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Temporomandibular Joint- The neglected joint of children with Juvenile Idiopathic Arthritis

Maria Bousnaki[1], Petros Koidis[2]

[1] *DDS, MS, PhD candidate, Department of Fixed Prosthesis & Implant Prosthodontics, Faculty of Dentistry, School of Health Sciences, Aristotle University of Thessaloniki, University Campus, Dentistry Building, Thessaloniki, GR-54124, Greece*

[2] *DDS, MS, PhD, Professor and Chairman, Department of Fixed Prosthesis & Implant Prosthodontics, Faculty of Dentistry, School of Health Sciences, Aristotle University of Thessaloniki, University Campus, Dentistry Building, Thessaloniki, GR-54124, Greece*

Abstract:
Background: *Juvenile Idiopathic Arthritis-JIA is the most common inflammatory rheumatic disease during childhood, and affects Temporomandibular Joint-TMJ among other joints. TMJ arthritis can proceed without clinical signs and symptoms and remain undiagnosed, with detrimental effects on child's normal craniofacial growth and mandibular development.*
Aim: *This review summarizes the current developments and contemporary literature on TMJ arthritis in patients with JIA and aims to provide the highest level of evidence on the subject.*
Design: *MEDLINE and Web of Science databases were searched using related keywords. From the selected abstracts, non-English and in vivo studies were excluded, while from the rest full-text was obtained for further analysis.*
Results: *The most common clinical finding in children with TMJ involvement is limited mouth opening, while deviation during opening and pain during chewing are also present. Furthermore, an analysis of the pathogenesis of JIA, the imaging techniques, the pattern of craniofacial development, as well as the treatment management is presented, along with a screening protocol for the assessment of TMJ for an early diagnosis.*
Conclusion: *It is of utmost importance for the attending paediatrician and paediatric dentist to monitor TMJ function periodically, due to its impact in craniofacial development.*
Keywords: *examination protocol, Juvenile Idiopathic Arthritis, MRI, orofacial structures, Temporomandibular Joint.*

I. INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is a chronic inflammatory disease, which affects children under the age of 16, that present with sings of inflammation to one or more joints for more than six weeks [1]. JIA is the most common rheumatic disease in children in the Western world, as it affects one child per 1,000, with the frequency and prevalence varying depending on ethnicity and geographic location [2]. Several names have been given to this entity in the past, such as Juvenile Chronic Arthritis and Juvenile Rheumatoid Arthritis, and different classifications have been made, with the most recent being the one made by the International League of Associations for Rheumatology-ILAR in 2004 in Edmonton [1]. The latest classification includes clinical and laboratory criteria within the first six months based on which diagnosis of the disease is made. The main objective of the revision of JIA criteria was to determine relatively homogeneous subcategories, for predictive and research purposes, and to differentiate JIA from adult Rheumatoid Arthritis (RA), which is a different disease entity [3]. JIA can be in remission in many patients after adulthood, but usually presents with flares of deteriorating clinical signs and symptoms [4]. This classification consists of seven subtypes, based on the number of joints involved, the presence of serum markers, the presence of systemic symptoms, and constitutes an "umbrella", which leads to the diagnosis by exclusion, as cases of arthritis due to infection should be excluded from the diagnosis [1]. Every subtype presents with different clinical presentation, has different progress and prognosis [5].

II. TEMPOROMANDIBULAR JOINT INVOLVEMENT

The JIA affects many joints in the human body, including the Temporomandibular Joint (TMJ). In the first paper in which JIA is described, Still mentions that three out of 21 cases present TMJ involvement [6]. Despite the fact that TMJ involvement is quite common, with rates reaching up to 87%, the diagnosis of JIA-TMJ arthritis is usually missed from the attending pediatrician or rheumatologist, as it does not present with the classical signs of inflammation, such as edema and pain [7-8]. This leads to a late diagnosis, after the establishment of deformation in the orofacial structures, thus being referred to in the literature as the "forgotten"

