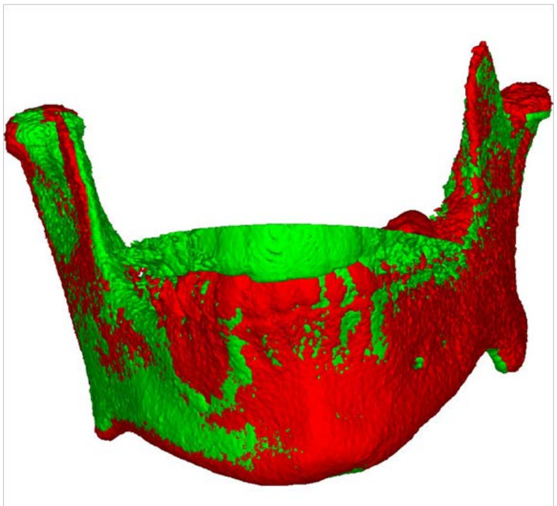
UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

DEPARTAMENTO DE ELECTRÓNICA E COMPUTACIÓN

PH.D. THESIS

CONTRIBUTIONS TO THE IMAGING STUDY OF THE AFFECTION OF THE TEMPOROMANDIBULAR JOINT IN JUVENILE IDIOPATHIC ARTHRITIS



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INFORMAMOS

Que o traballo recollido na presente memoria, titulada *"Contributions to the imaging study of the affection of the temporomandibular joint in juvenile idiopathic arthritis" (Aportación al estudio por imagen de la afectación de la articulación temporomandibular en la artritis idiopática juvenil)*, foi realizada por **María Florinda Otero González** baixo nosa dirección e constitúe a tese de doutoramento que presenta para obtar ao Grao de Doutora.

E para que así conste, asinamos a presente en Santiago de Compostela a 29 de xullo de 2016.

Asdo: Asdo: Asdo:

Jorge Mira Pérez Pablo García Tahoces Antonio J. Mera Varela

Asdo:

María Florinda Otero González

A mi pequeña hija Claudia,

"*Un canario que ladra si está triste,*
que come cartulina en vez de alpiste,
que se pasea en coche
y toma sol de noche,
estoy casi seguro que no existe"

María Elena Walsh

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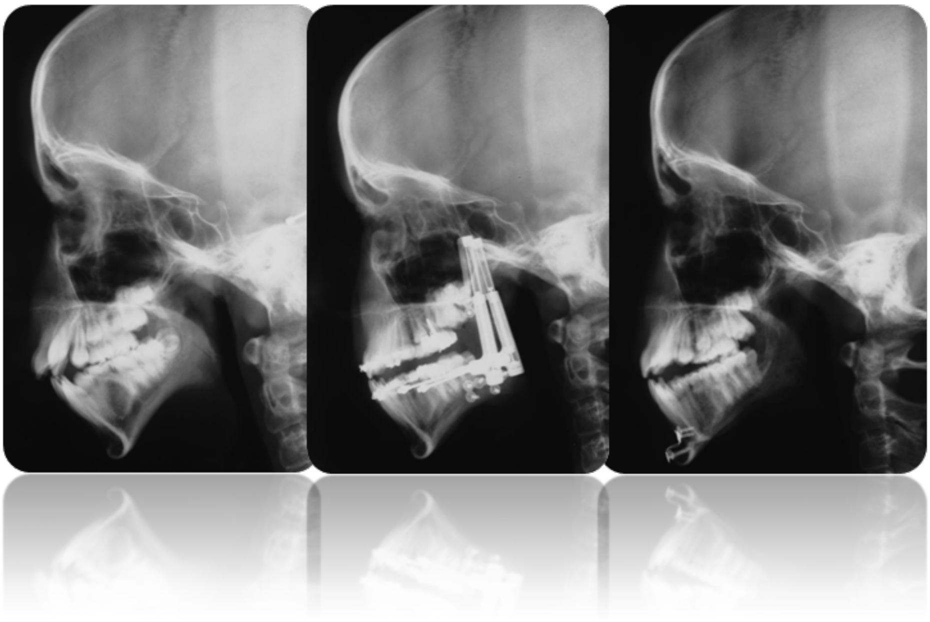
Chapter I: Introduction



1.1 Juvenile Idiopathic Arthritis (JIA)

1.1.1 Definition

Juvenile Idiopathic Arthritis is a chronic condition whose aetiology is unknown. It is characterized by the presence of arthritis (swelling within a joint, limitation of range of motion, tenderness or pain on motion, and increased heat) in one or more joints in children below the age of 16. The duration of arthritis least for 6 or more weeks, and other mechanical or identifiable causes are excluded (1).

The disease is characterized by variable degrees of joint inflammation, joint destruction, and progressive disability.

1.1.2 Classification

According to the latest agreement (International League Against Rheumatism) (1)(2) the JIA is classified into:

Systemic Type (4-17%): Arthritis in one or more joint with fever during 2 weeks and usually accompanied by erythematous rash, generalized lymph node enlargement, hepatomegaly, serositis and pericarditis. Initial stage: are often seen arthralgia and myalgia in connection with high fever.

Oligoarticular Type (27-56%): Characterized by four or less involved joints during the first 6 months of the disease. It is more frequent in the young ages and most often in girls. After 6 months of disease, this stage evolves into one of the following cases:

- Persistent oligoarthritis: Not more than 4 joints affected. ANA +
- Extended oligoarthritis**:** During the course of the disease and beyond the first 6 months, there is an increase in the number of Joint affected.

Polyarticular Type: It is defined as arthritis in five or more joints with 2 subcategories:

- The rheumafactor (RF)-negative (11-28%): Arthritis affecting 5 or more joints within the first 6 months of disease, (test of RF is negative).

- The rheumafactor (RF)+positive (2-7%): Arthritis affecting 5 or more joints during the first 6 months of disease, associated with positive RF test on 2 occasions at least 3 months apart.

Enthetesis-related Type(3-11%): Artrhritis and enthesitis, or arthritis or enthesitis with at least two of the following criteria;

-The presence of a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain.

- Confirmation of HLA-B27antigen.

- Onset in boys over 6 years of age.

- Acute anterior uveitis.

-History of ankylosing spondylitis, enthesitis related arthritis, sacroilitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative.

Psoriatic Type (2-11%): Arthritis and psoriasis or some signs like dactylitis or onycholysis together with arthritis

Undifferentiated arthritis (11-21%): Arthritis that fulfils criteria in no category or in two or more of the above categories.

1.1.3 Prevalence and pathogenesis

JIA is the most common rheumatic condition in children with a prevalence of 0.07-4.01 per 1000 children and an incidence of 0.008-0.226 per 1000 children per year (3). In the Northern European countries a prevalence of 60-80 per 100.000 children with an incidence rate of 15/100.000 children per year were observed, with considerable geographical variations between the different regions and countries (4). Mean age at onset was 6.8 years and the overall boy to girl ratio is 2:3 varying within the specific subtypes (4).

The aetiology of JIA is still unknown, but it is believed to be a multi-factorial condition occurring in a genetically predisposed child (5)(6).

The pathogenesis of JIA is not totally understood; histopathologically there is a synovitis in the affected joints. That inflammatory process is caused by immunological reaction with oedema and accumulation of plasma cells, macrophages and lymphocytes. The vascularity increase and is followed by exudation of fibrin into the joint space. The synovial lining cells increase in numbers due to hyperplasia and thereby the synovial layer increase in thickness. Gradually the hyperplastic synovium changes and lead to pannus formation with cartilage and bone erosion mediated by degradative enzymes. A contraction of the joint capsule is caused by the inflammation process and therefore a reduction in joint function.

1.1.4 Clinical symptoms

Juvenile idiopathic arthritis is not a single disease, but it constitutes a heterogeneous group of chronic inflammatory disorders. Clinical features in a child with arthritis are; swelling and limitation of motion of the joint accompanied by heat, pain with movements and tenderness.

1.2 Treatment of JIA

Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible; as long as the target has not been reached, treatment should be adjusted by frequent and strict monitoring from the specialists (7).

To achieve the goals of the JIA treatment, a wide range of specialists such as paediatric rheumatologists, physiotherapists, and occupational therapists is involved. In the case of temporomandibular involvement, specially trained orthodontists, orthopaedic surgeons, and maxillofacial surgeons are also necessary.

1.2.1 Multi-disciplinary Approach

The aims of treatment are to preserve cartilage, control pain and preserve range of motion, muscle strength and function; to manage systemic complications; to facilitate normal nutrition, growth, and physical and psychological development (6).

The JIA treatment combines antiinflamatory and immunomodulatory therapy and occasionally, surgery can be necessary when conventional therapy fails.

1.2.2 Medical Therapy

The pharmacological agents used to treat JIA can be grouped into five categories;

Non-steroidal Anti-inflammatory Medications (NSAIDs):

NSAIDs has been used in JIA during decades, and have analgesic, anti-pyretic and anti-inflammatory effects. The primary antinflamatory effect is mediated by inhibition of the cyclooxygenase enzymes in the metabolism of arachidonic acid to prostaglandin (6)(8).

Disease Modifying Anti-Rheumatic Medications (DMARDs):

DMARDs that have been shown to be effective in JIA include sulfasalazine, methotrexate and leflunomide (9).
Sulfasalazine: Is used commonly to treat oligoarticular JIA and HLA-B27 spondyloarthropathies, although a recent trial did not document efficacy.

Methotrexate (MTX): Methotrexate is considered by many rheumatologists to be the most important and useful DMARD, largely because of low drop-out rates for reasons of toxicity. Methotrexate is often preferred by rheumatologists because if it does not control arthritis on its own then it works well in combination with many other drugs, especially the biological agents. MTX is an anti-inflamatory and immunomodulatory agent and acts as a potent inhibitor of cell-mediated immunity including reduced production of TNF-α , interferon γ, IL-1, IL-6 and IL-8 (10)(11).

Leflunomide: Being JIA an off-label indication for this drug in Europe and the United States in clinical practice the drug is primarily used as a second-line or third-line agent. Nevertheless, Leflunomide seem to be well tolerated and leads to improvements in joint and functional status in children with JIA, with approximately 30% of remission. The combination DMARD therapy such as methotrexate and leflunomide has been shown to have better clinical outcomes when methotrexate monotherapy fails (12).

Corticosteroid:

Is a very potent anti-inflammatory and immunosuppressive drug occasionally used in JIA treatment. It can be administered systemically, topically or locally.

Due to substantial adverse effects of long–term use, the indications for systemic corticoids has been revised and reduced and still is use as standard drug in the initial treatment of the systemic onset JIA subtype. There are long-term adverse effects of systematically administered corticosteroids like growth suppression and irreversible growth impairment, obesity, predisposing to infection and musculoskeletal complications. Corticoids cause growth retardation in two ways, direct effect (via corticosteroid receptors in the growing cartilage) and indirect (by interference with several growth-modulation pathways) (13)(14)(15). With reduction in disease activity and lower corticosteroid doses, some patients experience 'catch-up' growth; however, many have only a slight improvement in height standard deviation during puberty or after cessation of corticosteroid treatment (14).

Intra-articular corticosteroid injections:

Is a safe and rapidly effective treatment for synovitis but the duration of the effectiveness is relatively short. Triamcinolone hexacetonide is the preferred formulation in paediatric practice (16).

Intra-articular injection is an effective and safe therapy for inflammatory joint disease in JIA, particularly in the oligoarticular form (17).

Biologic agents:

The introduction of biological agents, or biologic response modifiers, within the recent years has revolutionized the treatment of JIA. We do not know if growth alterations or remodelling process can be controlled by the use of biologic response modifiers. According to Tynjala P et al. the anti-TNF treatment, in polyarticular JIA, not only suppress inflammation, but also restores growth velocity (18).

The biologic drugs block the effect of pro-inflammatroy mediators, such as IL-1, TNF-alpha, and IL-6, thus limiting joint pain, inflammation and destruction. Among those drugs, Etanercept is the one that has been more extensively used compared to other biologic response modifiers, and therefore used and, therefore, its long-term efficacy and safety is the most documented up to date. It is a soluble fusion protein, which binds to TNF-α and TNF-ß, blocking TNF interaction with receptors on the cell surface. It can be use as a monotherapy but is often used in combination with MTX. Etanercetp is given systemically by subcutaneous injections, but local injections in the active arthritic joint space has been suggested, thus avoiding the use of corticosteroid injections (19).

The future researchs will bring light over long-term safety of other biologics, and should be therefore used on strict indication before the long-term effects are known.

1.3 Involvement of TMJ in JIA

1.3.1 Prevalence

In the literature, the reported frequency of TMJ involvement varies from 17% to 87% depending on the population investigated, the subtypes of JIA represented, and the methods by which involvement is diagnosed (20).

TMJ involvement is often bilateral. In 40%, only one joint is affected, however it is commonly observed that involvement begins as a unilateral condition and later develops into to bilateral involvement.

Twilt et al. have been examined the annual incidence of TMJ involvements in JIA, determinate a rate of 7,1% (2). Based on clinical evaluation and ortopantomographies (OPGs) 50% of unilateral TMJ involvement has been found (21). The two parameters associated with highest risk of future TMJ involvement are polyarticular disease course and early arthritis onset age (22)(23).

1.3.2 Symptoms / signs of TMJ involvement

TMJ functional reductions are predictors for TMJ involvement with a limited sensitivity because not all patients with TMJ arthritis experience clinical signs. Combining these symptoms with radiological abnormalities may lead to early detection of imminent condylar destruction (2)(24). Reduced opening capacity together with lack of palpable translation of the condylar head seem to be the only clinical parameters correlated with the diagnosis of TMJ arthritis in JIA patients (25).

1.3.3 Diagnose

Diagnosing TMJ arthritis in JIA is a difficult clinical task because no worldwide uniform criteria for the diagnosis of this condition have been established. The two parameters that have been mainly use to detect joint involvement have been joint pain and condylar erosions, the latter being identified with traditional radiographic methods, such as OPGs. However, OPGs presents significant limitations, and therefore, does not allow concluding on the presence of early inflammatory soft-tissue changes. Today, the golden standard in early TMJ arthritis diagnosis in JIA is carried out by the use of Magnetic Resonance Image (MRI). However, the technique is time consuming, requires sedation of the small patients and shows economical disadvantages, thus making MRI still not suitable for a routinely use. The use of clinical symptoms has been found to be unreliable (25), considering furthermore that patients with TMJ involvement often do not have any symptoms (20)(26).

Since the early detection of involvement of TMJ in JIA is a complex task, the protocol suggested at the paediatric rheumatologic clinic for dentofacial abnormalities, Aarhus Dental School, include early and regular evaluation by trained orthodontist of all the patients with diagnose of JIA.

The current clinical protocol include the registration of subjective symptoms and signs of impaired function such as: reduced ability to chew, decreased maximal mouth-opening capacity, objective signs of reduced condylar translation, decreased mandibular range of motion and signs of asymmetric mandibular growth (2)(21).

Cone beam computerized topographies (CBCTs) are furthermore added to the clinical and anamnestic data to evaluate condylar morphology. The diagnostic accuracy of CBCTs does not show synonymous superior properties compared to conventional radiographic methods in detecting condylar alterations (27)(28), although the use of 3-D reconstruction and morphological recognition seem to be promising (29).

1.3.4 TMJ arthritis and craniofacial development

The inflammatory process of the disease affects the mandibular growth. The resultant mandibular growth abnormalities include: condylar deformations, reduced vertical ramus growth, an unfavourable posterior mandibular rotation pattern, micrognathia, increased antegonial notching, malocclusion with a steep mandibular plane, an anterior open bite, and altered joint and muscular function occasionally associated with pain (30)(31), (figure 1.1)

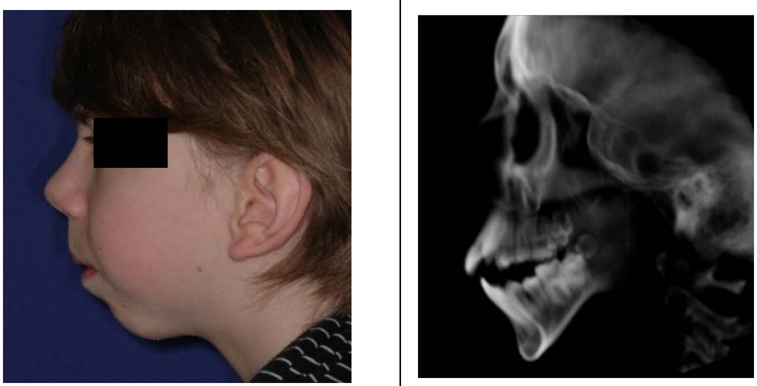


Figure 1.1. Representation of morphological alterations of a patient diagnosed with JIA. Clinical photo and lateral cephalogram. Patient from Ortho-Rheuma database, Department of Orthodontics, School of Dentistry, faculty of health Sciences, Aarhus University.

It is also described in the literature the presence of facial asymmetry in children with JIA. Unlikely other synovial joint, the TMJ mandibular growth plate is located just beneath the fibrocartilage of the mandibular condyle, which is particularly vulnerable to inflammatory damage. The destruction of fibrocartilage induced by arthritis can lead to significant limitation of mandibular growth and development and also can result in facial deformity such as asymmetry in several degrees of expression.

JIA subjects with TMJ involvement displayed patterns of facial asymmetry leading to mandibular asymmetry with displacement of the bony chin. This description was found in most of the patients in this study, and in some of them the asymmetry was notorious as it is possible observe in some figures of this document.

1.3.5 Factors influencing the craniofacial morphology

The condylar cartilage provides a capacity for responsive adjustment; it provides adaptive growth for that regional part of the mandible, leading to the best compromise fit of the lower jaw to the upper jaw and the basicranium (32). Growth and the muscles function provide signals and triggers to the osteogenic tissues-membranes in areas of tension, and to the cartilage-tissue in areas of pressure. This differentially activates their chondrogenic, osteoblastic, and osteoclastic components. The remodelling responses adjust the shape and the proportionate size of the mandible to accommodate the growth and the altered functions of the soft tissues. Any significant intervention (like a functional appliance or distraction splint) will likely result in some kind of responsive effect in the magnitude or direction of remodelling, or both, in some part of the mandible, where the joint and muscles are functioning without symptoms (33).

Growth seems to be direct consequences of inflammatory and/or mechanical damage to the condylar cartilage. Evidence regarding the pathogenesis of cartilage destruction is available only from investigations of rheumatoid arthritis and osteoarthritis, both of which occur in adulthood and, therefore, do not result in growth disturbances, although they may entail marked remodelling of articular tissues. Notably, however, bony erosion seems to occur later in JIA than in adult rheumatoid arthritis, and condylar resorption seems to be present for some time before bone destruction is radiographically detectable (34). Thus, the destruction of condylar cartilage, irrespective of its severity, appears to entail significant disturbances of mandibular growth.

The principal factors reported in the literarure responsible for the alterations of the morphology and dimension of the TMJ are:

1. Condylar lesions: The most important single sign of mandibular growth being influenced seems to be radiographically visible condylar lesions, as result of inflammatory process on the joint structures. In addition, a higher degree of mandibular retroposition and smaller dimensions of the mandible are found in patients with complete destruction of the head of the condyle compared with those with partial destructions (35).

2. Osteophytes: Bone spurs form due to the increase in a damaged joint's surface area. Bone spurs usually limit joint movement and typically cause pain.

3. Disease activity and drug therapy: Early onset, long duration, aggressiveness of the disease and long-standing corticosteroid therapy have been found to be correlated to TMJ abnormalities and reduced growth of the mandible (36).

4. Type of disease onset: Polyarticular onset affects the facial morphology more severely than pauciarticular or systemic onset (37).

Stabrun et al (38) found reduced mandibular growth in affected children without visible condylar lesions. A correlation was found in this study between long duration of the disease and the type of onset and smaller mandibular dimensions, despite the absence of visible condylar lesions (39). As mentioned above, this might be due to early inflammatory changes having occurred in the TMJ of these children, but still undiagnosed with conventional radiography.

5. Muscular weakness (40)(41): Maximal bite force has been found to be only 60% in children with juvenile chronic arthritis (JCA) compared to that of normal, healthy children (42). In adults this percentage has been found to be as low as 20-25% .This might be caused by inhibition due to pain or muscular atrophy and in connection to this, disuse and inactivity of the whole musculoskeletal system.

Others have claimed that it is due to type II fiber atrophy, caused by direct involvement of muscle fibers in the inflammatory process (40).
The actual factor of influence remains unknown, but there seems to be a correlation between muscular weakness and the development of long-face proportions in non-rheumatic individuals (43), and therefore, this factor should not be ruled out in rheumatic individuals as well.

1.4 Treatment of involved TMJ

The purpose of treating inflammatory TMJ changes is to reduce TMJ symptoms if present, and to secure optimal joint function to reduce unfavourable mandibular growth alterations (44). Therefore, the optimal treatment is to reduce the inflammation of TMJ by means of general or local drug administration and implemented by the use of functional therapy with the aim of supporting mandibular function and growth. If the orthopaedic treatment leads to insufficient results, orthognatic surgery may be needed.

