stabilization of the stomatognathic system, the reduction of TMJ overload and the balance of sagittal and vertical mandibular growth.

In addition, it is important to create guidelines to standardize the treatment of JIA patients.

Implications for future research

The design of the few existing studies and the diversity of JIA subtype make necessary further studies to increase the quality of scientific evidence. It is essential to know the long-term effects of the IACI on the mandibular growth, consolidate the etiology of JIA and implications when TMJ was enrolled.

Furthermore, there is not any adaptation to the treatment depending on the patient's condition when there is an adequate diagnosis. In other words, the techniques used are the same as if it were a non JIA patient. The implications of this type of approach are not known and studies do not help to define treatment guidelines. For the future, we need more and better study designs.

CONCLUSION

This systematic review highlights the inherent limitations of data about the orthodontic treatment in patients with juvenile idiopathic arthritis, which should be enhance in future studies. Evidence for effect and efficacy for such treatments are still inconclusive.

There is limited evidence that dentofacial orthopedic treatment using functional appliances can improve mandibular retrognathia and reduce pain in adolescent patients with JIA. Although, orthopedic treatment can prevent an approach that is much more complex and with greater morbidity than orthodontic and surgical treatment in adulthood. However, there is still no concordance about interceptive treatment effectiveness due to the rheumatic condition and differences between patients. On the other hand, the self-awareness of the condition brings a better compliance to the treatment.

The management of TMD pain and functional limitations that are related with degenerative processes are important for activities of daily living such as mastication, speech, and oral hygiene. Improvements in mouth opening and micrognathia are critical for airway management. 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.

Considering that most of the patients take systemic medication, it should be combined with orofacial pain management strategies such as functional orthopedic appliances, physiotherapy, and general information on pain-avoidance strategies. Additionally, it is important a multidisciplinary approach, involving pediatric rheumatologists, maxillofacial surgeons, orthodontists, radiologists, pediatric dentists, occupational and physiotherapists, and orofacial pain specialists in order to give the best possible diagnosis and treatment to the patient.

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ACRONYMS

JIA- Juvenile idiopathic arthritis

ILAR- The International League of Associations of Rheumatology

HLA- Human Leukocyte Antigen

TMJ- temporomandibular joint

CT- computed tomography

MRI- magnetic resonance imaging

US- ultra- sonography

FOA- Functional/orthopedic appliance

RME- rapid maxillary expander

DO- distraction osteogenesis

CBCT- cone beam computer tomography

IACIs- Intra-articular corticosteroid injections

MTX- Methotrexate

DMARD- Disease-modifying anti-rheumatic drug

NSAIDs- non-steroidal anti-inflammatory drugs