joint [9]. The reported prevalence of JIA-TMJ arthritis vary dramatically among the different studies, as there is no scientifically proven and widely accepted protocol for the assessment of TMJ that would lead to a valid diagnosis [10-13]. When clinical examination is followed by an orthopantomograph (OPG), the prevalence of JIA-TMJ arthritis ranges from 50% to 72 %, while with the use of Magnetic Resonance Imaging (MRI) there is an increase in reported prevalence that could reach up to 91% [8,11-12]. Despite the differences among different studies, such us ethnicity, imaging technique and assessment protocol, the prevalence of JIA-TMJ arthritis is considered to be over 40%. Unilateral TMJ involvement at initial examination, when conventional imaging techniques are used, is at 40%, while the use of MRI lowers this number, with an increase of bilateral TMJ involvement [11, 14]. In addition, unilateral TMJ involvement decreases with the progression of the disease; from 40% at initial examination it can reach 18% in adulthood, with increase in bilateral involvement [13]. TMJ involvement can present in all JIA subtypes, with higher prevalence in extended Oligoarthritis compared to Polyarthritis [15]. In some cases, TMJ could be the only joint affected by the disease [16].

III. DIAGNOSIS OF TMJ INVOLVEMENT

Temporomandibular disorders (TMDs) are conditions that affect the TMJ, its structures and masticatory muscles and impair normal function of the Stomatognathic System-SGS. Several attempts have been made to create scientifically sound and reliable questionnaires and protocols for both the examination and diagnosis of the TMDs in adults. The index created by Helkimo had wide acceptance, but it made a quantitative assessment primarily of symptom' severity that could not lead to a differential diagnosis [17]. Later, the Research Diagnostic Criteria for Temporomandibular Disorders- RDC/TMD were introduced by Dworkin et al. [18-19]. In 2014, those criteria were revised and redefined leading to the Diagnostic Criteria-DC/TMD, which consists of a questionnaire and clinical examination for the functional and psychosocial status of the patient [20]. The use of those criteria leads to a diagnosis, and has been shown to have high sensitivity and specificity [20]. Nevertheless, so far there is no specific, scientifically documented and widely accepted examination protocol or index for the assessment of TMJ and orofacial structures in children that could be used for the diagnosis of JIA-TMJ arthritis.

3.1. Clinical Signs and Symptoms from Orofacial Structures

TMJ involvement in children with JIA can present with a great variety of signs and symptoms, from a sense of fatigue and pain during function to reduced mouth opening and mandibular deviation upon mouth opening [21-25]. Table 1 presents the majority of the signs and symptoms found in the literature. The appearance of signs and symptoms from the TMJ seems to correlate with severity and activity of the general disease [26]. Restriction in mandibular movement during function and pain in the TMJ are the symptoms that occur most frequently in children with TMJ involvement compared to healthy subjects [21, 27]. The pain occurs mainly in the masseter region, and is intensified during daily function of the SGS [21, 28]. Other symptoms that appear quite often are pain during chewing, pain at the maximum mouth opening and a feeling of morning stiffness [28]. Nevertheless, the specificity of JIA-TMJ arthritis is that it can evolve in most patients despite the absence of clinical signs and symptoms. In the study of Twilt et al., only 12% of patients had pain in the region of TMJ, Billiau et al. found presence of sensitivity in the muscles or joint in 22% of patients, while in another study by Argyropoulos et al. it was found that only 5-8% of patients had pain or difficulty in chewing [10,29-30].

Table 1. Signs and Symptoms related to TMJ Arthritis

Symptoms	***Signs***
Pain/stiffness during mastication	Reduced mouth opening capacity
Pain during functional movements	Mandibular deviation during maximal opening
Morning stiffness in the TMJ	Reduced mandibular translation
Sense of fatigue in the TMJ	Reduced protrusion/laterotrusion
Headache	Deviation during protrusion
Neck pain	TMJ crepitation
	Pain or tenderness during TMJ palpation
	Pain or tenderness during palpation of masticatory muscles
	Reduced bite force