1.4.1 Reduction of TMJ inflammation

TMJ inflammation and craniofacial dysmorphology are reduced by systemic administration of DMARDs. Kuseler et al. showed that IACIs prevent the initial inflammation in experimentally induced arthritis (45) and recently other study (46) has published data supporting the beneficial properties of Injections Corticoids (IACIs) concerning pain control and function against TMJ inflammation in JIA.
Another consideration point is the long-term effect of IACIs on condylar cartilage and craniofacial growth. It is important to remember that corticosteroids are injected directly into the TMJs in close contact with the condylar cartilage. It should be taken in consideration these potential long-term side effects because may outweigh the beneficial short-term functional improvements of IACIs against TMJ inflammation in JIA.
A recently animal experimental study, (from the Department of Orthodontics of Aarhus University Hospital in Denmark) about reduced mandibular growth in

temporal mandibular joint treated with IACIs (47) founding that there is not indicate a positive long-term effect in the use of IACI in the TMJ as an early treatment intervention against TMJ inflammation in growing individuals. The animals in the group control without injections had greater sagittal and vertical mandibular growth compared with the other three groups. TMJ arthritis caused diminished mandibular growth. However, relative mandibular growth was significantly less in the group treated with ICAIs.

1.4.2 Functional therapy

The aim of the functional therapy in these patients was to increase function of the joint and to ensure continuous growth of the mandible. Functional appliance with activators has been applied in the treatment of initial involvement in children with JIA (30)(48).

The early treatment of JIA was performed at the paediatric rheumatologic clinic for dentofacial abnormalities (Department of Orthodontics, School of Dentistry, faculty of health Sciences, Aarhus University) by using a distraction splint (DS).

The treatment of the TMJ-problem in JIA-patients with DS includes (44)(49):

- Protection of the joint from overloading early in the pathological process before morphological changes become evident and during the active phase of the disease.
- Stimulation of condylar growth during the local remission phase.

Description of the appliance:

The purpose of the DS is to displace the head of the condyle within the elasticity of the joint, therefore of a very small amount to unload the joints and promote the vertical growth of the mandibular ramus, thus gradually ensuring a mandibular anterior rotation.

A DS, is an active appliance which alters the mandibular position by a gradual thickening of the splint in the posterior area (figure 1.2).
The treatment is started with a fully balanced splint which is used to stabilize the position of the mandible where the joint and muscles are functioning without symptoms. This introduces a moderate change in the position of the mandible

and a new path of function. In this position interdigitations are made, in order to prepare for the active distraction. After mounting in articulator, the height of the splint is adjusted within the elasticity of the joint checked clinically. The procedure has to be repeated every 6-8 weeks, thereby the muscles are stretched and the joints are unloaded.

After a period of constant use, individual for every patient, with the distraction splint and in case of remission of the disease, the second phase of treatment can be initiated.

The following changes and clinical modifications after treatment with this appliance have been described in a case-report study (49). The ramus of the mandible was found to increase in height together with an increase in the total mandibular size of the patient. The evaluation was made in 2D images. Clinically, the opening capacity of the mandible was increased, and the lateral excursion was found acceptable (49).

The presence of a splint creates the sensation of a full, stable occlusion and control of unpleasantness or pain in the joint. Unloading should be used continuously with the purpose of protecting the joint from even sporadic overloading and to provide greater comfort for the patient during an active inflammation in the joint. The protection may also create a stable situation in the joint with the possibility of healing of bone and re-establishment of the growth pattern (49).

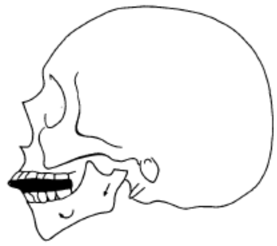


Figure 1.2. A mechanism of a DS appliance is to alter the mandible position towards a more anterior rotated position, at the same time the condyle is distracted from the cranial part resulting in an unloading of the joint.

1.4.3 Orthognatic surgery

Patients whose orthopaedic treatment yielded insufficient treatment (in patients where there is a limitation of growth) may be offered orthognatic surgery. Nevertheless a pre-operative orthopaedic treatment leads to a more sufficient treatment result because it reduces the post-operative soft-tissue induced relapse (44).

1.5 Medical Image and TMJ

Advancement in imaging technology is going parallel with the development of imaging protocols and diagnostic strategies. Diagnosis of conditions affecting the TMJ cannot always be based on a clinical examination alone, and the imaging technique has to be included.

At present, three-dimensional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are mostly utilized in complex craniofacial care (50). Shortcomings of two-dimensional images include lack of perspective, effects of projection and superimposition, imaging artefacts, and lack of motion. Volumetric information (depth, length and width) is synonymous of 3D imaging.

The parameters we can assess in a 3D image are the following;

- The morphology of the condyle
- The presence or absence of a clear cortical outline (51)
- The dimensions of the condyle in all three planes of space
- The positions of the condyle (52)(53)
- Volumetric assessment of the joint space.

1.5.1 Two-dimensional image

According to Christiansen and Thompson (54) the earliest reference to radiography of the TMJ was from 1910. Until 1950 imaging of the TMJ had been done mostly by medical radiologist, but a new technique, which made it possible for dentist with ordinary dental x-ray equipment to perform radiographic

examination of the TMJ using a transcranial projection, was (according to Christiansen and Thompson (54)) described by Updegrave in 1948.
In the following approximately 30 years, imaging of the TMJ was performed using plain film radiographs (radiographs made with a stationary x-ray source and film) with a transcranial projection. With this technique the osseous parts of the TMJ could be imaged, although not all parts of the joint were well visualized due to superimposition of adjacent structures.

Panoramic radiography

Due to the oblique orientation of the beam with respect to the long axis of the condyle, only obvious erosions, sclerosis and osteophytes of the condyles can be seen on a panoramic image. The high degree of distortion and difference in enlargement seen in panoramic images, does not provide reliable information on asymmetries and dimensions, horizontal or vertical (55). The panoramic is easily available; gives a minimum of radiation exposure to the patient at a low cost, and therefore was widely used in the past for diagnosing TMJ involvement. It can still be used for long studies because, historically, this technique was the most used in studies with the evaluation of TMJ alterations.

Conventional Tomography

These images provide a multiple thin section of the region of interest, thereby eliminating the problem of superimposition of different structures. It has to take into account the position of the beam, if the orientation of the beam is not based on an axial radiograph, the validity is questionable as the orientation of the condyle may vary. Conventional tomography cannot display the soft tissue components of the joint. The equipment to produce the most reliable type of tomography is quite expensive, both from a pecuniary as well as from radiation dose point of view and it is not always available. During the 1970s tomography was considered the method of choice for imaging of the TMJ. It became generally accepted that tomography is superior to transcranial radiography for assessment of the osseous structures of the TMJ (56)(57), and even today tomography is in general considered the most accurate conventional radiographic technique for imaging of the TMJ (58)(59).

1.5.2 Three-dimensional image

During the 1970s computed tomography (CT) and magnetic resonance (MRI) imaging was explored, but it was not until the early 1980s that studies on CT of the TMJ were reported (60). The following years several studies were conducted and focus was at first set on the ability of CT to image both the osseous and soft tissues of the TMJ (61). It later became apparent that because of inferior soft tissue resolution, CT should only be method of choice when the main concern was assessment of the osseous structures of the joint (62).

From the mid-1980s focus was on MRI imaging, which is fundamentally different from the other techniques mentioned since it uses a magnetic field and radiofrequency pulses instead of ionizing radiation to produce the images. Brooks and co-workers stated in a position paper of the American Academy of Oral and Maxillofacial Radiology (1997) that detail of the osseous structures is not as well depicted with MRI as with conventional tomography or CT. Until nowadays MRI is the selected imaging technique for soft tissues analysis in arthritic patients.

Recently cone beam CT (CBCT) has been developed as an alternative to medical CT. The CBCT technique produces image slices like conventional CT. Instead the complete volume is depicted by rotating the cone beam around the patient making images at certain degree of intervals. With advanced image reconstruction algorithms, the imaged area can be reconstructed in 3D (63). CBCT produces images of high quality and results in a lower patient radiation dose compared to conventional CT (63)(64)(65).

Computerized Tomography (CT)

CT can be used to diagnose internal derangement and other disorders of the TMJ. It provides information about the condyle, the mandibular fossa and articular eminence, being unable to show the soft tissues of the joint. In a systemic review from Hussain et al. Different diagnostic imaging techniques were compared, to assess which modality had the best ability to detect TMJ erosions and osteophytes. He concluded that the axially corrected sagittal tomography (ACST) was the best imaging choice whereas CT did not add any significant information, considering the radiation dose received by the patient.

Cone Beam Computed Tomography CBCT) on the other hand might prove to be a cost- and radiation dose-effective alternative.

Magnetic Resonance Imaging (MRI)

The MRI was developed to overcome the impossibility of seeing soft tissues with a CT. MRI creates an image without exposing the patient to ionizing radiation and provides the ability to perform the imaging in multiple planes. Used with contrast, it is an effective method in diagnosing early inflammatory changes and is considered the gold standard procedure to detect the inflammation of the joints (66). Its conventional use is still too expensive and time consuming, and it is often difficult for children to sit for a long time, thus reducing the quality of the scanner images.

Cone Beam Computerized Tomography (CBCT)

CBCT has many of the advantages of computerized tomography (CT), but with substantially less radiation dose given to the patient, lower costs, better availability and faster acquisition of images (67). It constitutes a new technology for 3-D volumetric imaging has been developed specifically for dentistry.

CBCT utilises a two-dimensional or panel detector coupled with a low output X-ray generator, which allows generating a 3D data set of the entire head with a single rotation of the X-ray and detector complex around the head of the patient. This is different from conventional CT scanners, in which multiple “slices” are stacked to obtain a complete 3D-image.

The two principle differences that distinguish CBCT from traditional CT scanner are the type of image source-detector complex and the reconstruction algorithm employed. Both imaging technologies allow for the capture and display of anatomy (deconstruction of the anatomy in 2D and reconstruction and analysis of anatomy in 3D). A 3D volume (CBCT), using software tools, can be reformatted or sliced along any plane, oblique plane or curved plane to reveal internal anatomy.

The variables that have significant influence on quality of a CBCT include voxel size (smallest element in a 3D digital image), dynamic range (number of gray levels) and signal to noise ratio. In general the best image quality is comprised of small voxels, large number of gray levels and high signal to low noise ratio. CBCT voxels can be isotropic (equal size in all dimensions x, y, and z) and range in size from 0.1 to 0.4mm. The entire craniofacial structure may be captured using a CBCT scan and with a software tools we can scale and match the regions of interest, such as TMJ.

1.5.3 Three-dimensional image tools

A volumetric 3D image has a global reference or coordinate system that is display as three orthogonal planes (axial, coronal and sagittal). Multiple image sets can be combined into the same 3D matrix and this process is called registration.

Anatomic segmentation is a process where an object is creating and can be used for morphometric analysis. Anatomic reconstructions can be used to analyze a specific model (visual representation) of a patient, and also to measure size and shape of a particular area of interest like the condylar head.

Although historically for 2D super-imposition, it has been used landmarks, planes, or 2D projections of surfaces, now software tools optimally align 3D CBCT data sets at different time points with subvoxel accuracy after identification of the anatomical structures. The computed registration is then applied to the segmented structures to measure changes with time or treatment procedure taking the best proximal fit.

Image-analysis procedures include reconstruction of 3D models, registration and superimposition of models at various time points, and calculation of the distances between the 3D surfaces. The automation of these methods, by using in-house computer tools, allows image analysis procedures to be largely independent of observer errors (68).

The three-dimensional (3D) information was use already in some studies with JIA patients. Elisabeth Huntjens et al.(69) were using CBCT to determinate the degree of condylar asymmetry in children with JIA.

Guidelines for imaging of the TMJ have been proposed (70), but indications for a radiographic examination are not well defined. The goal of radiographic imaging of the bony structures of the TMJ is to evaluate the osseous parts when disease is suspected, to confirm or rule out other expected pathological findings and to evaluate the extend and stage of disease. The radiographic examination should also contribute in reaching the proper diagnosis and influence the management strategy for the patient.

This dissertation was born first to improve the image as quantitative tool in an area difficult to observe, in disease stage, and second to get the best quality of the image with the software developed for our department, using only the CBCT to observe the bone and soft tissues structures of the TMJ.

1.5.4 Advance in Medical Image and software development

It is not surprising that medicine looks towards advanced technologies to provide the effort, time and cost savings that have been so successfully achieved in product design and engineering. In order to manufacture a rapid prototype model of any human anatomy it must first be captured in three dimensions in a manner that allows the computer processes that control the RP (Rapid prototyping) process to be used.

A number of scanning modalities can be used, ranging from substantial hospital facilities normally found in radiology departments to small hand-held scanners that can be used in the laboratory or clinic. Examples include Computed Tomography (CT), Magnetic Resonance (MR) imaging and positron emission tomography (PET). Each modality uses a different physical effect to generate cross-sectional images through the human body. The cross-sectional images are arranged in order so that the computer can construct a three-dimensional data set of the patient. Software can then be used to isolate particular organs or tissues. This data can then be used to make an exact replica of the organ using RP techniques.

The different physical effects used by each type of scanner result in different types of tissue being imaged. These machines require highly specialised staff to operate and require large capital investment. Computed Tomography works by passing focused X-rays through the body and measuring the amount of the X-ray energy absorbed. The amount of X-ray energy absorbed by a known slice thickness is proportional to the density of the body tissue. The computer generates a grey scale image where the tissue density is indicated by shades of grey, ranging from black indicating the density of air to white representing the density of the hardest bone. However, the density difference between different soft tissue structures is not great and therefore it may be difficult to distinguish between different adjacent organs in a CT image. Artificial contrast agents that absorb X-ray energy may be introduced into the body, which makes some structures stand out more strongly in CT images.

CT images are generated as a grey scale pixel image, just like a bitmap computer image. If the distance between a series of axial images, called the slice thickness, is known, they can be interpolated from one image to the next to form cuboids, known as voxels. Therefore, a three-dimensional CT scan generates a voxel representation of the human body.

When CT data is captured, the resulting images are divided up into a large number of pixels. Each pixel is a shade of grey that relates to the density of the tissue at that location. The resulting images are, therefore, an approximation of the original tissue shapes according to their density.

Modern CT scanning software allows different kernels (digital filters) to be used. These modify the data to give better three-dimensional reconstructions and can help to reduce noise. Typically, the options will range from ‘sharp’ to ‘smooth’. Sharpening filters increase edge sharpness but at a cost of increasing image noise. Smoothing filters reduce noise content in images but also decrease edge sharpness.

Magnetic Resonance (MR) imaging exploits the phenomenon that all atoms have a magnetic field that can be affected by radio waves. Atoms have a natural alignment and MR works by using powerful radio waves to alter this alignment temporarily. To construct an MR image the strength of the radio waves emitted by the atoms is measured at precise locations. By collecting signals from many locations, a cross-sectional image can be created. As in CT scanning the resulting cross-sectional image is a grey scale pixel image, the shade of grey being proportional to the strength of the signal. As the water content of different soft tissues differs, MR is an excellent modality for investigating the anatomy of soft tissue organs, however, unlike CT, MR is not good for visualising bone.

It is added to the end of the document an annex where it is possible to find more information relating to the quality of medical imaging.

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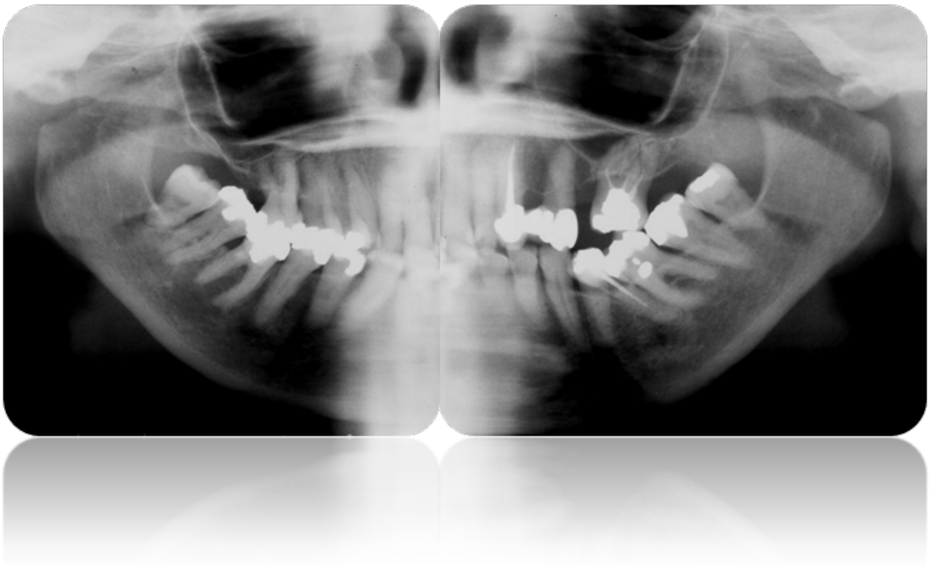
Chapter II: Assessment of the problem and objectives



2.1 Assessment of the problem

Juvenile Idiopathic Arthritis (JIA) is the most common inflammatory rheumatic disease in childhood. JIA is a term that covers different subtypes of an autoimmune disease with onset before the age of 16 and is characterized by inflammation in one or more joints. The JIA diagnose is defined with the presence of arthritis (characterized by either swelling of the joint or by one of the two following features: decreased motion, pain on motion or increased heat around the joint) persisting for at least six weeks in a child below 16 years of age. No laboratory tests are considered specific when diagnosing JIA. The aetiology is unknown, but most likely an auto-immunological cross-reaction triggered by an unknown agent such as a virus may initiate the inflammation.

Different subtypes have been defined, depending on the number of involved joints and symptoms present. The *systemic* type is characterized by daily fever for at least two week’s duration and accompanied by erythematous rash and/or lymph node enlargement, hepatomegaly and serositis. Artralgia and myalgia are often seen in the initial stage, especially in connection with high fever. 75% of the patients develop arthritis 3-12 months after the onset and 50% of all patients with systemic type experiences a course of persisting arthritis, often of polyarticular nature. The oligoarticular type is charactherized by four or less involved joints during the first six months of the disease. The onset of the disease is frequent at young ages (less than six years) and most often in girls.

After six months, the oligoarticular type is separated into persistent oligoarthritis (it affects no more than four joints thought the disease course) and extended oligoarthritis (it affects a cumulative total of five joints or more). The polyarticular type is defined as arthritis in five or more joints with two subcategories: the rheumafactor (RF)-negative and the RF-positive. The enthesitis-related type is defined as arthritis and/or enthesitis (inflammation in the attachment of the tendons) with at least two of the following criteria: sacroiliac joint tenderness and/or inflammatory spinal pain, presence of HLA-B27 and/or family history in at least one first- or second-degree relative of a medically confirmed HLA-B27 associate's disease. The psoriatic type is defined as arthritis in combination with psoriasis or as arthritis in combination with at least one of two of the following symptoms: dactylitis (diffuse swelling), nail-psoriasis and/or family history of psoriasis confirmed by a dermatologist in at least one first-degree relative. The last defined category is the group of the other types of arthritis, which includes children with arthritis of unknown origin (that persists for at least six weeks but does not fulfil the criteria to be included into any of the other categories) or those who fulfil criteria for more than one of the other categories.

General growth retardation is a common phenomenon, especially among children with systemic and polyarticular arthritis, and it is a result of the general disease activity and of the fact that they often are in long-term corticosteroid treatment. Untreated joint arthritis affects the epiphyseal growth and may cause an increase or decrease and even arrest in growth.

JIA is the most common rheumatic inflammatory rheumatic disease in children, with a prevalence of 0.07-4.01 per 1000 children and an incidence of 0.008-0.226 per 1000 children per year. In the Northern European countries a prevalence of 60-80 per 100.000 children, with an incidence rate of 15/100.000 children per year, were observed, with considerable geographical variations between the different regions and countries. Mean age at onset was 6.8 years and the overall boy to girl ratio is 2:3 varying within the specific subtypes.
In Spain, between 8,000 and 10,000 children suffer from a rheumatic disease. Among them, juvenile idiopathic arthritis (JIA), which accounts for the 75% of the pediatric rheumatology consultations (of which are diagnosed annually between 80-90 new cases).

The involvement of the temporomandibular joint has been described in up to 87% of the children with juvenile idiopathic arthritis (when based on magnetic tomography), which may be asymptomatic, and can lead to serious long-term complications. Untreated TMJ involvement may cause severe alterations of normal growth in the craniofacial complex.

Studies have shown that it is important for the outcome of the treatment to initiate the treatment before real bonny destruction has taken place. It is therefore important to detect the early changes in the TMJ. At this stage, the TMJ involvement is often without symptoms and the clinical signs are few.

In recent years there has been progress in the knowledge of JIA, both in the classification criteria, improvement, remission and inactive disease as tools to measure the activity and quality of life. It is essential to conduct a detailed history and a complete physical examination (which should include TMJ) to guide the diagnosis of these diseases. Additional tests, such as image, can help to confirm the suspected disease or to rule out other diseases included in the differential diagnosis of rheumatic diseases, having variable presentation. Even a therapeutic decision depends on the sensitivity of the test image to detect inflammation.