The most common clinical finding in children with TMJ involvement is limited mouth opening [10, 12, 15]. It is also an early finding, as patients with arthritis but without structural damage in the TMJ present with significant limitation in mouth opening [12]. In JIA patients, limited mouth opening and deviation during opening are the two clinical sings most frequently seen to be related with TMJ involvement [10, 12, 23, 25]. Maximum mouth opening is used in studies related to the TMJ, both to assist in the diagnosis and as a reference point for the evaluation of a therapeutic intervention [31]. However, it appears to have little predictive value

when a specific cut-off value (<40 mm) is used, which is considered to determine the limit that separates physiology from pathology [32]. This can be attributed to several factors, such as the limited repeatability of measurements in the studies or the fact that there limited studies in children that result in a range of values, depending on age, on functional mandibular movements in the absence of disease, in order to have certain cut-off values as in adults [33-36]. In one study with a very large sample, it appeared that there is a mouth-opening capacity had a very wide range of values among children of the same age, which reaches up to 18 mm between the 10th and the 90th percentiles [37]. Thus, researchers concluded that the use of a cut-off value has little predictive value, and continuous monitoring of the range of mandibular motion is necessary to allow comparative assessment and early diagnosis [12, 37].

3.2. TMJ Imaging

Taking into consideration that TMJ involvement might not present clinical signs and symptoms, and pass unnoticed from the attending pediatrician, it is necessary to be accompanied by an imaging method so that can be properly diagnosed [8,11-12]. In the past, OPG was the method of choice, while other methods used are transcranial radiography, computed tomography (CT), cone beam CT, and ultrasonography [13, 21, 38-40]. Studies that used x-ray imaging techniques, like OPG, had findings from the bony components of the joint. The most common radiographic findings were erosion, flattening or total destruction of the condylar head [9, 21, 39, 41]. Twilt et al. documented the appearance of new condylar lesions at a rate 7,1% per year [42]. Other findings from x-rays are flattening of the articular eminence, enlargement of the glenoid fossa, deviation from normal S-shape of the glenoid fossa and the articular eminence, which are sometimes followed by sclerotic lesions [39, 41]. However, in many cases, despite the destruction observed in the morphology of the condylar head, the outer contour of the cortical bone seems intact, which may result from the healing and remodeling processes that follow destruction [41].

Nowadays, MRI is referred to as the "gold standard" in the literature, mainly because it can depict joint inflammation and lead to an early diagnosis, prior to the establishment of structural damages in the osseous articular surfaces [11-12, 25]. MRI enables the imaging of all the articular parts, as well as the presence of inflammation [43]. The manifestations of inflammatory activity that appear in MRI in patients with TMJ involvement are synovial contrast enhancement, joint effusion and bone marrow edema [11, 15, 44]. Most studies, nowadays, use contrast-enhanced MRI for the diagnosis of early TMJ involvement, because if its' ability to depict joint inflammation. MRI findings usually appear before the establishment of clinical signs and symptoms, and in studies where MRI has been used as a diagnostic tool the prevalence of JIA-TMJ arthritis was higher compared to studies where only clinical examination was performed [11-12, 15, 25]. Furthermore, it remains the only non-invasive method that can diagnose the presence or absence of active inflammation, while it is also used as a reference for the assessment of reliability of other diagnostic methods, such as ultrasonography [12]. Nevertheless, von Kalle et al. in their study questioned the reliability of contrast-enhanced MRI to diagnose active inflammation, as they found that contrast enhancement is a physiological finding observed in the soft tissues and the condyle of children without TMJ arthritis [45]. MRI with contrast enhancement is considered the most reliable method for the assessment of early signs of inflammation [46]. However, there is no common agreement on the degree of contrast enhancement of normal TMJ in growing children when compared to inflamed TMJ. Von Kalle et al. (2013) concluded that contrast enhancement is a normal finding for the joint tissues on children and in adolescents, and subtraction analysis of pre- and post-contrast images can enable the assessment and evaluation of the joint and the presence or absence of pathology [45]. In a more recent study, it was pointed out that contrast enhancement alone does not allow for a clear differentiation between healthy and inflamed joint, and a further extension or thickening of the joint tissue seems to be the earliest sign of inflammation seen on the MRI [47]. Last but not least, Tzaribachev et al. concluded that MRI imaging characteristics of children without TMJ pathology do not overlap with findings from children with JIA-TMJ arthritis, despite the fact that they might exhibit mild enhancement or small joint effusion, which is indicative of normal TMJ during growth [48]. Disadvantages of MRI is the long duration of the examination in which children can be difficult to stand still, and might necessitate sedation, the high cost, as well as the fact that an MRI machine may not be accessible by everyone [49].