We have observed the absence of an observational methodology in the TMJ (on the history and physical examination of patients with JIA, TMJ is not being examined). It is interesting to draw attention to the underestimation of this joint, in children with JIA on health systems.

Despite the good work of doctors and rheumatology associations in recent years, in Spanish medical services there is no protocol of clinical assessment of TMJ in patients with JIA nowadays. Perhaps the absence of this action protocol may be due to the fact that there is not sufficient degree of crosscutting between orthodontists and different medical specialties involved, as for example in other countries. It has also been observed the ignorance of this problem by most orthodontists and dentists in our country. We believe that the attention to the effects of the TMJ in JIA patients is being undervalued by different specialists when conducting clinical analysis.

As a first approximation to the solution of this deficit, a plausible idea would be to adopt the schemes used in those European countries that have already addressed this issue in their health systems. For example, in Denmark, in the field of oral health, orthodontic care units are within university hospital grounds.

Thus, each child with JIA who arrives at the pediatric rheumatology is sent directly to the orthodontist for an evaluation of the TMJ.

We will not compare the different European health systems; our only aim is to notify the lack of attention on TMJ and, therefore, the need for comprehensive care of children affected by arthritis, in order to prevent the possible alterations in facial growth caused by this disease. If we manage to communicate the deficiency to the affected population and to the various professionals involved, this could result in the creation of multidisciplinary workspaces, which would result in an improvement in the service and therefore the quality of life of these patients.

The objectives of a joint effort of different public and private health professionals or associations related to AIJ should be aligned to achieve:

1. A better and faster diagnosis: the diagnosis of rheumatic diseases in children is complex and requires specialized training.

2. Better care: a multidisciplinary approach to the management of chronic rheumatologic diseases allows an improvement in the quality of the life of the patients (rehabilitation, imaging, radiologists, orthopedists, orthodontists, maxillofacial surgeons, etc.)

3. Participation in international collaborative studies: the way to improve the diagnosis, treatment and monitoring of these patients with rare diseases.

2.2 Objectives

2.2.1 Main objective

The aims of the present Ph.D. Thesis are divided between primary and secondary objectives:

Main objective:

The main objective of this research is to observe and confirm, through intervention by image, the degree of arthritis present in the TMJ, the degree of bone involvement and the degree of alteration in the mandibular growth in patients diagnosed with AIJ.

With this purpose, the following steps were conducted:

1. To assess the tests by imaging, in the detection of the degree of involvement of the TMJ in a group of children with JIA. To use three-dimensional image to quantify inflammatory and mandibular growth changes caused by the disease, as well as to evaluate the mandibular orthopedic treatment designed by the Department of Orthodontics at the University of Aarhus.

2. To observe and quantify, separately, the joint space, with the aim of obtaining a number or mark to distinguish between healthy state and disease state. For this, we will raise the need for an early diagnosis of JIA to avoid alterations of facial growth. For this part, we will use image quantification techniques.

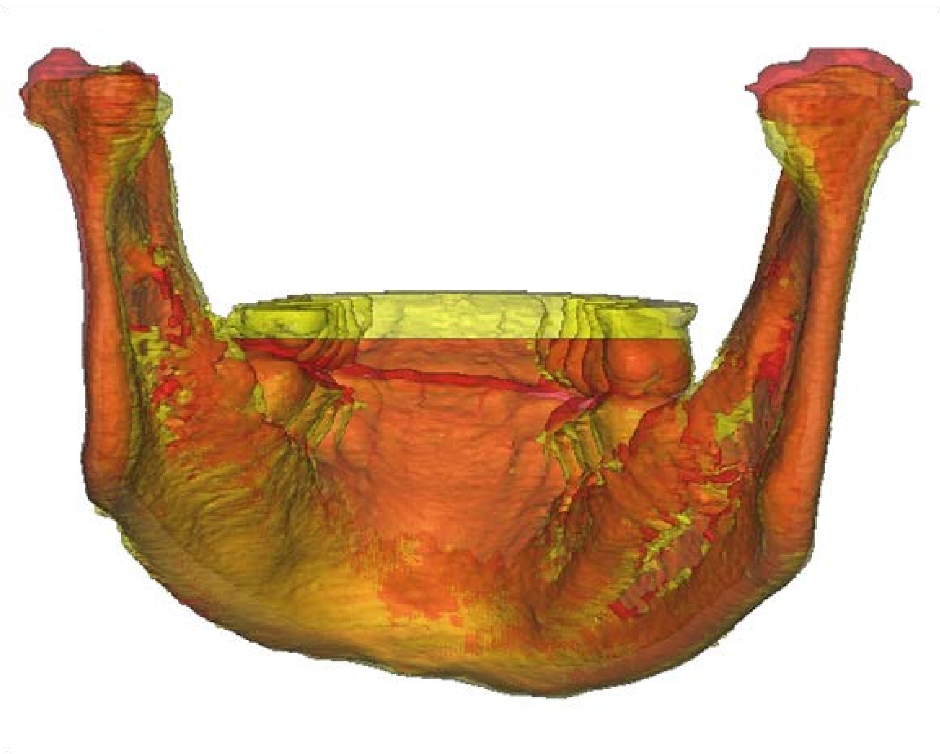
3. To study the properties of the image as an analytical tool for early diagnosis of the joint damage. New algorithms for image display will be developed. Besides this, we will assess the need to establish new imaging protocols and consensus for better use of the existing resources, also in order to avoid the duplication of the imaging tests.

2.2.2 Secondary objectives

During the work of this Thesis we will check deficiencies in the systemic organization of the Spanish Health System. Therefore, we have deemed necessary to add the following secondary objectives:

1. The definition of an observational clinical protocol related to the involvement of the TMJ, in order to prevent the secondary functional sequels of a chronical disease like this, which is nowadays inadequately controlled at the level of facial development.
2. To make a proposal of indications or treatment guidelines for patients affected with arthritis in the TMJ, following the protocol established systems in other European countries.

Chapter III: 3D evaluation of mandibular skeletal changes in juvenile arthritis patients treated with a distraction splint- a retrospective follow-up study



Summary

The aim of this chapter is to evaluate three-dimensional condylar and mandibular growth in relation to unilateral temporomandibular joint (TMJ) arthritis in juvenile arthritis (JIA) patients treated with a distraction splint.

For this purpose, Cone-Beam CT scans were taken for sixteen JIA patients with unilateral TMJ involvement before treatment (T_0) and 2 years after (T_1). All patients received orthopedic treatment with a distraction splint. Eleven non-JIA patients, undergoing orthodontic treatment without functional appliance or Class II mechanics with CBCT scans before and after treatment, served as controls. Reconstructed 3D models of the mandibles at T_0 and T_1 were superimposed on stable structures. Intra- and inter-group growth differences in condylar and mandibular ramus modifications and growth vector direction of the mandibular ramus were evaluated.

The results were that, in JIA patients, we found asymmetric condylar volume, distal and vertical condylar displacement and different ramus lengths. The ramus length was smaller on the affected side. Condylar displacement was more distal and less vertical in the JIA group than in the control group. A larger distal growth of the condylar head and a more medial rotation of the ramus on the affected side were found in the JIA group.

Therefore, the orthopedic functional treatment for JIA patients allows for condylar adaptation and modeling, thereby hindering a further worsening of the asymmetry (although with a widely variable response). Unilateral affection has a possible influence on the growth of the non-affected side.

3.1 Introduction

The involvement of the temporomandibular joint (TMJ) in patients affected with juvenile idiopathic arthritis (JIA) is a known phenomenon and has been reported by several authors (1)(2)(3)(4). Condylar lesions have been regarded as the primary contributory cause to mandibular growth deviations in JIA patients with TMJ arthritis. The facial morphology of JIA children with condylar lesions might become increasingly abnormal during growth, reflecting a decelerated vertical development of the posterior face height, malocclusion with anterior open bite and altered muscular function (5)(6)(7). The prognosis of mandibular growth when TMJ arthritis has been diagnosed is based on the presence of condylar deformities, the onset, the severity and the activity of the disease (4)(8)(9).

TMJ arthritis seems to affect long-term growth, also during the sub-acute and chronic phases. Condylar growth takes place in periods, although sub-normal in nature and with related dentoalveolar compensations.

Initial medication has a certain effect on the inflammation (8) and is therefore of vital importance, but its effect on dentofacial growth and development is still an open question. Functional/orthopedic treatment aims to support normal growth and controlling the dentoalveolar development. Thus, current literature recommends early functional/orthopedic treatment (2)(10)(11).

In the past, the morphological skeletal changes were usually analyzed by means of conventional 2D radiological images, but the development of 3D technologies has improved the possibility of following the effects of disease and treatment in three planes of space, thus increasing the understanding of the clinical value (12)(13)(14). Anatomic reconstructions can be used to analyze a specific model of a patient, and also to measure the size and shape of a particular area of interest, such as the condylar head. These image analysis procedures include reconstruction of 3D objects, superimposition of the objects at various time points, and quantification of measurements between the 3D surfaces.

The aim of the present study was to evaluate condylar morphology and mandibular growth changes using 3D reconstructions and superimpositions of the mandible based on Cone Beam Computed Tomography (CBCT) scans of patients with JIA and unilateral TMJ affection treated with a distraction splint.

3.2 Materials and Methods

In a retrospective longitudinal study, condylar morphology was analyzed by comparing the affected condyles with the non-affected ones within the same JIA patient. Furthermore, the morphology of the non-affected condyles was compared with that of a control group. All patients were referred to the Clinic for Dento- and Craniofacial Anomalies, Section of Orthodontics, Institute of Odontology, Aarhus University, Denmark, for management of the TMJ arthritis and dentofacial growth deviation. The use of the database with patients' information was approved by the national Danish committee for data protection (Datatilsynet j.nr. 2011-54-1291). According to the treatment protocol this group had been treated with an orthopedic functional appliance, a so-called distraction splint (DS). Inclusion criteria of the *study group* were: 1) diagnosis of JIA according to the ILAR criteria, 2) unilateral radiographically diagnosed deformity of the condyle, 3) number of activations of the functional orthopedic appliance more than two, and 4) CBCT scans taken before the start of treatment (T_0) and two years after (T_1). The diagnosis of involvement was made according to the following findings: reduced chewing function, decreased maximum-opening capacity, reduced condylar translation and mandibular range of mobility and clear sign of asymmetric growth.

Exclusion criteria were: a) no confirmed JIA diagnosis, b) bilateral TMJ affection developing during treatment, c) changes in treatment due to other types of functional/orthopedic appliances, fixed orthodontic appliances and/or bone distraction. Sixteen patients were included in the study group, who had a mean age of 11.9, ranging from 6.6 to 15.6 years and the male/female ratio was 7:9.

The *control group* was selected among patients referred for orthodontic treatment at the Section of Orthodontics, Institute of Odontology, Aarhus University. The inclusion criteria in this control group were as follows: a) absence of temporomandibular disorders, b) no treatment with functional/orthopedic appliance, and c) CBCT scans taken similar to the study group. Eleven individuals were chosen with a mean age of 11.7, (range= 7.7 to 14.5 years) and a male to female ratio of 3:8.

3.2.1 Image acquisition

Two sets of full-head CBCT-scans were obtained using a NewTom 3G CBCT scanner (3G, QR, Verona, Italy), available at the Section of Radiology, Institute of Odontology, University of Aarhus, Denmark. A single 360° rotation, 36 seconds scan, comprising 360 single projections, using the 12-inch field-of-view, was taken for each patient, resulting in datasets with a diameter and height of 20 cm. All CBCT-scans were reconstructed with a voxel dimension of 0.3x0.3x0.36 mm^3, which is the native resolution of the scanner. The images were saved in DICOM (Digital Imaging and Communications in Medicine) format.

3.2.2 Mandibular segmentation and 3D reconstruction:

The DICOM images were imported in the Mimics® (Mimics 13.1, Materialise, Leuven, Belgium) software for 3D reconstruction. In the single-slice images bone and soft tissues were separated from each other by setting a threshold value, between 500 and 700 Hounsfield units (HU) (it should be noted that the HUs used here are not the original HUs for computed tomography. However, it is and adapted gray values scale for CBCT), resulting in a so-called bone mask, containing those pixels representing bone. Any pixels connecting the condyle to the fossa were manually removed and from this cleaned bone mask of the mandible a 3D object was generated.

A following coordinate system was defined based on several landmarks related with the anatomy of the mandible (figure 3.1):

a) The mandibular axial plane was defined as the plane passing through the three most stable structures of the mandibular body; the upper contour of the posterior mandibular foramen on the right (CR) and the left (CL) and the inner part of the posterior cortical plate of the symphysis on the midline (MS).

b) The coronal plane was defined as being perpendicular to the mandibular axial plane, while passing through CR and CL.

c) The sagittal plane was defined as being perpendicular to both the mandibular axial plane and the coronal plane, while passing through MS.

3.2.3 Mandibular superimpositions:

Each 3D mandibular T_0-object was superimposed on the corresponding T_1-object. These superimpositions were performed using the point-to-point registration routine of Mimics® for nine anatomical landmarks consisting of the abovementioned CR, CL and MS plus the left and right anterior mental foramen and the anterior insertion of the muscles in the mental protuberance (triangularis and platysma in the external part and digastric in the internal part) (figure 3.1). The repositioning of the pre-treatment mandible was then calculated based on the least-squares difference between these nine corresponding points. Potential errors caused by placement of the landmark points are an integral part of the overall method error and the magnitude of these errors was assessed by double measurements.

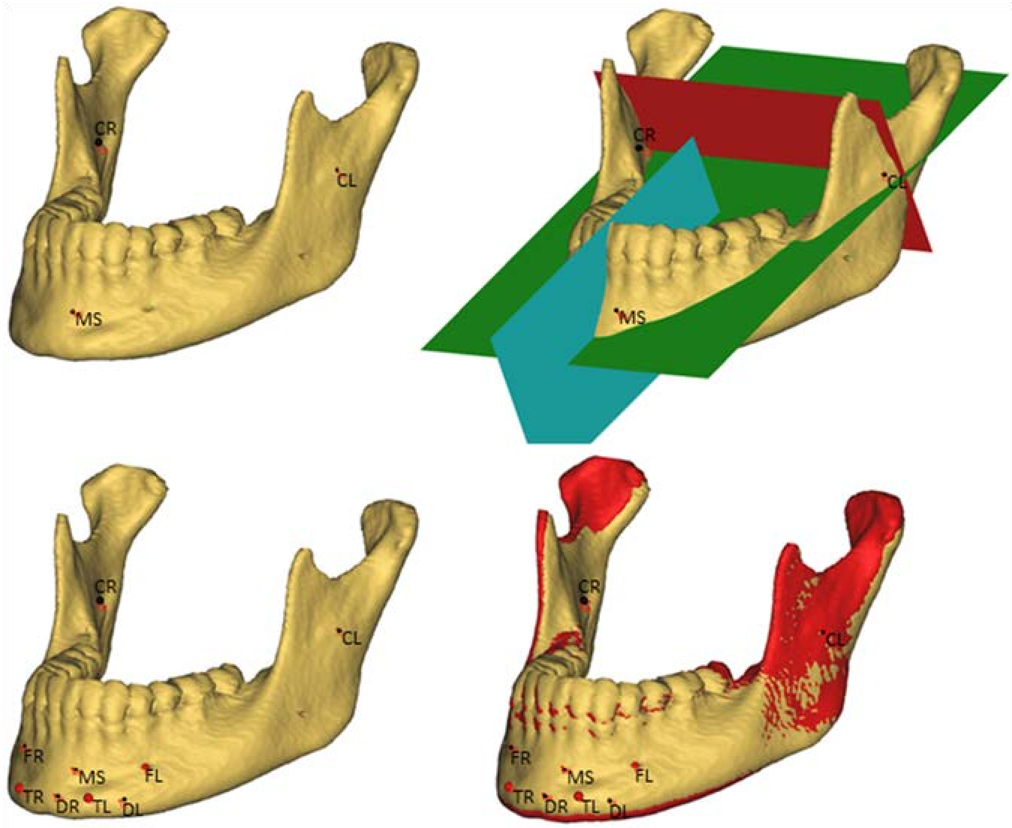


Figure 3.1. Landmarks defined as a reference for the coordinate system.

3.2.4 Measurements

The CBCT-scans were used for the evaluation of: a) condylar modifications with both linear and volumetric measurements (figure 3.2), b) mandibular ramus modifications, and c) calculation of the growth vector direction of the mandibular ramus.

Ad 1): The condylar modifications consisted of condylar width (*CW*), transverse, distal and vertical displacement (*TD*, *DD* and *VD* respectively), and volume (*CV*).

Ad 2): The ramus modifications consisted of ramus length (*RL*) and notch depth (*ND*).

Ad 3): The magnitude and direction of the growth vector was determined by finding the differences over time of the abovementioned variables expressed in the abovementioned coordinate system.

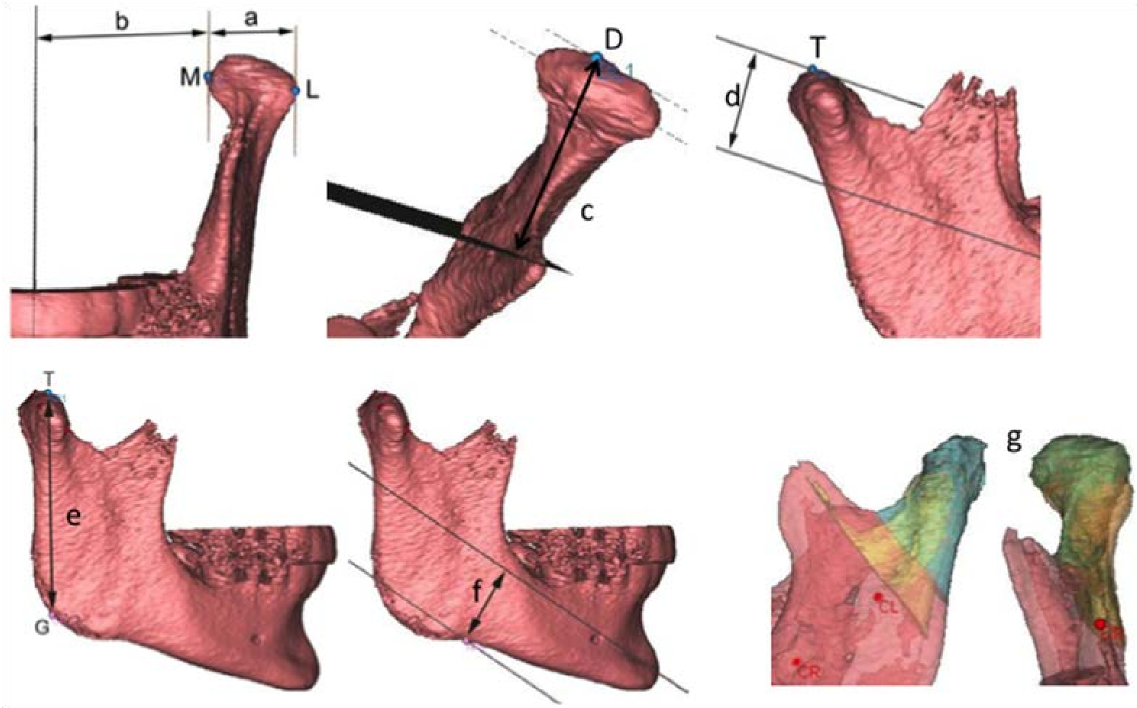


Figure 3.2. Overview of the measured distances between: (a) the most lateral (L) and most medial (M) points of the condylar head (CW); (b) M and sagittal plane (TD); (c) the most distal (d) point of the condylar head and transverse plane (DD); (d) the most coronal (t) point of the condylar head and axial plane (VD); (e) T and the gonion (g) point (RL); (f) the deepest point of the mandibular body and axial plane (ND). (g) In addition, the differences in condylar volume at T0 and T1 were measured (CV).

3.2.5 Statistics

The method error was calculated using Dahlberg's formula. Validity was assumed if this error was smaller than the standard deviation of the double measurements. Evaluation of the intra-observer variance of the manual segmentation and superimposition procedures was performed by duplicating 10 randomly chosen segmentations.

For ease of data handling, all affected JIA condyles were considered as left, the non-affected JIA condyles as right. Since no difference between right and left condyle was found in the control group, the left condyle was used for inter-group comparison.

The measured variables were compared over time within the same condyle and within the same patient. Paired t-tests were performed after verifying that the data were normally distributed. A independent-samples 2-tailed *t*-test was used to perform the comparison between groups. Statistical analysis was performed using SPSS software version 13 (SPSS Inc., Chicago, Illinois). A significance level of 5% was chosen.

3.3 Results

The results of the measurements and their statistical consequences are summarized in Table 3.1.

				JIA						*non-JIA*						
				mean (mm)	SD (mm)	min (mm)	max (mm)	p-value Left/Right	T_0/T_1	mean (mm)	SD (mm)	Min (mm)	max (mm)	p-value Left/Right	T_0/T_1	JIA/non-JIA
condylar modifications	width	**CW**	Left$_{T0}$	16,7	2,7	13,5	23,3	-	-	16,8	2,1	13,1	19,8	-	-	0,874
			Left$_{T1}$	17,4	2,8	13,9	22,8	-	**0,033**	17,6	2,3	13,2	20,7	-	0,093	0,835
			Right$_{T0}$	16,8	2,4	12,9	23,0	0,531	-	17,4	1,7	14,6	20,0	0,250	-	0,493
			Right$_{T1}$	17,5	2,6	13,9	23,9	0,637	**0,016**	17,7	2,0	14,4	20,2	0,777	0,287	0,821
	transv disp.	**TD**	Left$_{T0}$	40,1	4,7	33,1	50,8	-	-	38,6	3,4	34,8	48,2	-	-	0,401
			Left$_{T1}$	40,6	5,1	33,1	51,7	-	0,235	39,0	3,0	36,3	47,3	-	0,206	0,379
			Right$_{T0}$	36,8	5,1	28,6	48,4	0,146	-	38,4	2,7	35,0	44,4	0,864	-	0,357
			Right$_{T1}$	37,1	5,4	29,1	48,3	0,147	0,500	39,1	3,3	34,6	46,5	0,973	**0,020**	0,302
	distal disp.	**DD**	Left$_{T0}$	25,8	4,4	20,0	35,5	-	-	28,7	4,2	23,8	37,3	-	-	0,100
			Left$_{T1}$	28,1	4,6	22,5	36,6	-	**0,002**	29,7	4,6	24,1	37,7	-	0,128	0,380
			Right$_{T0}$	27,8	4,0	21,2	34,6	**0,027**	-	27,8	4,4	24,1	38,2	0,153	-	0,987
			Right$_{T1}$	30,5	3,8	25,7	38,0	**0,005**	**0,000**	29,1	4,3	24,0	39,1	0,482	**0,026**	0,392
	vertical disp.	**VD**	Left$_{T0}$	13,4	4,7	5,3	21,8	-	-	15,6	5,7	9,8	28,6	-	-	0,268
			Left$_{T1}$	13,7	4,7	5,3	22,1	-	0,599	17,1	6,2	9,5	29,2	-	**0,034**	0,121
			Right$_{T0}$	18,6	5,6	11,9	28,6	**0,000**	-	14,5	6,0	8,1	27,3	0,236	-	0,078
			Right$_{T1}$	18,8	5,4	12,1	29,8	**0,000**	0,733	17,0	6,5	9,1	29,8	0,850	**0,012**	0,436
	volume (mm^3)	**CV**	Left$_{T0}$	1574	472	805	2643	-	-	1885	435	1170	2798	-	-	0,096
			Left$_{T1}$	1675	589	723	2713	-	0,071	1988	460	1395	2650	-	0,198	0,152
			Right$_{T0}$	2049	671	1195	3588	**0,001**	-	1863	394	1332	2658	0,671	-	0,416
			Right$_{T1}$	2192	713	1416	3909	**0,000**	**0,041**	2004	546	1225	3269	0,866	0,119	0,468
mandibular modifications	rams length	**RL**	Left$_{T0}$	49,4	5,4	40,2	59,8	-	-	55,4	5,3	44,6	63,8	-	-	**0,008**
			Left$_{T1}$	50,3	7.0	37,6	64,6	-	0,144	57,1	6,2	44,8	66,8	-	**0,038**	**0,016**
			Right$_{T0}$	53,0	5,9	41,9	63,5	**0,002**	-	54,5	5,3	43,6	63,0	0,190	-	0,513
			Right$_{T1}$	55,1	7,2	44,1	67,8	**0,000**	**0,019**	57,0	6,2	43,6	66,6	0,854	**0,003**	0,493
	notch depth	**ND**	Left$_{T0}$	16,7	3,4	8,3	21,7	-	-	20,3	2,7	16,4	25,3	-	-	**0,007**
			Left$_{T1}$	17,6	3,5	8,3	21,8	-	**0,017**	20,4	3,1	15,3	26,3	-	0,826	**0,043**
			Right$_{T0}$	18,0	2,8	14,0	23,4	0,115	-	19,9	2,7	14,1	23,6	0,633	-	0,088
			Right$_{T1}$	18,8	2,8	13,7	23,6	0,112	**0,037**	20,3	3,1	15,0	24,2	0,811	0,377	0,207

Table 3.1 Results of the measurements.

3.3.1 Condylar modifications

CW and *DD* increased significantly during treatment in the study group. Furthermore, *DD* in the study group showed a significant difference between sides both at T_0 and T_1, the affected side being smaller than the non-affected.

VD was significantly smaller on the affected side and a clear inter-group difference was observed: it did not change over time neither on the affected and non-affected side in the study group, whereas it increased significantly on both sides in the control group.

Increased volume was observed in 11 affected condyles, and in 12 non-affected condyles. Decreased *CV* was observed in two affected condyles and in one non-affected condyle (figure 3.3).

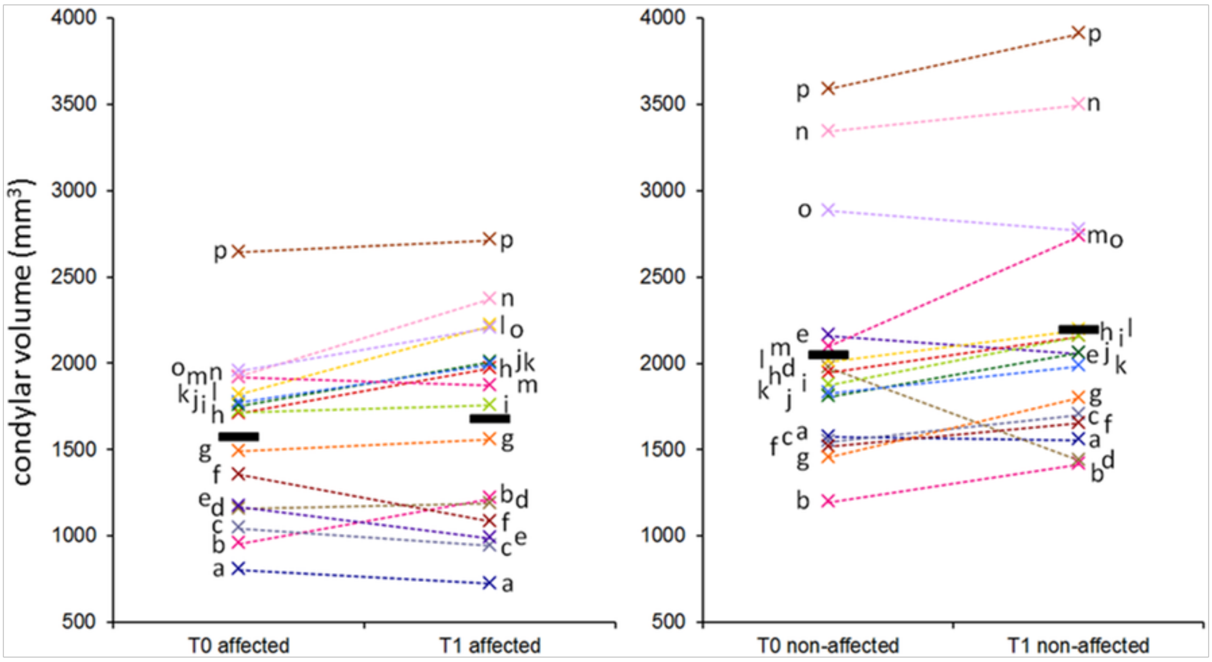


Figure 3.3. Condylar volume at T0 and T1 in the affected and non-affected side (patients coded by letters). Please note the individual variability of the response of the condyles on both sides.

3.3.2 Mandibular modifications:

The *RL* was significantly smaller on the affected side in the study group. The *RL* on the non-affected side and as well as in the control group significantly increased during treatment. These two findings are expressed as significantly smaller *RL* between the study and control group both at T_0 and T_1.

ND increased significantly on both the affected and non-affected sides during treatment in the study group. Despite this increase the values were significantly smaller than in the control group both at T_0 and T_1.

3.3.3 Growth vector

The growth vectors are illustrated in figure 3.4. The most interesting observation was the more distal displacement of the gonion in the mandible from the affected condyle as compared to the non-affected contralateral one, and also, in the JIA-affected hemi-mandible it tended to be less laterally than the non-affected and non-JIA ones. Inter-group differences showed that the lower point of the rami in the patients with JIA moved slightly more distal and less vertical as compared with the patients without JIA.

VD in the JIA patients was smaller compared to the non-JIA patients. In the study group both the affected and the non-affected condyles showed a more posterior and less vertical displacement as compared to the control condyles.

In the JIA patients the ratio between the non-affected and affected side was evaluated in terms of inter-side differences in ramus height and its displacement during treatment, and significant changes were found in ramus height in the non-affected side, as well as changes at the condylar level in both sides, yet these were not significant.

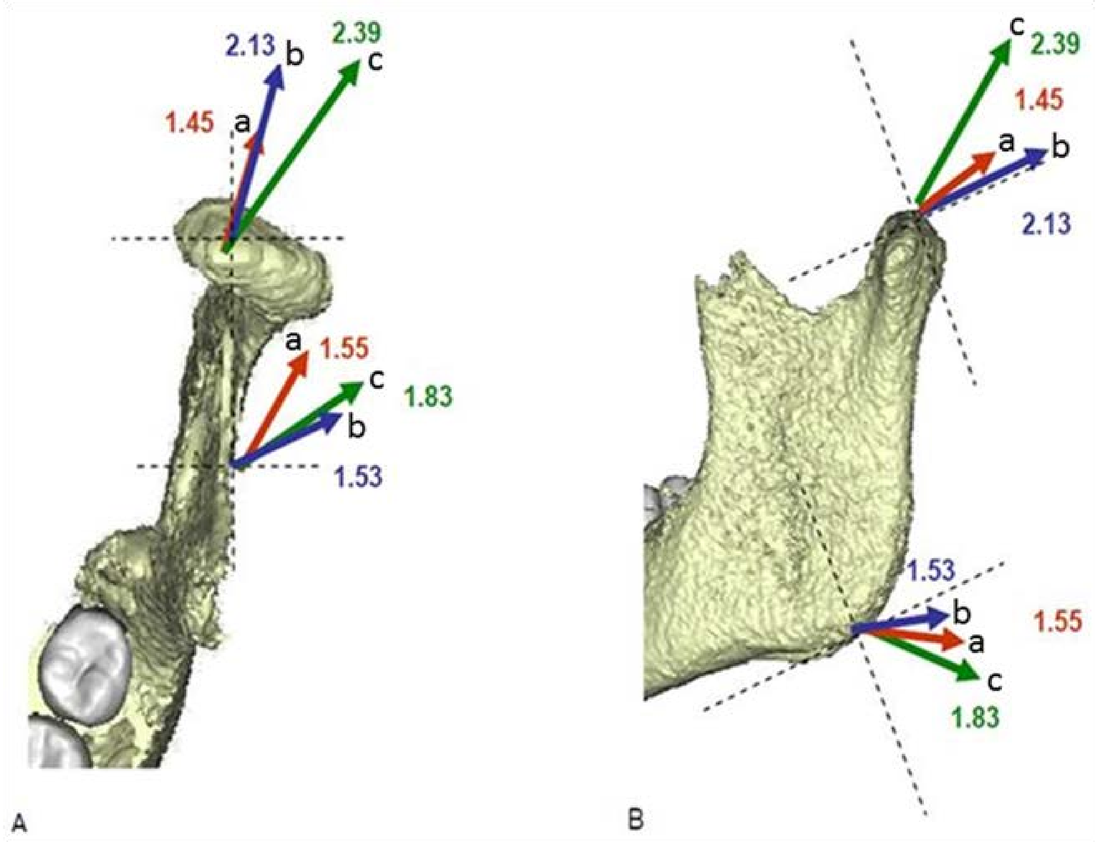


Figure 3.4. Growth vectors for the top of the condyle and the gonion. (a) JIA affected side, (b) JIA non-affected side, and (c) non-JIA.

3.4 Discussion

The present study resulted in three main findings: 1) the asymmetry in JIA patients was expressed in condylar volume, distal condylar displacement, vertical displacement, and ramus length, all being smaller on the affected side, 2) the affected patients showed more distal condylar growth on both sides, and 3) the affected side showed always the smallest displacement and a more medial growth of the gonion angle.

3.4.1 Asymmetry

In the JIA patients we confirmed the occurrence of asymmetry. The differences between affected and non-affected sides in CV, DD and VD, and RL were maintained over time and the asymmetry did not worsen. In relation to the CV, both groups did not show any significant increase in condylar volume in time. In our study, we calculated the entire volume of the condyle; the changes in total volume of the condyle would be a measure of growth and/or remodeling during treatment. For patients with JIA, there is no consensus in the literature (14). A recent animal study carried out in the Department of Orthodontics of Aarhus University Hospital (Denmark), concluded that changes in growth did not result from a mineralization defect, meaning that the bone produced is of normal quality and structure, but endochondral growth velocity may have been slowed down and may worsen the process of bone and growth deformities in times of active inflammation (15).

3.4.2 Growth directions

Our results indicated more DD than VD, as from linear measurement, in the JIA study group than in the control group. (Fig.7). The RL increased as expected in the control group (16) and in the non-affected hemi-mandible within the JIA group. The affected side showed a slower growth pattern. In the JIA group ND became less pronounced in both affected and non-affected sides, while it remained unchanged in the control group. This may be the result of the overall impaired function in the patients affected by JIA.

The distal growth pattern of the condyle was observed, although in a smaller scale, also in the non-affected condyles with a non-uniform response (Fig. 4), leading to the hypothesis that the non-affected side is influences by the affected one. The distal growth pattern reflects the typical mandibular growth direction in JIA patients with affected TMJ (6)(7)(9)(17), being, together with mandibular posterior rotation, one of the most pronounced clinical features. The rotational pattern of facial growth was not analyzed in this study. Araujo et al. reported that functional treatment in non-JIA patients induces significantly greater posterior displacement of gonion and condylion (18), compensating for the mandibular advancement. This is in agreement with our results, although more accentuated at the condylar level. The fact that the amount of displacement of the control condyles were the largest is not surprising, as they were neither affected directly by the disease nor indirectly by a different functional demand.

The growth vector in the horizontal plane in the affected hemi-mandible is more medial than in the non-affected and the control group. This growth pattern has not been reported in other studies.

A significant inter-individual variability was observed. Using the non-affected condyle as control for the same patient allowed control for inter-individual variability. The lack of substantial changes in the asymmetric pattern could be due to the short observation time, together with the small sample size, the heterogeneity of the patients`age, variation of cooperation and pharmacological treatment. The latter varied widely, according to the course of the disease. Some patients showed a clear positive response to the functional therapy. The question is whether healing is an expression of growth or of modeling towards a normal shape due to a functional therapy (DS), taking into consideration the influence of medications over tissue response. A definitive answer to this question could not be provided by our results. The large number of variables potentially involved in the answer requires a much larger sample size and longer observation time in order to be able to identify the best combination of pharmacological and functional treatment in future studies.

The distraction splint is constructed in order to provide distraction on both condyles of an asymmetric amount, i.e. larger on the affected side. Therefore, both condyles were submitted to distraction forces. All measurements after 2 years were positive, meaning that both condyles responded to the therapy or displayed some degree of growth, although with a large individual variation. To be able to analyze the effect of therapy as compared to growth, an untreated JIA control group should have been used. However, as previously mentioned, those data are not available, at least not as 3D datasets.

An advantage of using 3D technology is to have unbiased volumetric information of the joint components in their real anatomical size. The possibility of looking at the superimposed condyles from several viewpoints greatly improved our appreciation of the morphological changes.

3.5 Conclusion

The presented 3D investigation protocol for condylar and mandibular measurements in patients affected by JIA provides quantitative data on condylar adaptation and demonstrative images of the condylar and mandibular structures and its dimensional relationships.

In JIA patients, functional treatment allows for condylar adaptation and modelling, although the treatment response is characterized by a wide individual variability. The DS therapy is therefore considered an effective tool for the treatment of JIA patients with unilateral TMJ arthritis.

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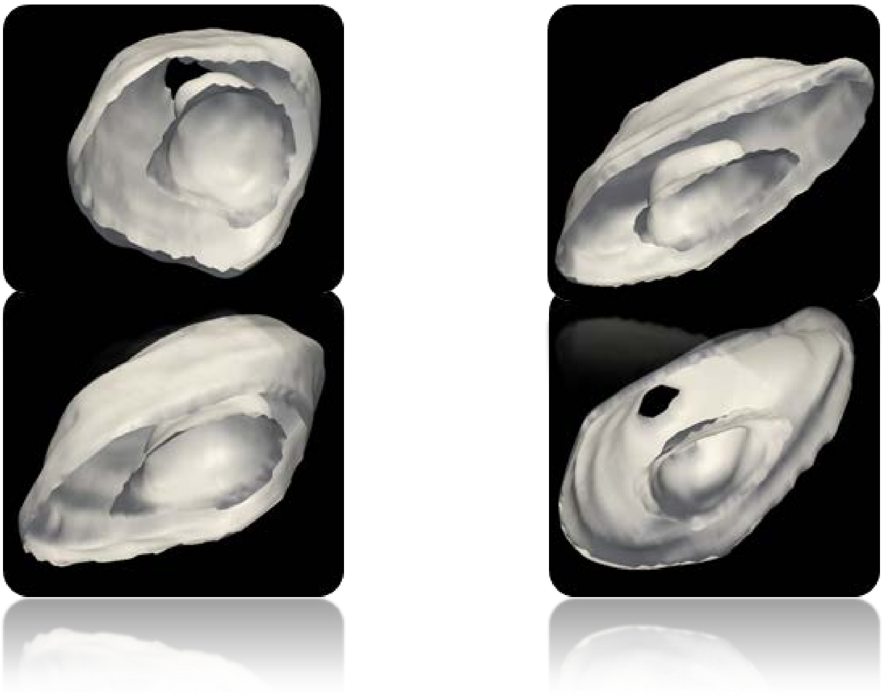
Chapter IV: Quantification of the temporomandibular joint space in patients with juvenile idiopathic arthritis assessed by cone-beam computerized tomography



Summary

The aim of this chapter is to evaluate the intra-articular volume of the temporomandibular joint (TMJ) determined by cone-beam computed tomography (CBCT), as a marker of joint disease inflammation in juvenile idiopathic arthritis (JIA) patients.

For this purpose, axial single-slice CBCT images of cross-sections of 22 TMJs of 11 JIA patients (mean age: 11.9 years) were employed. The patients had either bilateral (n=4) or unilateral (N=7) TMJ involvement. From the top of the glenoid fossa, in caudal direction, an average of 26 slices that include both condyles (right and left) were taken. TMJ volumes were calculated by adding the areas of the synovial joint space extracted from each slice. Such areas were manually delimited by using software that includes a graphic interface developed for this task and handled by a human expert.

The main finding was that, once measured the space into the TMJ (corresponding to the soft tissues), this space was twice as large in the JIA group as in the control group. We found differences between TMJs affected by JIA and non-affected TMJs in both volumes, but only the corresponding part of the synovium and the articular disc (soft tissues) within the joint space showed a significant difference.

Therefore, after this chapter we conclude that this method, based on CBCT, could establish differences in the joint space of TMJs between groups and delimit a threshold of disease due to inflammation based on differences in volumes

4.1 Introduction

Juvenile idiopathic arthritis (JIA) is characterized by an inflammatory condition in synovial joints (1). The TMJ is a bilateral synovial articulation between the mandible and the glenoid fossa of the temporal bone. It is frequent an involvement of the TMJ in these patients. The reported prevalence has ranged from 17 to 87 per cent based on the JIA subtype, the methods used for diagnosis, and the population studied (2)(3)(4)(5)(6).

The TMJ has an upper and a lower compartment separated by the articular disc. The synovial membrane covers the intra-articular surfaces except the fibrocartilage. Thus, the intra-articular volume of the TMJ would be expected to yield information about the increase in the synovial tissue volume, thereby indirectly expressing the severity of the arthritis and, therefore, providing an outcome measure in the treatment of TMJ arthritis.

Routinely, the evaluation of the synovial joints is generally based on a physical examination and imaging of the joints. Laboratory parameters are also used for arthritis activity assessment. The amount of synovial tissue can be anticipated to be related to the severity and period of active arthritis (7).

Recently, the use of magnetic resonance imaging (MRI) and ultrasonography (US) has been accepted for joint examination, due to the ability of these techniques to image both bone and soft tissue reactions, including synovitis (8). At present, both techniques are used to evaluate disease activity in the joints (and the results correlate with the clinical assessment) (8), although the interpretation is currently discussed. Previously, reports on MRI studies suggest that MRI should play an important role in the diagnosis and assessment of TMJ involvement in children with JIA (5)(3)(9)(10).

Until now, MRI is considered the gold standard to evaluate TMJ involvement (11)(12) even though no consensus exists for image description or assessment of degree of arthritis. MRI has some limitations, including the high cost, long scan time and patient compliance particular in young children. Moreover, the use of a contrast medium is necessary in order to depict inflammation and must be deselected in patients with kidney insufficiency or allergic reactions. The limitations of US are especially related to the limited accessibility of the TMJ structures.