Ultrasonography (US) has been successfully used as a screening tool for the assessment and follow-up of children with JIA and TMJ involvement, bearing many advantages over the other imaging methods, as it is radiation-free and simple-to-use [50]. It is also easily accessible and relatively cheap. Nevertheless, the reported sensitivity in detecting active inflammation varies widely, showing that it is operator dependent [11, 50]. Additionally, when compared to the gold standard, which is MRI, US sensitivity in the early detection of TMJ inflammation was low [11-12]. Another disadvantage is that it has limited access to the medial part of the joint [12].

IV. EXAMINATION OF OROFACIAL STRUCTURES

4.1. Patient History

Patient medical history should precede clinical examination, along with the record of details and information on the state of the general disease (JIA). Patient's history should include questions related to the history of pain in the orofacial area and any difficulties and problems encounter by the child in the its daily routine. JIA-TMJ arthritis can interfere with normal function of the orofacial structures, which may affect the quality of life of a child [21, 26]. So there should be appropriate tools to assess both the disease activity, and quality of life of the patient and his family associated with the disease, as exist for evaluating the overall disease. Such tools are JADAS (Juvenile Arthritis Disease Activity Score), which assess disease activity, and CHAQ (Childhood Health Assessment Questionnaire), which is a questionnaire that evaluates the quality of life of the child [51]. JADAS is a valid instrument for the assessment of JIA disease activity which is based on information from four measurements: two measurements from the pediatrician, active joint count and physician global assessment, one from parent/patient (global assessment of the disease) and one that measures inflammation in acute phase (Erythrocyte Sedimentation Rate-ESR) [52]. CHAQ, on the other hand, is an instrument that evaluates a child's capability to perform activities in their daily environment, by assessment of child's health status and physical function [53].

4.2. Clinical Examination

Clinical examination of SGS should include the assessment and record of:

a. Patient symptoms.
b. Clinical signs.
c. Morphology of craniofacial structures and growth pattern.

More specifically, the clinical examination should initiate with the assessment of the presence of pain during the function, the location of the pain and the intensity and frequency of this. It should be followed by palpation of the TMJ, the masticatory muscles intraorally and extraorally, and the neck muscles. Finally, there should be examination of the range of mandibular movement during functional excursions, such as maximum opening, protrusion, lateral movements, as well as detection for deviation of the mandible during opening [33]. Unfortunately, there is still no specific questionnaire for the evaluation of children with JIA, neither any standardized guidelines for the clinical examination of these patients.

Steenks and his team attempted to create a screening protocol for the assessment and diagnosis of TMJ involvement in children with JIA [54]. This protocol was based on patient history and clinical signs and symptoms, without the use of an imaging technique, so its sensitivity in diagnosis is under dispute [54]. Nevertheless, if it is used at regular intervals by the attending pediatrician it can detect changes in the range of mandibular movement that would lead to further investigation for the diagnosis of TMJ involvement [54].

V. ETIOLOGY AND PATHOGENESIS OF JIA

JIA is an autoimmune inflammatory disease of unknown origin, however, it is considered to be multifactorial, with genetic and environmental factors to play an important role. In studies on JIA genetics in families, in monozygotic twins there was found a concordance rate of 25% for JIA, while siblings of those affected by JIA had a much higher prevalence of JIA (15- to 30- fold increase) [55-56]. From the genes that have been studied, HLA Class I and II alleles have been found to be related with the pathogenesis of several JIA subtypes, with Class II anti-gens HLA-DRB1*11 (a subtype of HLA-DR5) and HLA-DRB1n08 found to have a strong association with oligoarthricular JIA, while there are also many non-HLA genes that have been implicated [57]. The fact that genetic background does not seem to be 100% responsible for the etiology and pathogenesis of JIA, there are many environmental factors that have been implicated. Several microorganisms, viruses and bacteria (such as mycoplasma, enteric organisms, rubella virus, Parvovirus B19) have been investigated whether they can trigger an immune response in genetically susceptible individuals [58]. However, there is little or no scientific evidence to support those hypotheses. Many mechanisms have been proposed in an attempt to explain the overstimulation of the immune system from external factors. Some of these mechanisms are persistent antigenic stimulation, molecular mimicry, and the hygiene hypothesis; however none of these mechanisms have been proven [58]. In the early stages of inflammation in the TMJ, there is an increase in vascularity and infiltration of inflammatory cells, which is followed by hyperplasia and hypertrophy of the synovial lining [59]. From dysregulation in the immunoregulation and the inflammatory reaction, there is an increase of the immune complexes, activation of the Major Histocompatibilty Complex, and dysregulation in the balance between TH1 and TH2 cells, with TH1 cells predominance in the synovial tissue [59]. Inflammation of the synovial tissue and pannus creation results in erosive lesions and destruction of articular cartilage, which is extended to the osseous surfaces [59]. The pathophysiological mechanism of the development of TMJ arthritis is not quite clear, but from some a recent study it appears to result from deregulation of local inflammatory cytokines [60].