Computerized tomography (CT) is superior to conventional radiography for evaluating internal derangements of the temporomandibular joint and over the past 10 years Cone Beam Computed Tomography (CBCT) has been introduced specifically for use in dentistry.

The advantages of the CBCT technique are a lower radiation dose than for medical Computed Tomography, the ability to image small volumes on certain systems, and the higher resolution image obtained (13).

Scan time ranges from five to eight seconds, which makes it feasible also for small children. Several studies refer to CBCT as a technique for TMJ assessment (14)(15)(16)(17)(18)(19)(20).

An indirect quantitative measure of the enlargement of the synovium, using CBCT, might increase the possibilities of the assessment of the disease severity and also to yield an objective parameter to help in the evaluation of treatments.

The objective of the present study was to evaluate this CBCT-based-methodology, by determining volumes of the intraarticular soft tissue and measuring the joint space, in order to compare the volumes between JIA patients and healthy controls. Furthermore, it was aimed to obtain a threshold in inflammatory derived volume increase for assessing early arthritis.

4.2 Materials and Methods

<u>Patients studied</u>

The study group consisted of patients diagnosed with JIA according to the ILAR criteria (n=11) and referred by the Pediatric Rheumatology Clinic, Aarhus University Hospital, Skejby, Denmark to the Clinic for Dentofacial Anomalies, Section of Orthodontics, Department of Dentistry, University of Aarhus, Denmark, for examination, monitoring and treatment of TMJ involvement and dentofacial deviation. The gender distribution was 9 females and 2 males and the mean age (± SD) was 11.9 (± 2.4) years. TMJ involvement was diagnosed in all cases and CBCT scans were performed simultaneously to the clinical examination.

The control group was selected among patients without a diagnosis of JIA (n=11) and referred for orthodontic treatment to the Section of Orthodontics, Department of Dentistry, University of Aarhus, Denmark. Gender distribution was 8 females and 3 males and the mean age (± SD) was 11.7 (± 2.3) years.

Image acquisition:

The CBCT images were acquired by means of a NewTom 3G CBCT scanner (3G, QR, Verona, Italy) at 110 kVP with a voxel dimension of 0.30 x 0.30 x 0.36 mm^3. A single 360° rotation, 36 seconds scan, comprising 360 single projections, using the 12-inch field of view, was taken for each patient.

Axial, coronal and sagittal views were available simultaneously by software intervention (this software was created for CITIUS center and it was done in C ++ with Qt graphics libraries).The TMJ was defined on 0.3 mm-thick axial slices. The images obtained were saved in a DICOM (Digital Imaging and Communications in Medicine standard for distributing medical images regardless of scanner) format for future analysis in our software.

The images of the joint space in each corresponding slice were segmented in the axial plane to obtain the volume of each TMJ. Right and left sides were segmented individually. Figure 1 depicts a 3D graphic rendering of the segmented volumetric model.

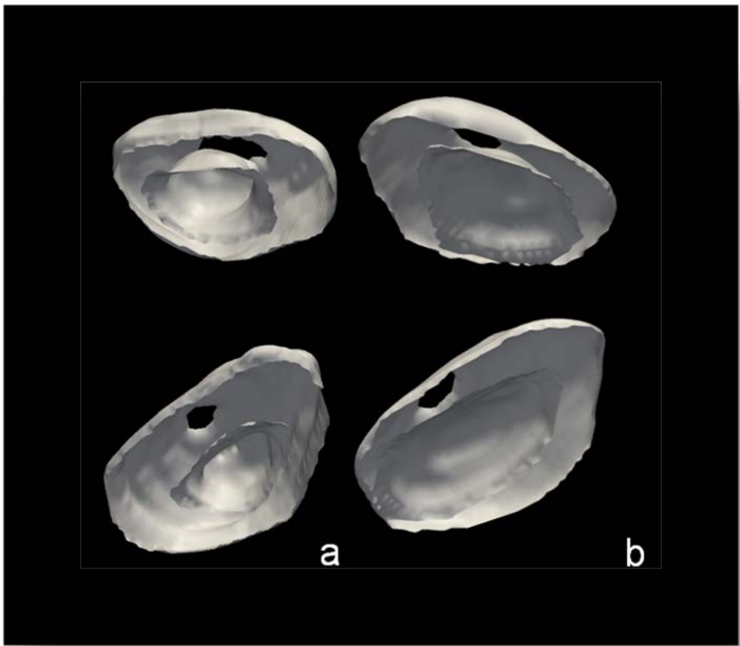


Figure 1: 3D graphic rendering of the volumetric model; a) Patient affected with JIA, b) Patient non-affected with JIA. This picture shows the 3D-visual evaluation of the ROI and the differences between groups.

Data processing and volume assessment

By means of the image processing software designed for this purpose, the soft tissues area and head of the condylar bone of each joint space in an axial CBCT slice were outlined and the areas automatically calculated. The evaluation of the CBCT data was conducted by the same evaluator and included measurements of the soft tissues area, margins of the condylar head and indices of the intra-articular swelling for each TMJ.

Scanned images were converted from DICOM format into an internal software format and the region of interest (ROI) was chosen by visual inspection of the axial images. Image segmentation was done for each single joint by scrolling down from the deepest point of the glenoid fossa where the temporal bone is divided into the squamous (preglonoid process*)* and the petrous part (postglonoid process*)*. In this way the presence of asymmetry in the individual patients concerning ramus and condyle length was addressed.

The anatomical parts in an axial slice from a CBCT scanner are shown in Figure 2.

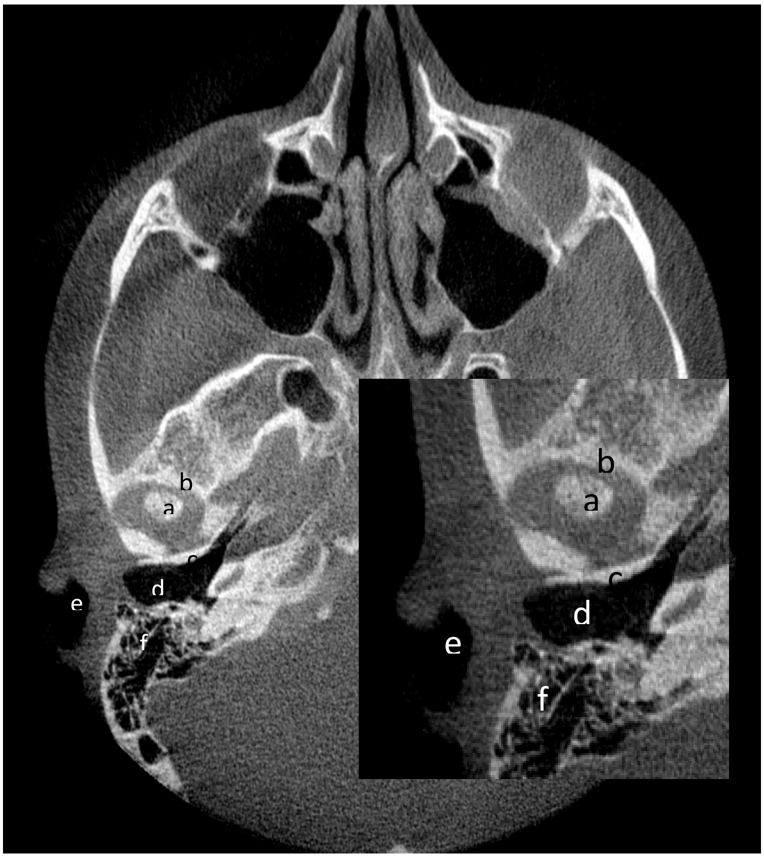


Figure 2: Synovial joint (TMJ) in an axial slice from the CBCT. Radiological description of the anatomical parts of the joint; a) Mandibular condyle of the TMJ, b) Preglonoid process (temporal bone), c) Postglenoid process (temporal bone). Anatomical areas uses to identify the TMJ in an axial slice; d) Eustachian tube, e) External auditory canal, f) Mastoid process.

The joint space (synovial area, soft tissues and condylar bone) of each slice of the TMJ within the selected ROI was manually extracted and the enclosed areas calculated.

To perform this action, the software loaded and displayed each slice, adjusting the contrast to enhance the visualization of the areas of interest (Figure 3), and it allowed the user to outline the interfaces of the different structures in the image by means of a pencil over a graphic tablet.

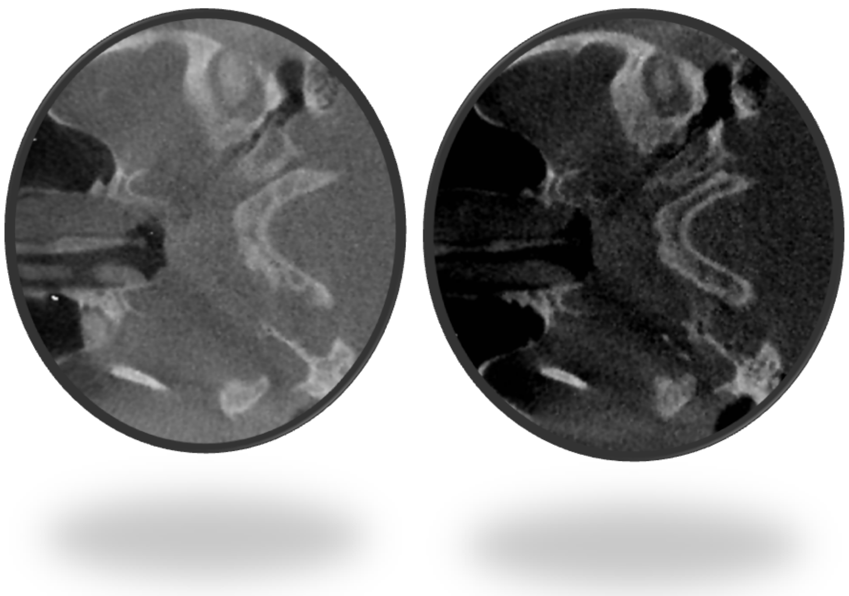


Figure 3: Contrast enhancement for visualising of the ROI.

Two volumes were defined: V_{e-i} and $V_{i,}$ where V_{e-i} is the external volume defined by the borders of the fossa minus V_i, the internal volume defined by the condyle. The lower limit of both volumes was defined by the lower plane from the lower border of the auditory canal and the most inferior point on the tuberculum of the temporal bone (preglonoid process). The upper limit for V_{e-i} was defined as a plane parallel to the lower plane, tangent to the deepest point of the glenoid fossa. For V_i, the upper limit was defined by a similar plane tangent to the most coronal point of the condyle. Figure 4 shows the lowest part of the ROI.

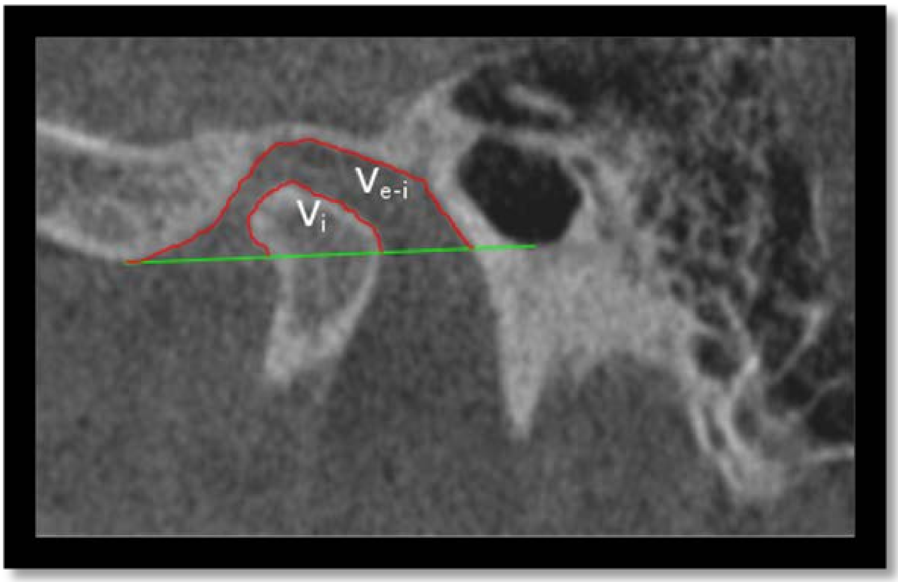


Figure 4. Lower part of the ROI demarcation in a sagittal view. It is included the studied volumes; Ve-i and Vi.

Once the two borders associated with both interfaces were outlined manually, the software computed each enclosed area (in pixel units) by adding the number of pixels surrounded by each border.

$V_{e\text{-}i}$ and V_i were found in the following way: A_{ek} is the area of the joint space, in slice k limited by the surrounding bone; A_{ik} is the area of the bony condylar head, in slice k (Figure 5). For each slice the area of the joint space is calculated as the difference between the areas A_{ek} and A_{ik}.

Figure 5; The two areas of interest correspond to the area of joint space limited by the surrounding bone tissue (A_e) and to the area of the condylar head (A_i).

Finally, the total volumes associated with the area A_{ek} - A_{ik}, $V_{e-i,}$ and the area A_{ik}, V_i, were calculated over the total slice set, by means of the following expressions:

$$V_i = ST \sum_{k=1}^{n_i} A_{ik}$$

$$V_{e-i} = ST \sum_{k=1}^{n_e} (A_{ek} - A_{ik})$$

where n_i and n_e represent the number of slices for which V_i and V_{e-i} were respectively outlined and ST is the slice thickness extracted from the DICOM heads of each imaging file (0.3 mm).

Taking both volumes as a reference, we define the index of intra-articular space of the TMJ (**IF_{index})** as:

$$IF_{index} = \frac{(V_{e-i})}{(V_i)}$$

In this way, the higher the inflammation, the higher Ve-i. We use Vi as a normalization factor, in order to scale the different sizes of the patients.
To evaluate differences between sides we made a subdivision in the group affected by JIA. Within this group there are patients with a bilateral affection (n=4) and patients with unilateral affection, where the affected condyle was described as the right one (n=7).

Statistics:
To assess double measurements in this study, the Dahlberg's formula was used (Dahlberg, 1940). The evaluation of the intra-observer variance in the manual segmentation method was performed by duplicating seven randomly chosen segmentations.

The statistical comparison of the joint volumes was performed using a non-parametric independent-samples Mann-Whitney U-test due to the small number of samples in the groups. The description analysis for all data included the mean and standard deviation.

In the study group the data was further divided according to TMJ involvement. Four patients had bilateral TMJ affection and seven had unilateral affection for clinical description. The condyles of the control group (for which there was no difference between the right and the left condyle) were used for comparison. Due to the low numbers of patients in the groups, the differences between the right and left side for individual cases were tested with a non-parametric related-samples Wilcoxon signed rank test.
The significance level was set at 0.05.

4.3 Results

We have calculated both volumes (V_{e-i} and V_i) for each patient, 11 children affected with JIA and 11 controls without JIA.

The results show that the amount of soft tissues present into the joint space (V_{e-i}) was significantly higher in the JIA group compared to the healthy controls (Table 1).

Table1. Comparison of the joint volumes in the study and control groups

	Study		*Control*		*T-test*
	Mean	*S.D.*	*Mean*	*S.D.*	
V_{e-i} right (mm^3)	1241	526	468	153	*<0.001*
V_i right (mm^3)	394	196	320	176	*0.300*
V_{e-i} left (mm^3)	1192	451	512	214	*<0.001*
V_i left (mm^3)	405	335	345	195	*0.797*

Table 2. Right/left comparison of the Intra-articular inflammatory index (IF_{index}) for the study and control groups.

	IF_{index} right		*IF_{index} left*		*Wilcoxon test*
	Mean	S.D.	Mean	S.D.	p-value
Bilat. affect. (n=4)	*2.9*	*0.5*	*2.3*	*0.4*	0,068
Unilat. affect. (n=7)	*5.6*	*3.1*	*3.5*	*1.7*	0,237
Control (n=11)	*1.8*	*1.1*	*2.0*	*1.6*	0,755

In Table 2 it can be seen that, for the bilaterally affected JIA group, the mean value of the IF index goes from 2.9 in the right side to 2.3 in the left side. The affection of the TMJs in this bilateral JIA group is rather symmetrical; but, in the unilateral affected JIA group, the differences between both sides increase: it goes from 5.6 in the right side to 3.5 in the left one. It can be observed furthermore that there is no statistical difference between the IF in the left and right sides in the control group. But for the JIA patients, especially the bilaterally affected ones, there is a trend of larger IF indeces on the right side.

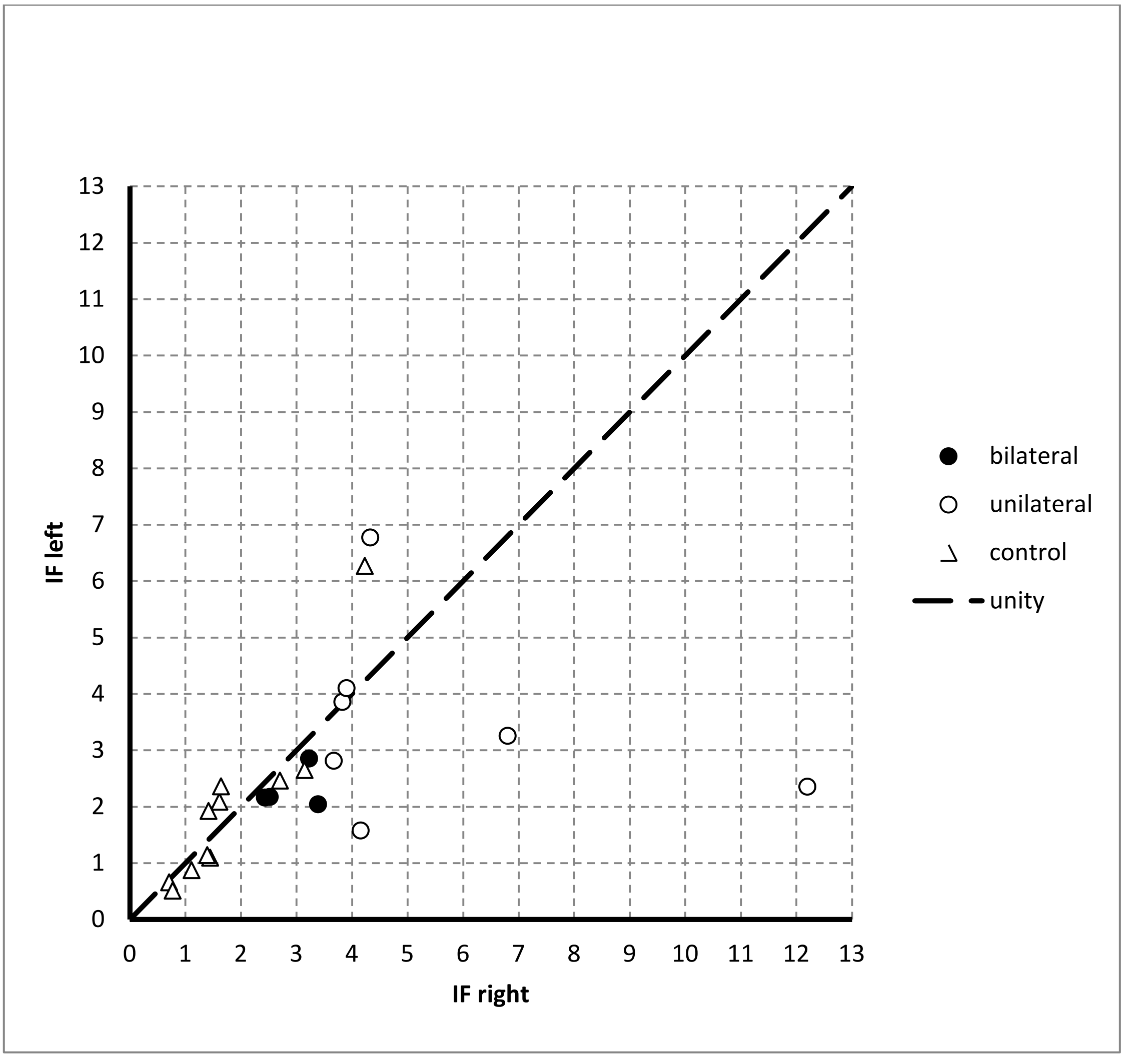


Figure 6. Left- and right-sided distribution of the intra-articular filling indexes.

From figure 6 we could define an area, defined by the rectangle $IF_{right} < 2.3$ - $IF_{left} < 2.3$, where there is not presence of patients affected by JIA.

We also see that there is a case in the control group with IF values far outside this area. Therefore, this area seems to define a rough approximation to a boundary to identify healthy TMJs versus the JIA-affected ones.

4.4 Discussion

In JIA, as in other inflammatory arthritis, the mass of synovial tissue is markedly increased. Histopathologically, JIA is characterized by hypertrophic inflammatory synovitis with cellular infiltration and proliferation of blood vessels. Thus, a quantitative measure of the amount of synovial membrane may provide useful information on the severity of the disease.

Synovial joint space volume estimations have been obtained until now either by manual computer-assisted outlining, based on visual analysis of the images (as in the present study), or by semi-automatic computerized counting of pixels above a certain threshold. Several quantification methods have been developed to assess synovial volumes in humans by MRI in several joints (21)(22)(23), but not in the TMJ of JIA patients.