VI. CRANIOFACIAL DEVELOPMENT IN CHILDREN WITH JIA

During normal craniofacial development, there is a coordinated growth of the maxilla and the mandible, where they are both displaced in a forward and downward direction relative to the cranial base [61]. Two models that describe mandibular growth have been proposed, one with a forward direction (counter clockwise), and another with posterior direction (clockwise) [61]. Facial growth continues up to the 20th year of age, but after the 10th year the greatest amount of growth takes place in the vertical dimension, with an increase in the length of the ramus of the mandible, with compensatory eruption of maxillary teeth and growth of dento-alveolar bone [62]. In children with JIA and TMJ involvement, mandibular growth is disturbed due to the presence of inflammation in the joint. TMJ is unique, compared to the other joints, as the growth center of the condyle is positioned in the articular cartilage, located below the outer surface of the articular condyle, and is the part where endochondral ossification occurs, in contrast to other joints where the growth center is different from the articular cartilage [63]. Thus, in cases of inflammation, due to proximity, inflammatory cytokines, present in the synovial fluid, can have a direct effect on the development of the condyle at very early stages of arthritis, and therefore a dramatic effect on the development of the mandible [64]. Also, as mentioned above, the overall development of the mandible during childhood is important, and accordingly important the potential impact of arthritis in development. Many studies have found that the presence of JIA-TMJ arthritis in patients with can result in alterations in the normal craniofacial development, in asymmetries, even in signs of deformation [29, 38, 65-67]. The presence of inflammation in the joint results in destruction of the cartilage and the articular surfaces, and in combination with the ongoing overloading of the joint from normal function results in resorption of the condylar head and destruction of the disc and articular fossa [68]. These destructive procedures are followed by a gradual change in the position of the mandible, where the head of the condyle is placed more anteriorly in the glenoid fossa [68]. This results in reduction in the vertical growth of the mandible, leading to mandibular development with a posterior rotation, but not in agreement with the normal growth patterns (Fig. 1) [69]. As dysplastic growth continues, bone apposition takes place in the gonial area, and there is compensatory reduction of bone height in the posterior region of the maxilla [69-70].