Magnetic resonance imaging (MRI) allows direct visualization of the inflamed synovial membrane in knees, wrists and TMJ (22)(23)(24)(25) Most of these studies were initiated in order to facilitate an early diagnose of the disease. Østergaard *et al.* (7) have been working to establish quantification methods for clinical trials in synovial volumes but in different joint from the TMJ. They concluded that synovial membrane volumes can be determined by MRI with a maximal analytical error of approximately 20 per cent. Furthermore, they have added that attempts should be made to apply the synovial volume measurement technique to the joints most commonly involved in early arthritis, i.e., the small joints of the hands and feet. Related to that, several radiographic studies of children with JIA have documented high frequencies of temporomandibular joint (TMJ) involvement; thus we consider it important to analyze this joint for possible clinical applications.

In this work we propose a marker to assess the intraarticular volume in the TMJ: the evaluation of the synovial joint space volume by means of computer software that allows outlining and calculating the area of a given region of interest (ROI) on CBCT-images. The determination of this volume in TMJ has not been reported so far on a CBCT basis. The present study introduces an estimation of the synovial joint volume in TMJ affected by JIA, achieved by outlining the joint space on CBCT images.

The determination of this volume in TMJ has not been reported so far on the basis of CBCT. The present study introduces an estimation of the synovial joint volume in TMJ affected by JIA, achieved by outlining the joint space on CBCT images. It is worth mentioning that CBCT techniques are widely used in conventional clinical practice and, therefore, this result reinforce the role of the CBCT for the assessment of the volume.

In patients affected by JIA it is also frequent the presence of facial asymmetry (26)(27)(28)(29)(30). CBCT is a common diagnostic tool for orthodontic treatment of patients affected by JIA and also to determine the degree of asymmetry in these patients.

After measurement of these CBCT TMJ images, it was found that the space volume was statistically significantly higher in TMJ affected by arthritis than in the clinically healthy group. This observation is in accordance with the findings of Østergaard *et al.* (7) in arthritic knees and wrist with activity, whose inflammatory mechanism is the same as in the TMJ. Another study using the synovial membrane volume (SVM) as a marker of disease was the one by Loeuille *et al.*(31). In inflammatory diseases the SVM is highly correlated with local clinical signs of inflammation and histological parameters. Loeuille et al. (31) measured (with MRI) SVM in knees affected with osteoarthritis and compared the results with macroscopic, microscopic and clinical findings. They demonstrated that SMVs are well correlated with macroscopic and total microscopic scores, but in relation with clinical signs the relationship was less strong.

In order to assess different pathologies in TMJ during years, the condyle-glenoid fossa relationship was evaluated by measuring the distance between two reference points, via lateral cranial radiography, on a 2D picture. There are numerous sources of variability associated with the measurement of the joint space width on radiographs. Our proposal is to profit from the advantages of evaluation of 3D structures. CBCT technologies allow the joint to be visualized as sections in different planes and it can also be rendered as 3D volumetric reconstructions to enhance diagnostic capabilities.

There is a study using the CBCT to evaluate changes in the condyle-glenoid fossa relationship after functional treatment (Arici *et al.*) (32). Arici and co-workers analyze the space joint of the TMJ using a similar methodology. The difference is that the segmentation of the area of interest is done in only one axial slice from the multiplanar reconstruction images and, in healthy patients, without sign of inflammation. They measure changes on TMJ space in Class II patients after functional therapy. They found that, although the volumes of the condyle and glenoid fossa increased more in the study group (Class II with functional therapy) than in the control group (Class II without functional therapy), the differences were not statistically significant. However, statistically significant differences were found between the groups in the volumes of the posterior joint space. In the Arici et al. group there was not inflammation of the TMJ, they divided the joint space in two sections (anterior and posterior) and the biggest changes in volume were found in the posterior joint space, this area is within V_{e-i} in our study. In this case it may be due to anterior displacement of the condyle, since there was not an increase in volume in all joint space.

Another study, by Kitai *et al.* (33), was based on a follow-up examination after the completion of orthodontic treatment with the Herbst appliance in a 20-year-old female who had suffered from polyarticular JCA. Both TMJs were examined using magnetic resonance imaging (MRI). The mandibular condyle, the glenoid fossa and the articular disc were segmented and a 3D reconstruction of these structures was carried out. They did not evaluate the volume, but they observed changes in the depth of the glenoid fossa, which was reduced, and the articular eminence was remarkably flat. In an inflammatory process it is clear that there are changes, adaptive or remodelling changes, in a joint affected by JIA.

In this study, we have tried to improve the above situations. First of all, we did not focus on a single slice, but on the whole volume, in order to extract a measurable quantity (V_{e-i}) to include as much of the synovial joint space as possible. With this we obtained a score that reflects the amount of inflamed tissue. We were not evaluating the changes in the joint space due to an appliance; the important point is to know the slewing of the TMJ joint space as an inflammation process in all the joints affected by JIA.

The purpose of this study was to determinate the feasibility of this method to distinguish between the various degrees of TMJ inflammation using quantitative measurements of the joint space. Specifically, to establish the threshold from a normal TMJ to an affected TMJ, with a fast quantitative test in JIA patients.

So far, we have found that the volume determinations by the method we are now proposing was acceptable, mainly when the synovial joint volumes were low, i.e. when they are within our approximate boundary to define a healthy TMJ. All of the patients with an inflammatory process (or a swollen state) in the joint disease were outside the area defined by such boundary.

An additional limitation related to the retrospective nature of the study was the fact that the CBCT examinations of the study were selected through an imaging database rather than consecutively through a systemic monitoring system. In this database we possibly found different states of inflammation and different TMJ involvement in the patients affected by JIA.

As expected, the volumes of these synovial joint spaces were statistically significantly higher in TMJ_s with JIA than in non-JIA-TMJ_s. Furthermore, the unilateral affected patients had significantly more range of variations than the bilateral and control groups, probably due to chronic changes and perhaps, to some extent, due to subclinical inflammation in both sides.

Second, with this study, we are facing the analysis before structural damages appear in the patients, namely, before the appearance of changes in the depth of the glenoid fossa. With our approximation, we pretend to detect the disease as soon as possible, by inspecting the space into the TMJ occupied by soft tissue. In this way, as CBCT is a more available technique in conventional clinical practice and it is much faster than MRI, this approach could be a good tool to filter easily a large number of patients.

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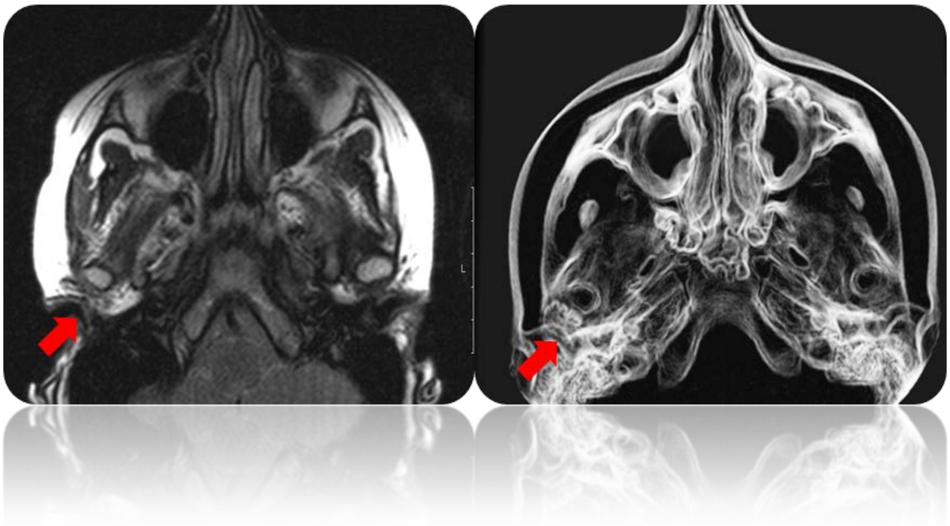
Chapter V: Assessment of TMJ soft tissues by enhancing image contrast of cone-beam computed tomography data



Summary

The aim of this chapter is to assess the soft tissues structures in the TMJ of patients with JIA using CBCT and to know the potential of this technique on this issue.

For this purpose, we have developed a software to enhance the contrast of the different anatomical structures arising from a CBCT scanner and we have compared the resulting images with those obtained by means of Magnetic Resonance Image (MRI).

After this, we obtain a contrast enhancement in soft tissues of the TMJ, increasing the differences between the anatomical structures that are present within the joint, even without the use of a contrast agent. It also improves the visualization of the synovial differences between the TMJs of the same JIA patient.

As a result, CBCT could be used as a tool for soft tissue analysis. Our image processing technique yields images that improve the range of use of CBCT for the analysis of the TMJ. The improvement of the anatomical description of the TMJ by means of CBCT opens the door for using such modality as a tool for the analysis of soft tissues, and widens its clinical applications.

5.1 Introduction

The TMJ is a bilateral synovial articulation between the mandible and the temporal bone (1)(2)(3).The TMJ is formed by the mandibular condyle fitting into the mandibular fossa of the temporal bone and the articular disc, that separates these two bones from direct contact. The disc is a biconcave structure with a central thin portion (comprised of dense fibrous connective tissue) and anterior and posterior thicker portions known as anterior and posterior bands. This disc, along with its attachments, divides the joint into superior and inferior spaces. These spaces are filled with a plasma-like synovial fluid secreted by cells of the synovial lining. Synovial fluid facilitates movement within the joint; it also acts as a vehicle for providing metabolic requirements for these tissues.

Degenerative diseases of the TMJ occur from the loss in equilibrium of anabolic and catabolic processes (4). The general term *inflammatory joint disease* refers to arthritis and the arthritis features within the TMJ showed a marked enhancement of the synovial membrane (5). Temporomandibular disorders (TMD) or dysfunctions are the most common clinical conditions that need a check by imaging, as well as pathologies specific to the bone and the joints. The complexity of the TMD, however, demands a clear and precise image of the region for effective management of the patient. Different imaging modalities are available to image the TMJ, each with inherent strengths and weaknesses.
JIA is the most common form of arthritis in children (6)(7). All joints can be involved in JIA, including the temporomandibular joint (8)(9). The rate of TMJ involvement in patients with JIA varies from 17 to 87% (10) (11). Also a high rate of TMJ involvement (12) was found in JIA subgroups with increased numbers of joints affected by the disease and the TMJ may also be the initial joint affected (13). In JIA it is described a risk for facial growth disturbances (14). As an added complication, the involvement of the TMJ in JIA often occurs without clinically detectable signs and symptoms, therefore delaying diagnosis (15). It is important to prevent the complications of JIA, therefore it would be important to establish a diagnosis guide of TMJ arthritis in an early stage. The

sensitivity and specificity of the clinical examination by different imaging methods leads to a wide range of reported TMJ involvement (16).

The imaging of the temporomandibular joint (TMJ) is continuously evolving with advancement of imaging technologies. CBCT is a low dose scanning system, a result of advances in computer and electronic technology, which has been specifically designed to produce three-dimensional images of the maxillofacial skeleton. The CBCT volumetric data set is usually reconstructed in orthogonal orientations to allow viewing of the images in the axial, sagittal and coronal planes.

A disadvantage of CBCT for visualizing TMJ is that the soft tissue detail is not displayed as with conventional CT. Thereby, CBCT would not be particularly suitable for examining lesions involving both soft tissues and bone, which are the key for evaluating the damage of arthritis in the TMJ. It is for this reason that CBCT has become the modality selected for bone assessment and magnetic resonance imaging (MRI) is considered the gold standard to reliably diagnose of TMJ inflammation in JIA patients (17)(18)(19).

It is well stablished that the quality for x-ray medical image can be described in terms of three basic concepts: contrast, spatial resolution and noise. Moreover, the subject contrast (the contrast before the capture of the image by the recording system) is modeled by two factors; the thickness and the linear attenuation coefficient, which is related with the density of the material. Visualization software tools such as the window/level, allow the brightness and contrast of the greyscale images to be adjusted by modifying the look-up table at the output system. The larger the difference in gray shades between two different tissue types, the easier it is to make important clinical distinctions.

As we have mentioned, it is difficult a clear visualization of all structures of the TMJ because of the heterogeneity (in grey levels) of elements such as ligaments, articular surfaces and articular disk. To obviate this limitation, we aimed at observing this joint using a 3D perspective, which allows a complete analysis of TMJ, and we propose an algorithm for contrast enhancement of the

CBCT images that we call Enhancement Pooled Filter (EPF). The algorithm works in two phases; a) smoothing the noise in the reconstructed CBCT images and b) enhancing the image contrast to delineate the different structures into the TMJ joint. We have applied the EPF over the cross sectional images from the CBCT of each patient and, then, we have compared the result with a MRI report, evaluated by an expert radiologist, from the same patient. The purpose of this study was to evaluate the impact of our technique based on CBCT images in order to provide the visualization of soft tissue in the TMJ region.

CBCT scanners are more and more available with time; due to this and to the continuous improvements in software, this technique is becoming more and more used for diagnosis. This paper is intended to examine how CBCT can be used to increase its benefits in the dental field and, particularly, in relation with inflammatory or degenerative joint diseases into the TMJ.

5.2 Materials and Methods

In this study, the participants were recruited from the Rheumatology Service of the University Hospital in Santiago de Compostela (Spain). The participants were patients affected by JIA. This group of JIA patients is being treated systemically at the Rheumatological Service and, in order to establish a care protocol, we obtained the approval of the ethical board of the institutional ethics committee of the clinical research of the Autonomous Community of Galicia before conducting this investigation (Ethics Approval Number 2012/438), to ensure our compliance with the recommendations of the Declaration of Helsinki and Tokyo for humans. Accordingly, our protocol complied with these guidelines. Moreover, we obtained written consent of the participating patients to use the data of CBCT images for this study and to evaluate their craniofacial growth. Some of these JIA patients were sent to MRI scan to evaluate the activity of the disease in the TMJ according to the protocol established by the Rheumatological Service. From this group of JIA patients who have done both CBCT and MRI images, we randomly selected four patients for TMJ evaluation, in order to compare the two imaging modalities in the dental field.

5.2.1 MRI scans

All scans were performed on the same MRI scanner, using the same surface coils and scanning protocols, and made by the same radiologist. MRI was performed using a 1.5 T MRI system (Magnetom Symphony, Maestro Class; Siemens, Erlangen, Germany) and a double-loop array of coils in a closed mouth (neutral) position for the TMJ.

The MRI scanner used in this study allows to describe and to delimitate the different anatomical parts of both TMJs (mandibular condyle and surrounding soft tissues). Images of bilateral sagittal, coronal and axial planes of the TMJs were acquired. In this study we focused only on observing the axial plane, because it is the plane that we compare with the images from the CBCT. The following sequences were used in this study: pre-contrast T1-weighted axial fast spin-echo (slice thickness of 3.0 mm; gap of 3.0 mm; repetition time (TR) of 3000 ms; echo time (TE) of 101ms) and contrast enhanced axial fat-saturated T1-weighted fast spin echo (slice thickness of 3.0 mm; slice gap of 3.0 mm; TR of 559 ms; TE of 13 ms). The post-contrast axial images were acquired within 5 min after intravenous (IV) administration of gadolinium-based contrast (Gadovist, Schering Pharma, Berlin, Germany).

The variables evaluated by the radiologist were the enhancement of the synovial membrane and the condylar morphology. The enhancement of the synovial membrane, which indicates synovitis (synovial inflammation), was defined as an increase in the signal intensity of the synovium. In order to observe this tissue enhancement after the injection of the intravenous contrast, we have compared the axial fat saturated T1-weighted post-contrast (static) MR images with the corresponding pre-contrast axial images.

In order to evaluate and compare with the CBCT images, in this study we used only the contrast enhanced axial fat-saturated T1-weighted fast spin echo.

The MR images from this study were intended to serve as an anatomical reference of the TMJ, in order to be useful in the interpretation for the CBCT images after the EPF.

5.2.2 CBCT scans

CBCT scans were made with an i-CAT® Cone Beam 3D scanner (Philadelphia-area, Pennsylvania), at 120 KVP, 5mA x-ray tube current and 4 ms of exposure time. Each case was composed of 328 images that were acquired with a field of view (FOV) of 12cm x 16cm and a slice thickness of 0.3 mm. The volume element, or voxel, has isotropic resolution, thus each slice was composed of 536x536 points, with a pixel size of 0.3mm. Axial, coronal and sagittal views were available simultaneously by software manipulation.

The TMJ was defined for this study only in the axial view. The images obtained were stored in a DICOM (Digital Imaging and Communications in Medicine) format, processed by our software and converted into a 3D virtual model for the study.

The image processing technique yields images that improve the range of use of CBCT for the analysis of the TMJ.

5.3 Results

The modus operandi consisted on the delimitation and differentiation (by means of the processed images of CBCT) of the main structures (condyle and synovial joint space) that had been observed in the MRI scan, and to determine up to which point the CBCT image is competitive with respect to the MRI one.

The images obtained after the application of our technique to CBCT data, yield an enhancement in the contrast, which improves the visualization of different anatomic structures, including the TMJ´s synovial joint space. Figure 1 shows the differences between the standard view of an axial CBCT slice (corresponding to a 16 years old girl affected by JIA in inactive phase) and the result of applying our Enhancement Pooled Filter (EPF).

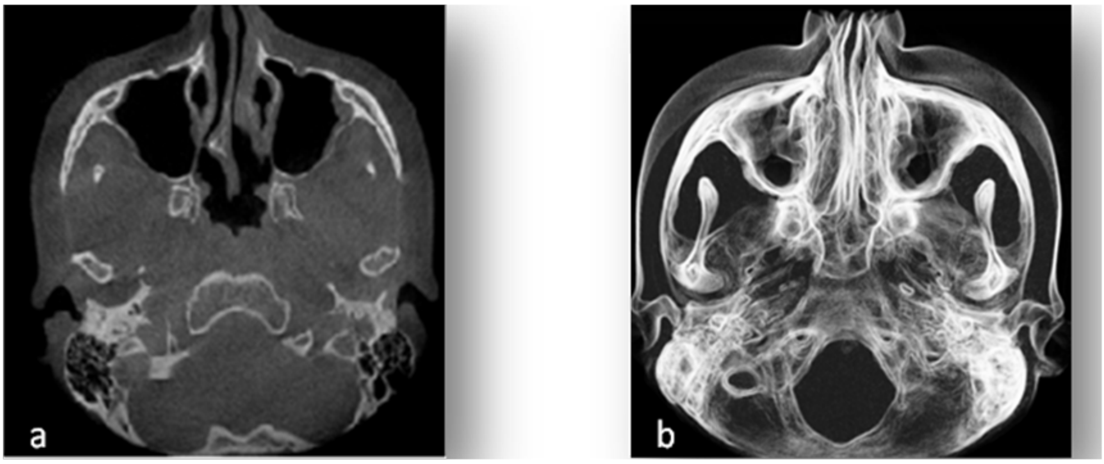


Fig.1: a) Raw data of a single CBCT slice (0.3mm). b) Image "a" processed, integrating 20 slices; this image offers more contrast and can be analyzed from a 3D point of view.

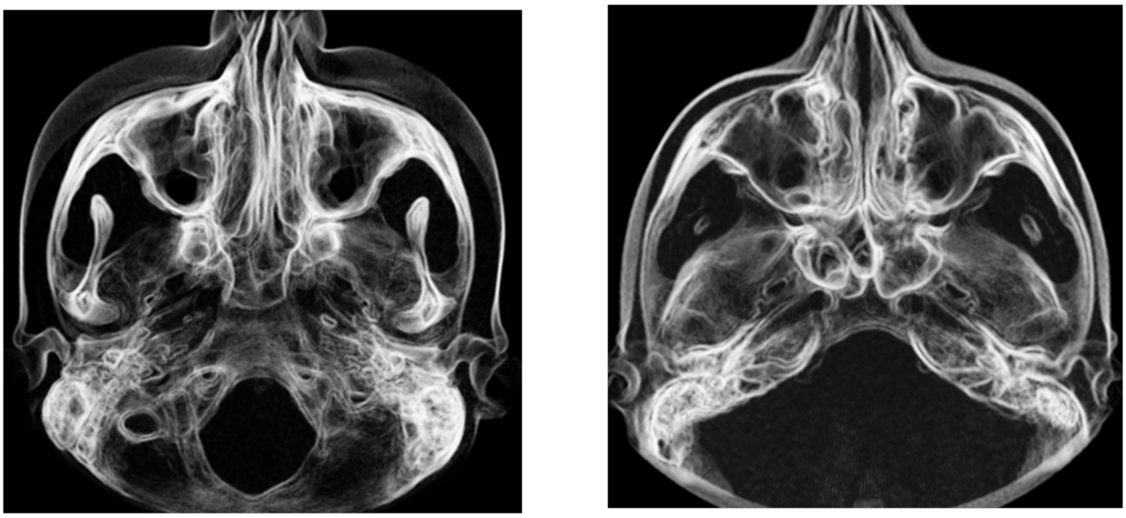


Fig.2: The application of different adjustments for the look-up table allows to visualize different anatomical structures of the region of interest: the bone condyle and the articular disk (arrowhead) after the application of the EPF to the raw data of the patient of figure 1. In panel (a) the threshold for the ranges of grey is increased to observe the bone part of the TMJ. In panel (b), however, for the same 3D object we applied the EPF with a different threshold in order to make soft tissue visible.

The use of the EPF permits to identify the articular disc, joint capsule and the condyle. Each of these tissues shows variable shades of grey; the synovial fluid is the lowest attenuating structure. In figure 2 (the same patient of figure 1) we show two different views of the same 3D object, where it is possible to observe the difference in shades of grey to emphasize the anatomical structures of the TMJ. In this figure, the application of different adjustments for the look-up table allows to visualize the high density material. In figure 2b, however, the threshold was adjusted to yield an image useful to assess soft tissues.

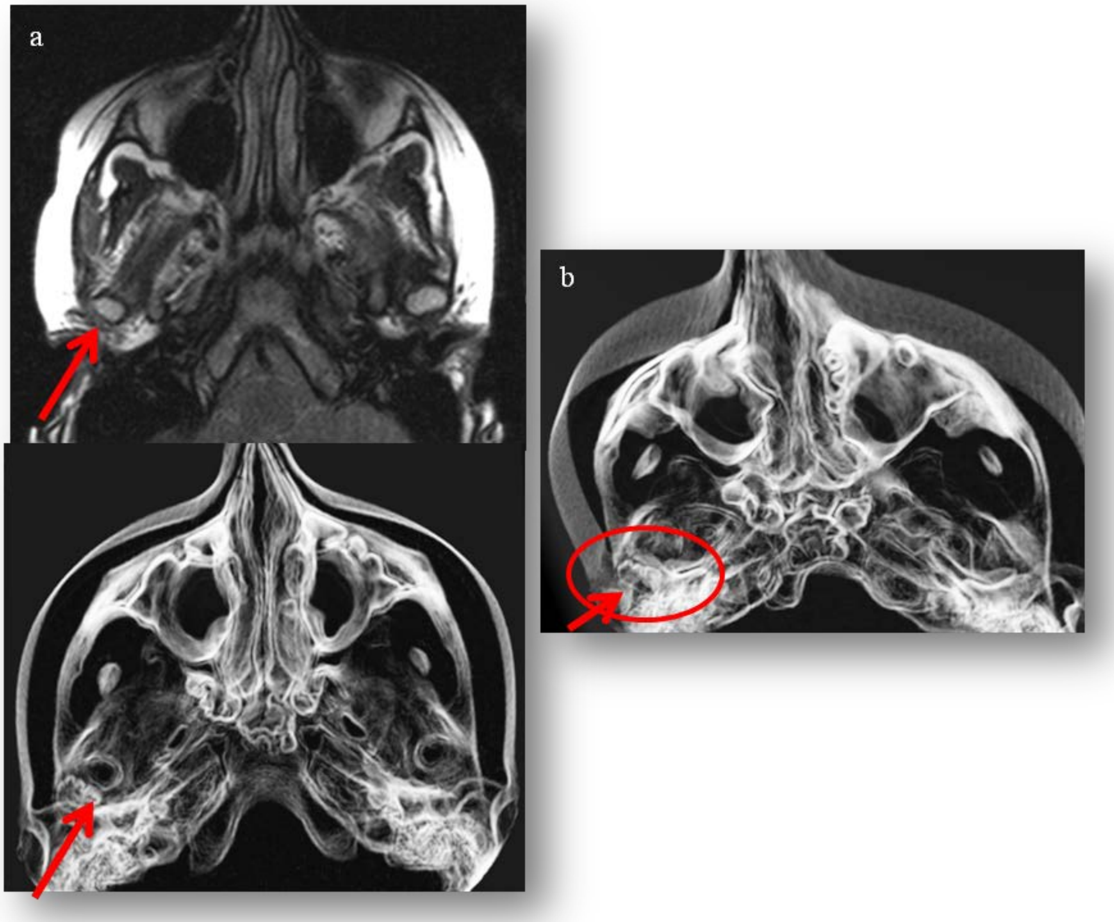


Fig.3: A 13-year-old girl with oligoarticular juvenile idiopathic arthritis without systemic treatment. a) Represented MRI and CBCT view. The axial view of the MRI image does not show thickening in the temporomandibular synovia of both temporomandibular joint (TMJ). Also, the MRI report from the specialist describes a normal condylar position, no presence of osteophytes and no signs of arthropathy. After applying our EPF, and after the generation of a 3D object, we can observe a shape in the lateral-distal part of the left condyle (arrowhead).b) This shape is also present in different views or planes of the 3D object when it is rotated for observation.

Figure 3 depicts a 13 years old girl, affected with JIA. The MRI report given by the specialist described a normal condylar position, no presence of osteophyte and no signs of arthropathy. However, with our CBCT data processing, we discovered a dense material in a lateral-distal position of the right condyle.

Moreover, this observation was confirmed by the clinical records; the patient presents limited open capacity and pain in both joints. In this case the evaluation/result of the two different imaging techniques was different.

Figure 4 represents a 3D model of the bone-skull of a 11 years old girl patient affected severely by JIA, made from the CBCT data. With it, we created a volumetric skull where it easier to appreciate an asymmetry. It was also possible to assess the differences in the condylar shape.

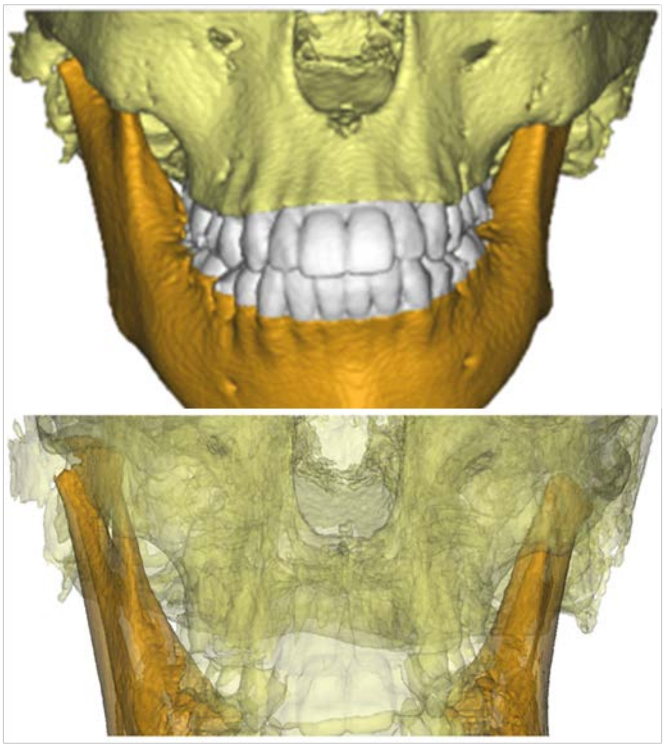


Fig.4: A 11-year-old girl with oligoarticular juvenile idiopathic arthritis and under systemic treatment. This patient is still in the active phase. The 3D rendering of the CBCT data shows a notorious face asymmetry: the left side of the patient is smaller.

In figure 5 (corresponding to the same patient as in figure 4), and according to the report of the radiologist (based on MRI images), synovial enhancement is seen on postcontrast images in both TMJs, and, more remarkably, in the left joint. Both condyles are smooth and rounded in shape, being smaller the left one. Once again, we applied our EPF to the CBCT data, and we have found, in the region of interest (ROI), similarities with the MRI data in this specific patient.

The most remarkable point is that we found the volume of synovial joint space was twice as big as in the left TMJ.

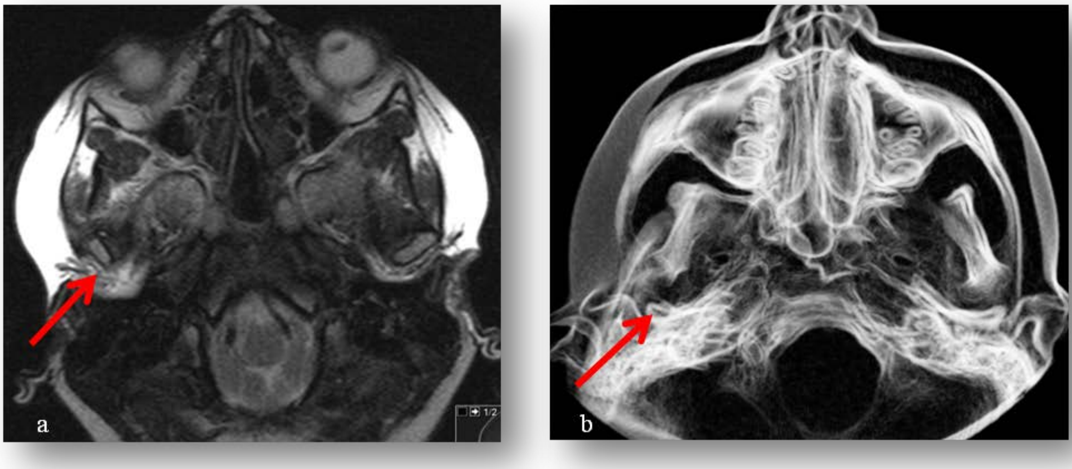


Fig.5: MRI and CBCT from a patient of figure 4. a) It is seen that the left condyle is smaller in the latero-medial direction. In a close mouth position it is not possible to observe the disk position in this left condyle. The condyle is normal in the right joint. Note the presence of synovial enhancement on the corresponding axial fat-saturated postgadolinium T1-weighted image of both TMJ, but remarkable in the left one. b) CBCT view.

Fig.6: A 10-year-old girl with oligoarticular juvenile idiopathic arthritis without systemic treatment. This patient is in inactive phase. According to the report from the MRI specialist, both TMJs are similar, affected with anterior disc displacement in closed month. a) Note the presence of synovial enhancement in the corresponding axial fat-saturated postgadolinium T1-weighted image of both TMJ. It is also seen a slight irregularity in the condylar shape. b) CBCT view after the application of our EPF. The arrow describes the same anatomical position in both images.

Figure 6 represents MRI and CBCT images from a fourth JIA patient (girl, 10 years old) where similarities between both images and the report from the specialist were also found. Figure 7 describes the CBCT images of the same patient from figure 6 in detail. As it is a 3D object, we are able to rotate the figure and observe the anatomic parts of the TMJ from different planes.

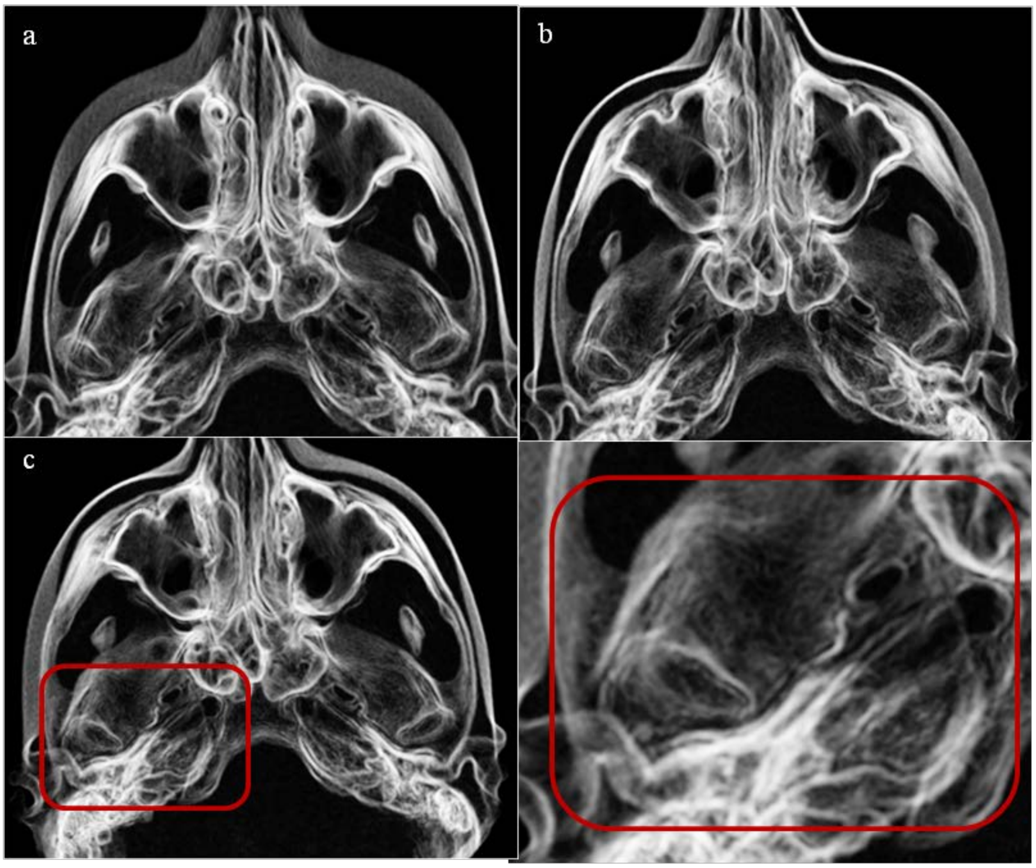


Fig.7: Analysis of the CBCT data after applying our EPF, in the same patient of figure 6. As it is a 3D object, we are able to rotate the figure to observe, from different planes, the anatomic parts of the TMJ. Therefore it is also possible to observe the articular disk (arrowhead) and its differences in a, b and c. Once we are satisfied with the result of the image, we select that area and we zoom on it to obtain an intensified view, as in panel (c).

5.4 Discussion

In medical imaging, the quality of the image must be adequate for the diagnosis of lesions. An adequate imaging quality should show a good compromise between contrast-to-noise ratio performance and soft-tissue discrimination. Also, the interpretation of the radiograph is dependent on the clinicians' appreciation of the limitations of conventional radiography as well as their knowledge and experience in assessing these two-dimensional shadowgraphs.
What determines the contrast in a radiograph of the human body is, of course, the difference of the types of tissue found in the body region being imaged (in this study we focus on the TMJ). The identification of the edges of low contrast structures is one of the most common tasks performed by those interpreting medical images.

In this paper we show that the visualization of the different structures from the synovial joint space within the TMJ, using a CBCT, should be also possible, despite the limited contrast resolution of CBCT for soft tissues. Starting from the point that CBCT is the chosen modality to assess bone tissue (20)(21)(22) and MRI the one to assess soft tissues (23)(24)(25), our observations indicate that our technique achieves images with a good anatomical resolution, high contrast between different structures, and excellent tissue-like differentiation as the MRI images.

In this pilot study, we have compared two different imaging modalities in terms of the quality of the image and its availability for clinical diagnosis of TMD problems: CBCT versus the assumed gold standard contrast-enhanced MRI for the diagnosis of TMJ arthritis and possible TMD in a group of JIA patients. We aim to describe the global anatomy of the TMJ from CBCT data after the application of our EPF, and to compare it with the anatomy obtained by MRI images.

The CBCT has a well-known superior spatial resolution, however, its inferior soft tissue contrast (26)(27) might limit the observable differences between non-calcified tissues, such as tendons, ligaments, adipose tissue, and cartilage. The aim of this study was not to differentiate between the non-calcified tissues, but to improve the use of a CBCT test as global visualization tool. Here we are able to visualize bone and, after the EPF processing, also to differentiate it from the soft tissues structures within the synovial space of the TMJ. Therefore, we should be able to use the same imaging technique to assess a global pathological state of the TMJ. After the enhancement contrast we improve the imaging capability for visualizing bone and the articular disk. Until now, MRI is the selected imaging technique to assess articular disk in TMJ (28)(29)(30).

To the best of our knowledge, no study has been published yet on the evaluation of CBCT images for assessment and visualization of the TMJ as a whole. However, research in medical imaging is moving into this field. In this context, a recently published paper (31) evaluates the visualization, by CBCT, of the soft tissues of a musculoskeletal extremity. The authors conclude that CBCT proved excellent image quality for bone visualization and adequate image quality for soft tissue visualization tasks.
On normal CBCT images, the condyle shape and its spatial position can be seen together with the adjacent structures (as shown in figure 1). In typical CBCT axial slices, the thinner areas will be less radiolucent (leading to areas with darker grey level values on image) than the thicker areas of similar tissue. Besides this, for regions with a higher proportion of calcium, like the cortical bone, an equal thickness of soft tissue will appear far more radiodense. In addition, it is also possible to rotate on the CBCT data the computer-generated 3D ROI to improve the assessment of some pathological structures. In figure 2, the EPF also provides the visualization of more than one picture from the same data of a given area, by modifying the window/level parameters. We could focus first, for example, only on soft tissues. This would give a lower degree of information about the bone, but, after this, we could change the window/level to generate another image to have a better contrast for the bone (figure 2). Each of these soft tissues showed variable shades of grey.

In general, for any imaging technique, low spatial resolution will give either blurred edges or a grainy appearance to the image: this is the common effect that we have found in the MRI images of this study. With computer enhancement features applied to the CBCT data, it is possible to magnify areas of interest and to readjust the gray scale and image contrast to enhance areas such as the ones mainly composed of soft tissue. Our hypothesis is that, after the application of our EPF to the CBCT data set, we should have an image with information enough for the diagnosis of a TMD, with a quality similar to that obtained by MRI. Moreover, the 3D approach (which adds the possibility of rotation of the image on a computer screen) seems to be providing certain new advantages, as proved in the case of figure 3: in this patient, our CBCT approach allowed us to discover features than matched with the clinical records. Such features could not have been discovered from the MRI report.

After applying the EPF algorithm over the cross-sectional slices of the CBCT from these JIA patients, we observe new interesting features. However, we are mindful that there are important variables playing on an accurate evaluation of the images. One of these variables is the slice thickness. We are aware that we have compared a simple MRI slice cut (3.0 mm of thickness in MRI) with a 3D CBCT object. From this 3D object we obtain several slices (0.3 mm of thickness for each cut in CBCT), that are then evaluated to generate an image corresponding to a thickness similar to the equivalent MRI slice. This means that the CBCT 2D image is a composition of around 25-30 slices of the CBCT 3D object.

From a clinical point of view, we aim to obtain the best possible image, with the highest degree of information. This adds and extra motivation for clinicians: with this tool, they could be in condition of making their own initial evaluations of the pathology, in order to assess whether to refer or not their patients to an specialist.

Also it is important to point out that there is a remarkable difference between the two modalities in the technique employed for improving the contrast of the image. In MRI pictures, in order to enhance the contrast of the images obtained, a contrast agent is usually needed: this is not the case for the presented CBCT-based technique, where the contrast is obtained by software (the EPF process).

The market for CBCT scanners will determine how quickly the translation of new technology into clinical practice will take place. The shorter acquisition image times, the higher partial resolution, and the lower costs and accessibility of CBCT over MRI, gives an input to the dental market. This new technique could provide an alternative for a more complete diagnostics of TMJ pathologies with only one imaging modality.

5.5 Conclusion

Cone-beam computed tomography is a new diagnostic tool that has revolutionized diagnosis and treatment planning in the dental field. An understanding of the underlying principles will allow the users of this technology to tailor the imaging protocol to the patient's individual needs to achieve appropriate imaging at the lowest radiation dose.

JIA is a childhood disease and it is important to detect the disease as soon as possible to avoid facial growth complications. Magnetic resonance imaging (MRI) is the most reliable examination method for early TMJ arthritis, but it has some disadvantages, among which is its low availability in daily clinical practice. This is not the case of CBCT, which is the imaging modality generally available in dental clinical practice.

We have presented a new approach for the generation of 3D medical images by CBCT, with a tool to enhance the contrast that could provide new information about the patient. The capabilities of CBCT are thus improved, together with an increase of the clinical value of the test. Besides scientific considerations, this opens the possibility of making a screening diagnosis of this disease before sending the patient to another imaging test. However further studies must be done about the parameters that affect image quality, in order to establish a gradient of observation to display the various anatomical parts of the TMJ in a CBCT data.