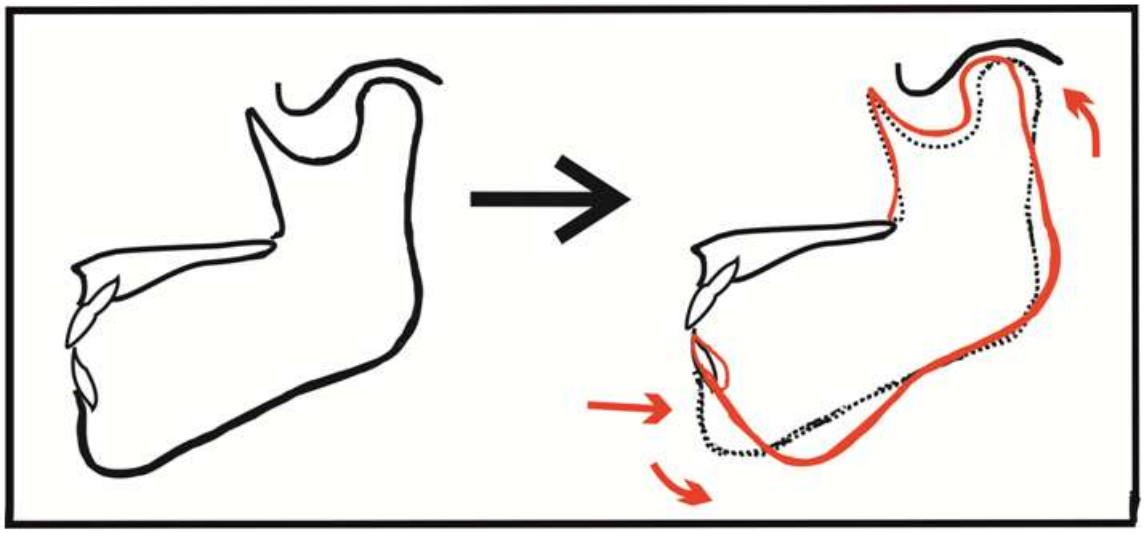

Fig. 1: Inflammation and destruction of the condylar head is followed by a gradual change in the position of the mandible, where the head of the condyle is placed more anteriorly in the glenoid fossa.

This pathological model of development is fairly common in children with TMJ arthritis, and is characterized as "bird-face", that presents with micrognathia or retrognathia and posterior rotation of the mandible relative to the maxilla. Twilt et al. in their study found that patients with TMJ involvement had a greater risk of retrognathia (82%) and posterior rotation of the mandible (58%), compared to those without TMJ involvement (55% and 47% respectively) [66]. Moreover, in similar studies, patients with bilateral TMJ arthritis presented with decreased mandibular dimensions (vertical dimension, ramus height, mandibular length), while in unilateral arthritis, decreased dimensions were present unilaterally, which resulted in noticeable facial asymmetry [29, 31, 38, 71-72].

TMJ involvement that presents with stiffness in the mandible and the presence of pain could lead to reduced masticatory function, which is intensified with the mastication of soft food. Children with JIA-TMJ arthritis also present atrophy of the masticatory muscles and reduced bite force, which contributes to abnormal and dysplastic development [73]. Long-term TMJ arthritis without any medical intervention and treatment can

have detrimental effects on normal mandibular growth and can result in facial deformation. Table 2 displays the craniofacial characteristics that can be developed in children with JIA-TMJ arthritis.

Table 2. Craniofacial characteristics of patients with JIA-TMJ arthritis

Skeletal Class II appearance
Increased anterior face height
Reduced ramus height
Appositional growth in the gonial area
Craniofacial asymmetry
Inclined occlusal plane
Anterior open bite
Proclination of mandibular incisors
Retruded position of the mandible

VII. TREATMENT MANAGEMENT OF CHILDREN WITH JIA

Treatment management of TMJ arthritis in patients with JIA should aim at:

1. Maintaining optimal joint function and eliminating symptoms from orofacial system.
2. Preventing the establishment of permanent damage on the osseous and cartilaginous structures and components of the TMJ.
3. Reducing, and if possible, preventing the creation of developmental malformations in the mandible and craniofacial structures [74].

For the accomplishment of those objectives, therapeutic interventions should reduce TMJ inflammation and developmental disorders with the normalization of development of the mandible. The therapeutic options that have been used are: 1) physiotherapy, 2) use of stabilizing splint, 3) functional appliances, 4) pharmacological interventions (intra-articular or systemic), and 5) surgery.

Physiotherapy aims at strengthening masticatory muscles and restoring functional mobility of the mandible. As low muscle activity and decreased bite force have been found to intensify problems in the TMJ, physiotherapy and exercise should be a part of the treatment [74]. However, its use in the literature is limited in case reports or in cases that preceded surgical treatment in the TMJ [16, 75].

The use of stabilization occlusal splint was proposed by Pedersen, who, based on his clinical experience, suggests its use in the first part of the treatment, for the improvement of mandibular function and reduction of TMJ overloading [68, 74].

The use of functional appliances is suggested in JIA patients with established lesions on the articular surfaces, facial asymmetry or growth disturbances [69]. Distraction splint is a modification of the stabilization splint that acts as a functional appliance, where with gradual increase on its posterior height the upper occlusal plane is controlled and space is created for normal development of the mandible, especially the condyles [68]. In a study by Stoustrup et al., the use of distraction splint led to improvement in mandibular growth and reduction of asymmetry, with normalization of growth [76].

Other functional appliances that have been used with satisfactory results is a modified distraction splint by Farronato et al., and the Bow activator by Kjellberg et al. [77-78]. After the use of functional appliances, most patients follow orthodontic treatment for the establishment of functional occlusion [69].

Intra-articular steroid injection has been used in the treatment of TMJ arthritis, as it has been applied in other joints with positive results [11, 79-81]. Despite the fact that in many studies a high percentage of the patients presented with improvement in subjective symptoms and maximal mouth opening capacity, those studies should be dealt with caution as they all have a high risk of bias [11, 31, 79-81].

In addition, none of these studies reported improvement in dentofacial growth or any positive effect on mandibular asymmetries that were already established [11, 31, 79-81]. In a recent study from Stoustrup et al, intra-articular corticosteroid injections only lead to temporary improvement in the TMJ pain and mobility, which was partly resolved in the long-term, suggesting a palliative role of this kind of intervention [82]. Unfortunately, there is limited evidence on the effect of intra-articular steroid injection in the TMJ structures and tissues, which makes it impossible to draw conclusions on the long-term effects on mandibular growth [31].

Systemic administration of drugs for the treatment of JIA is not cleared if it affects the TMJ [83]. Studies' results are conflicting. Stoll et al. observed inflammation in TMJ in patients under medication, while general disease was in remission [84]. Conversely, Ince et al. observed reduction of radiographic findings in patients who had been administrated with methotrexate in contrast to those who had not received any medication [85]. In the study of Twilt et al. TMJ activity seemed to follow that of other joints, as patients with low activity of general disease were found to have a greater improvement in TMJ than those with higher activity of general disease [67].

Surgical treatment is recommended in cases where medication and functional devices fail to improve the clinical sings, and facial asymmetry or micrognathia/retrognathia still remains [86].

VIII. CHALLENGES FOR THE FUTURE

The search for specific biomarkers that will enable the detection and diagnosis of JIA has recently attracted increased interest. The research is focused on biomarkers that will monitor disease activity with high sensitivity and specificity and will also be able to predict the course of the disease and its response to treatment. For JIA, several biomarkers have been used, such as rheumatic factor (RF), antinuclear antibodies, and C-reactive protein (CRP), but lately more sensitive markers of disease activity have been identified, which are several proinflammatory S100 proteins [87]. Levels of these proteins, especially the S100-A12, were significantly up-regulated in the serum of patients with active JIA compared to healthy controls or patients in remission [88]. The analysis of the expression of S100-A12 showed that this protein is secreted in the synovial fluid in sites with inflammation by the neutrophils granulocytes [89]. Upon secretion, it binds to the Receptor for Advanced Glycation End products- RAGE, which further leads to the NF-κB activation and production of proinflammatory molecules (as shown in the Fig.2)[87-88,90]. In a study by Asiez et al, a strong correlation was found between MRI TMJ findings and serum levels of S100-A12 in patients with JIA, indicating that this protein could be a marker for the estimation of active disease in the TMJ in the absence of disease activity in other joints [91]. The identification of biomarkers with high sensitivity and specificity for the TMJ will enable early diagnosis of the disease before the establishment of pathology to the orofacial structures.

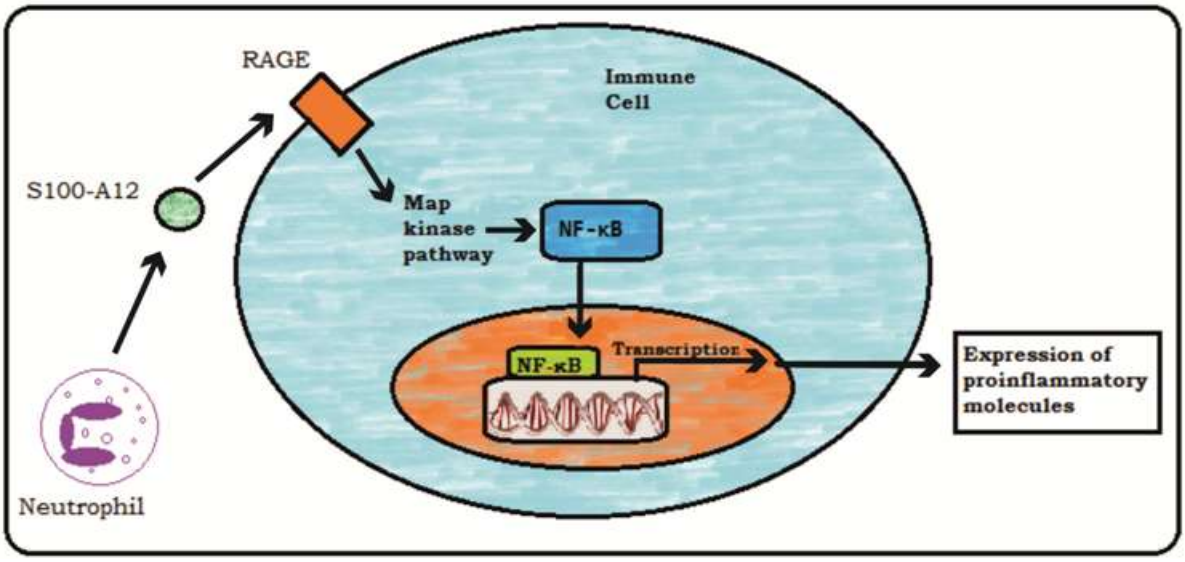

Fig. 2: Proinflammatory molecule production through the S100-A12/RAGE/NF-κB pathway.

While contrast-enhanced MRI remains the most reliable method for the assessment of active inflammation in the TMJ, the absence of well established criteria and guidelines that can differentiate between images of healthy growing joints and inflamed joints creates difficulties even in well-experienced radiologists. The establishment of such criteria is mandatory.

Treatment with the distraction splint seems to be beneficial for the mandibular growth leading to reduction of asymmetry, with normalization of growth. However, it possesses several difficulties, as the splint is made of cold curing acrylic and needs constant relining procedures in the dental office to keep up with the growing patient and the eruption of permanent dentition. The creation of a "smart" material that will enable the eruption of permanent teeth without disrupting them and will also be able to stabilize occlusion without the need for weekly equilibration, would be beneficial for both the patient and the pediatric dentist, as well as time-saving and easy-to-use.

IX. CONCLUSION

JIA is a disease that affects TMJ at a rate exceeding 40%, so its examination is imperative at regular intervals, both by pediatrician and by the pediatric dentist. This in turn requires appropriate training of doctors and dentists vigilance. The difficulty of early diagnosis of arthritis in TMJ is internationally recognized [49,92]. Unfortunately, there is still no scientifically documented and widely acceptable TMJ examination protocol, nor a reliable way of diagnosing early arthritis before installation of malformative lesions. Contrast-enhanced MRI remains the only reliable way of diagnosing TMJ inflammation at an early stage. Due to the specificity of TMJ arthritis, as well as the detrimental effects it can have on growth and development of the craniofacial complex, early diagnosis and immediate therapeutic intervention is important. In TMJ, despite the presence of inflammation, the presence of pain is not as common as in other joints, thus changing the hierarchy of therapeutic targets. The management of the destructive process that occurs in the joint and the changes that

occur in craniofacial development is of utmost importance. Although in recent years there has been significant progress in the field of drugs used for JIA, papers on their application in TMJ are scarce; their results are ambiguous, while mandible growth problems still remain [93]. In conclusion, the appropriate management is close monitoring that will enable early intervention before the establishment of severe malformations.

Why this paper is important to doctors and dentists:

1. TMJ should be monitored closely in children with JIA by the attending physician and dentist, as it could present without clinical signs and symptoms and missed in a routine exam.
2. MRI is the gold standard in imaging techniques, as it enables the assessment of active inflammation in the soft tissues as well as bone lesions, and should be considered as a tool for the correct diagnosis.
3. S100-A12 serum protein can be used as a biomarker, while not specific, for the assessment of active disease in the TMJ. In the future more specific biomarkers for the TMJ should be identified.

Compliance with Ethical Standards

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Competing interests: The authors have no competing interests.

Conflict of Interest: We declare that we do not have any conflict of interest.

Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors

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