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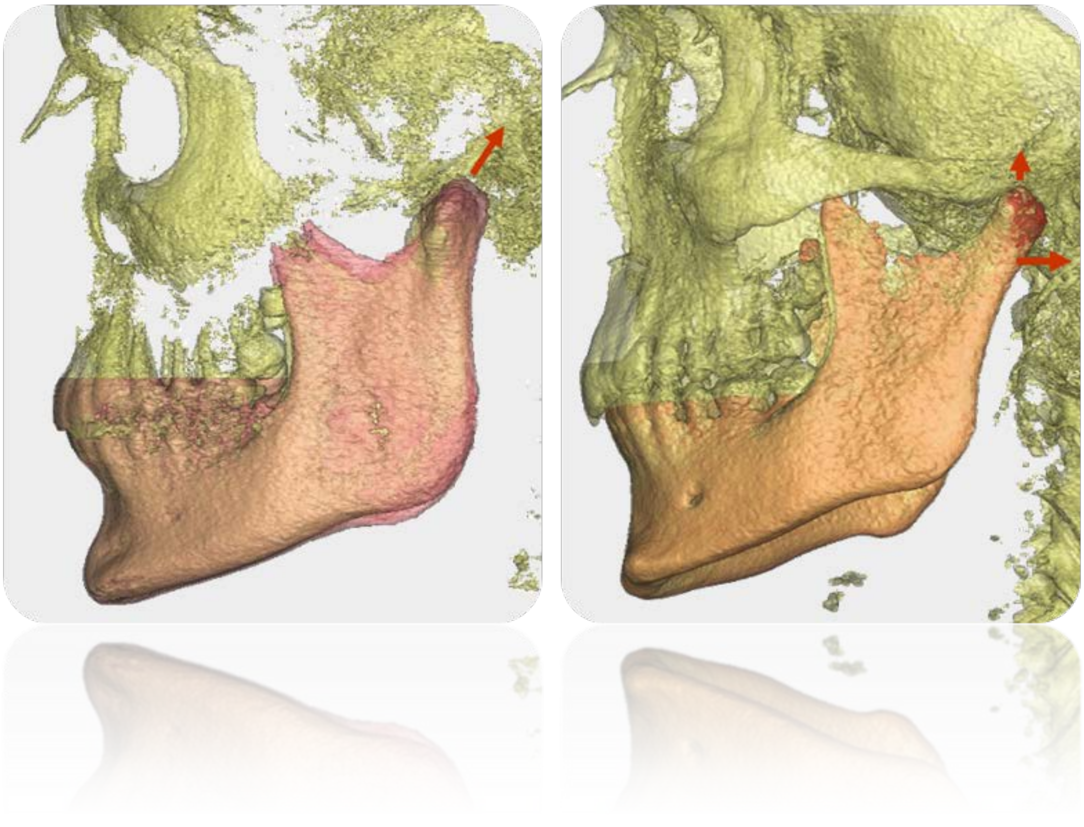
Chapter VI: Conclusions



This Ph. D. Thesis addresses, for the first time in Spain, the problem of the involvement of the Temporomandibular Joint (TMJ) in patients affected by Juvenile Idiopathic Arthritis (JIA).

JIA belongs to a group of systemic inflammatory diseases which results in the destruction of the hard and soft tissues in one or more joints. In a significant number of patients, one or even both temporomandibular joints may also be involved. The importance of this disease is its chronicity in children.

This Thesis has used the image to observe and measure changes over time in a specific joint (TMJ), affected by arthritis.

The main contributions and conclusions of this study regarding this process are described:

1. *To observe, and simultaneously certify, in an isolated three-dimensional object from the rest of the skull, the degree of arthritis present in the TMJ and the mandible of children affected by JIA.*

We have used advances in imaging reconstruction of articular tissues. New metrics, that define the structural and spatial changes in the mandibles of patients with JIA, have been incorporated. To analyze and monitor the changes, we have isolated the area of interest (the mandible) from the rest of the skull through a process of manual segmentation.

To perform the segmentation process and to differentiate between soft tissue and bone, a value between 500 and 700 Hounsfield Units (HU) was set. This results in a copy of the jaw that contains the number of pixels which represent the bone. Due to this three-dimensional model, it has been perfectly observed any degree of erosion in the condylar morphology and also a possible alteration of the mandible at real scale. Therefore, this three-dimensional object could also be used to compare the differences (condyle and mandible) among patients with JIA and the differences between healthy patients and patients with JIA.

2. The use of three-dimensional image for the metric analysis of the mandibular condyle in patients with JIA. This has provided quantitative data on the adaptation of the condyle in an evolutionary process of the disease.

The methodology designed in this work, in order to make the overlap of the three-dimensional objects of the jaws obtained after the segmentation process, has allowed us to measure the differences, over time, between the jaws belonging to the same patient. Anatomical structures on the mandible were selected as reference points and, from specifically designed planes, we measured the distance to the anatomical reference points of the jaw.

The results of these measurements indicated that the value of the vertical displacement (VD in the acronym used in this thesis) was significantly smaller in the group with AIJ and, although with some variability, in both TMJs. We can say that in the children affected by JIA the condyle has less activity growth in the vertical direction than in healthy children.

Another interesting finding of the study is that the length values of the mandibular ramus (RL its acronym in English) are significantly smaller in patients affected by JIA and TMJ arthritis. However, in patients affected by JIA, but on the side of the TMJ without arthritis, the value of RL is similar to the value of RL in healthy children. These data can reinforce the use of a bite splint (or splint distraction, DS) and orthopedic treatment in children affected by JIA.

3. We have calculated, with the overlapping of three-dimensional structures, the direction of growth in the jaw of patients affected by JIA (within these, on the side affected by arthritis and on the unaffected one).

By having a control group, it has been possible to perform the same overlapping process and compare the differences in mandibular growth between JIA patients and healthy patients over a period of 2 years. This analysis indicates that, to the TMJ level, the condylar growth is quite different between the two groups of children. In the children affected by JIA, the vector of growth is much smaller than the vector in the group of healthy children. Also, the direction of this vector is different in both groups: the control group shows a significant increase in vertical growth to the condylar level, on the contrary the study group shows smaller vertical growth.

With these results, we provide a tool for medical decisions regarding the management of this disease, for example in relation to the treatment. Based on the fact that inflammation is reduced with the appropriate drugs, our results suggest that, in patients with JIA, a functional treatment (orthopedic) allows condylar remodelling; although the response to the treatment, in relation to this value, is characterized by great individual variability. Therefore, this functional therapy appliance, DS, is considered an effective tool for treating patients affected by JIA and arthritis in the TMJ, especially in patients unilaterally affected.

It is also possible the use of this analysis as an observational and analytical test in any type of treatment, both from the orthopedic and systemic point of view. Related to this point, we have included in this Thesis the Annex IV, where it can be seen the differences between some of the patients studied in this Thesis and affected by JIA. It is a small sample, and we have not been able to make correlations between different variables, but it is still possible to detect the visual differences between them. This introduces the need for further clinical studies to assess the effects on the TMJ of the different systemic treatments used in JIA.

4. Measurement of the volume of the joint space into the TMJ. This part allows, apart from the morphometric analysis of the mandible, a volumetric analysis of the TMJ on CBCT images.

Concerning the joint space, and during the review of the different techniques published on image segmentation and volumetric measurements, we have found that this technique had not been applied so far in the joint space. As far as we know, this is done for the first time in this Ph. Thesis.

There are cases where the volume of the synovial space in affected joints of arthritis patients was calculated, but, to date, no attempt has been made to estimate the whole volume of the joint space in the TMJ.

Our volumetric analysis of the joint space (of the TMJ) showed significant differences between the volume found in patients with JIA and the volume found in healthy patients, being almost double in patients affected by arthritis in the TMJ.

Following this idea we calculated and established a boundary threshold of disease. It was intended to obtain a numerical value that, through the volume, could define an inflammatory state (therefore ill), or a healthy state of the TMJ in children affected by JIA.

5. Analysis of the different properties of the imaging techniques used to date for the analysis of TMJ affected by JIA, in order to improve the quality of such techniques for better use in diagnosis and disease control.

In this Thesis we have presented a new approach to generate medical imaging in 3D view and using a CBCT. We have processed the original image from the CBCT with a tool that enhances the contrast; this allows enhancing the edges of the different structures in the TMJ. With this process, the capabilities of CBCT are improved and also provide a test with a clinical value, by providing new information about the patient.

In addition to the possible scientific contributions, this process can help on the early detection of the disease and also reduces the risk of overlapping several diagnostic tests. However, further studies must be done about the parameters that affect the quality of the image, in order to establish a gradient of observation to display the various anatomical parts of the TMJ in images from a CBCT.

Capítulo VII: Resumen de esta tesis

7.1 Introducción

Esta tesis pretende fomentar lo que es, por su propia naturaleza, un trabajo multidisciplinar y colaborativo. Si bien no pretende ser la revisión más exhaustiva de todo el trabajo realizado hasta la fecha, se trata de un esfuerzo consciente para fomentar la colaboración multidisciplinar, proporcionando una fuente de material de referencia accesible a los campos interesados; los clínicos para saber que pueden obtener de la imagen y los físicos para saber que necesitan los clínicos.

Después de mi experiencia trabajando en la Universidad de Aarhus (Dinamarca) con pacientes con Artritis Idiopática Juvenil (AIJ) surgió la idea, al regresar a España, de instaurar prácticas clínicas relacionadas con el diagnóstico y tratamiento del daño causado por esta enfermedad en la Articulación Temporomandibular (ATM). En un ámbito universitario donde la curiosidad y aprendizaje son los pilares de trabajos como este, se dieron las condiciones necesarias para crear esta tesis.

Un ortodoncista con conocimientos de la AIJ se encuentra con reumatólogos interesados en colaborar y poner en práctica un ejercicio clínico más amplio en beneficio del paciente. La idea es observar y evaluar el posible daño en la ATM de los pacientes gallegos con AIJ. Acostumbrados los clínicos a necesidades de respuesta para confirmar diagnósticos o iniciar tratamiento, nos gusta apoyarnos en equipos multidisciplinares y es, en este punto, donde necesitamos a los físicos que son los especialistas en el engranaje de pruebas de imagen médica.

El diagnóstico de las alteraciones que afectan a la articulación temporomandibular debe basarse en la información obtenida a través de la anamnesis médica y de la exploración física. Si bien todo lo anterior es imprescindible en muchas ocasiones debemos apoyarnos en las diferentes técnicas de diagnóstico por la imagen para poder etiquetar el cuadro clínico que aqueja al paciente.

En el presente trabajo revisamos y actualizamos los conceptos referentes al diagnóstico por la imagen de los trastornos que afectan a esta articulación. Principalmente nos centramos en la afectación de la ATM de niños con AIJ para intentar descubrir el daño lo antes posible y evitar así futuras lesiones, como erosiones del cóndilo o alteraciones en el crecimiento facial. También estamos interesados en saber cómo afecta la artritis al hueso condilar y a la mandíbula. Para realizar estos análisis y medir los cambios producidos por un determinado tratamiento o bien por la enfermedad en sí, necesitamos usar la imagen médica.

Las técnicas radiográficas clásicas se ven dificultadas por las características anatómicas de la zona y en la actualidad se está utilizando la Resonancia Magnética, (RM) y el Cone-Beam Computed Tomography (CBCT) escáner para la realización de pruebas de este tipo. La investigación presente y futura se está centrando en las propiedades tanto de hardware como de software de estas técnicas de imagen para su mejora.

La presente memoria contiene 8 capítulos. El primero es una introducción al estudio de la enfermedad, así como de las propiedades de las diferentes técnicas de imagen utilizadas durante años en este campo y en particular en esta área anatómica.

En el segundo se recoge un análisis del problema, se hace una valoración del estado de la AIJ y del manejo de la misma por los servicios sanitarios. Después de la evaluación del problema presentamos también en este capítulo los principales objetivos que pretendemos abordar con esta investigación. En los capítulos 3-5 se presentan los resultados de este estudio.

El capítulo 3 está dedicado al estudio del crecimiento de la mandíbula en niños diagnosticados de AIJ. Medimos los cambios del crecimiento tanto en la zona articular como mandibular. Se describe la metodología diseñada en esta tesis para realizar esta medición. También se presenta una comparación del crecimiento de la zona a estudiar con el crecimiento de un grupo control sano. Además del estudio del crecimiento mandibular en los pacientes con AIJ nos interesa tratar esta desviación de crecimiento, por eso, en este mismo apartado evaluamos además un aparato funcional bucal, llamado Distraction Splint (DS). Dentro de este estudio hemos podido comparar los cambios producidos en la ATM durante dos años en pacientes con AIJ y pacientes sanos. Se divide la muestra en tres subgrupos (ATM sana, ATM con artritis y ATM sin artritis).

En el capítulo 4 se presenta un estudio donde intentamos analizar el grado de inflamación de la ATM en un grupo de niños con AIJ. Calculamos el volumen del área correspondiente a la sinovial de la ATM de los pacientes con AIJ. Hacemos el mismo cálculo en un grupo control de pacientes sanos. Describimos también la metodología que hemos diseñado para el cálculo volumétrico y lo comparamos con el grupo control. La idea es encontrar un intervalo numérico que nos marque un umbral diferenciador entre un estado enfermo y un estado sano. Pretendemos diagnosticar lo antes posible una afectación de la ATM por la AIJ para evitar futuros daños.

El capítulo 5 está dedicado al estudio de las propiedades de la imagen. Intentamos reforzar con este trabajo la utilidad de la imagen como prueba diferenciadora para el diagnóstico de la AIJ. Analizamos y discutimos las propiedades de dos técnicas de imagen que se están utilizando para el análisis de la AIJ en la ATM. Estas técnicas son la RM y el CBCT. En este capítulo realizamos una interpretación cualitativa de ambas técnicas para la exanimación de los diversos daños que se pueden encontrar en la ATM. Cómo se puede mejorar la calidad de imagen y cómo se puede ampliar su rango de acción. Comparamos las dos técnicas en el mismo grupo de pacientes con AIJ y discutimos las diferencias encontradas en este trabajo entre las dos técnicas.

En el capítulo 6 se reúnen las conclusiones de esta tesis doctoral y, en los capítulos 8 y 9 se propone un protocolo clínico de observación de esta enfermedad en España (dadas las carencias asistenciales que se han detectado), así como una propuesta de aplicabilidad de este trabajo para el territorio español. Por razones obvias, estos capítulos se redactan en castellano.

En el anexo I se incluye más información sobre la calidad de la imagen médica y los factores que afectan a dicha imagen. En el anexo II se recoge el protocolo Europeo existente en este momento para el manejo clínico de los pacientes con AIJ en relación a la ATM. En el anexo III se presenta una breve descripción de las técnicas empleadas en este trabajo. Finalmente, en el anexo IV se ilustran unas figuras pertenecientes a algunos pacientes con AIJ de la muestra danesa para poder observar los cambios en crecimiento mandibular durante un período de dos años.

7.2 La situación en el sistema sanitario español

La artritis idiopática juvenil es la enfermedad reumática inflamatoria más común de la infancia. En España, entre 8.000 y 10.000 niños padecen alguna enfermedad reumatológica. Entre ellas destaca la artritis idiopática juvenil (AIJ), que supone el 75% de las consultas de reumatología pediátrica y de la que, anualmente, se diagnostican entre 80-90 casos nuevos.

La afectación de la articulación temporomandibular se ha descrito hasta en un 87% de los niños con artritis idiopática juvenil cuando se basa en la tomografía magnética; que puede ser asintomática y puede conducir a complicaciones graves a largo plazo.

En estos últimos años se ha avanzado en el conocimiento de la AIJ, tanto en los criterios de clasificación, mejoría, remisión y enfermedad inactiva como en herramientas para medir la actividad y la calidad de vida. La realización de una anamnesis detallada y una exploración física completa, (donde se debería incluir la ATM) son fundamentales para orientar el diagnóstico de estas enfermedades. Las pruebas complementarias, como la imagen, pueden ayudar a confirmar la enfermedad sospechada o a descartar otras patologías incluidas en el diagnóstico diferencial al tener las enfermedades reumáticas una variable forma de presentación. Incluso una decisión terapéutica depende de la sensibilidad de la prueba de imagen en detectar la inflamación.

Durante la realización de esta tesis se ha observado la ausencia de una metodología observacional de la ATM, (en la anamnesis y exploración física de los pacientes con AIJ la ATM no está siendo examinada). Se hace pues interesante llamar la atención sobre la infravaloración de esta articulación, en los niños con AIJ, por los sistemas sanitarios.

En España la Reumatología Pediátrica inicia su andadura como especialidad en los años 70. En el año 1992 se crea el examen de certificación en Reumatología Pediátrica por la Academia Americana de Pediatría. Por lo que respecta a España, el año 1991 se crea en Palma de Mallorca, bajo los auspicios de la Asociación Española de Pediatría (AEP), el Grupo de Trabajo en Reumatología Pediátrica, realizándose en esos primeros años varias Jornadas de actualización en temas de interés reumatológico. En 1996 este Grupo se formalizó como Sección de Reumatología Pediátrica dentro del seno de la AEP. El año 1998 se firma el acta fundacional como Sociedad Española de Reumatología Pediátrica (SERPE).

El objetivo de estas sociedades médicas es dar a conocer las novedades en el abordaje de las enfermedades reumáticas en la infancia, así como lograr un espacio de reunión donde diferentes especialistas en esta área pueden discutir y valorar proyectos en marcha e iniciar otros nuevos. En definitiva, este espacio de reunión lo que persigue es, principalmente, concienciar a la sociedad médica, a las Administraciones y a las Unidades especializadas en este tipo de enfermedades.

Son estas Sociedades las que trabajan en la realización de protocolos e indicaciones que servirán para la mejora de la calidad de vida de la población pediátrica con AIJ y además permitirán una mayor homogeneidad en el seguimiento de todos los pacientes por parte de los reumatólogos, pediatras y otros especialistas involucrados en esta enfermedad como por ejemplo los ortodoncistas.

Pese al buen trabajo de los servicios médicos y asociaciones de reumatología en estos últimos años, en España no existe a día de hoy un protocolo de valoración clínica de la ATM en pacientes con AIJ. Quizás la ausencia de este protocolo de actuación pueda ser debido a que no existe un grado de transversalidad suficiente entre las diferentes especialidades médicas implicadas y los ortodoncistas, como sucede por ejemplo en otros países. También se ha observado durante el desarrollo de esta tesis el desconocimiento de esta problemática por parte de la mayoría de los ortodoncistas y odontólogos de nuestro país. Creemos que la atención a las afectaciones de la ATM en pacientes con AIJ está siendo infravalorada por los diferentes especialistas a la hora de realizar el análisis clínico.

Como primera aproximación a la solución de este déficit, una idea plausible sería la adopción de los esquemas al uso en aquellos países europeos que han abordado ya este problema en sus sistemas de salud. Así, por ejemplo, en Dinamarca, en el ámbito de la salud bucodental, las unidades de atención de ortodoncia se encuentran dentro de los recintos hospitalarios universitarios. De este modo, cada niño con AIJ que llega al servicio de reumatología pediátrica es enviado directamente al ortodoncista para una evaluación de la ATM.

No vamos a comparar los diferentes sistemas de salud europeos, solamente pretendemos con este trabajo notificar la falta y por lo tanto la necesidad de una atención integral de los niños afectados por artritis para evitar posibles alteraciones en el crecimiento facial, causadas por esta enfermedad. Si conseguimos comunicar esta deficiencia a la población afectada y a los diversos profesionales involucrados podría resultar en la creación de espacios multidisciplinares de trabajo, lo que se traduciría en una mejora en el servicio y por lo tanto en la calidad de vida de estos pacientes.

Los objetivos de una labor conjunta de los diferentes profesionales sanitarios, tanto públicos como privados o asociaciones, relacionados con AIJ deben alinearse para conseguir:

1. *Un mejor y más rápido diagnóstico*: El diagnóstico de las enfermedades reumáticas en los niños es complejo y requiere de una formación especializada.

2. *Una mejor atención:* La aproximación multidisciplinar al manejo de las enfermedades crónicas reumatológicas permite una mejora en la calidad de vida del paciente (rehabilitación, hospitales de día, pruebas de imagen, radiólogos, ortopedas, ortodoncistas, maxilofaciales, etc.)

3. *La participación en estudios colaborativos internacionales:* Única forma de mejorar en el diagnóstico, tratamiento y seguimiento de estos pacientes con patologías poco frecuentes.

7.3 Objetivos

7.3.1 Objetivo principal

El objetivo principal del presente trabajo de investigación es observar y confirmar, a través de la intervención por imagen, el grado de artritis presente en la ATM, el grado de afectación ósea y también el grado de alteración en el crecimiento mandibular de los pacientes diagnosticados de AIJ.

Con este fin, se plantearon los siguientes pasos:

1. Evaluar la intervención por imagen en la detección del grado de afectación de la ATM en un grupo de niños con AIJ. Utilizar la imagen tridimensional para cuantificar los cambios inflamatorios así como de crecimiento mandibular producidos por la enfermedad, y evaluar el tratamiento ortopédico mandibular diseñado por el departamento de Ortodoncia de la Universidad de Aarhus.

2. Observar y cuantificar de forma aislada el espacio articular, con el objetivo de obtener un número o marca para diferenciar estado sano de estado patológico. Para ello se plantea la necesidad de hacer un diagnóstico precoz de la AIJ para evitar las lesiones en alteración de crecimiento facial. Para la realización de este estudio se utilizarán técnicas de cuantificación de imagen.

3. Estudiar las propiedades de la imagen como arma analítica para un diagnóstico temprano del daño articular. Para ello se desarrollarán nuevos algoritmos de visualización de la imagen. Además se valorará la necesidad de instaurar nuevos protocolos de imagen y consensos para una mejor utilización de los medios existentes, evitando el solapamiento de pruebas de imagen.

7.3.2 Objetivos secundarios

En el transcurso del trabajo de esta tesis doctoral se han percibido carencias sistémicas a nivel de organización del sistema sanitario español. Por lo tanto, se ha considerado pertinente añadir los siguientes objetivos secundarios:

1. Proponer un protocolo clínico observacional de la afectación de la ATM para prevenir secuelas funcionales secundarias de una enfermedad crónica inadecuadamente controlada a nivel de desarrollo facial.
2. Proponer indicaciones o pautas de tratamiento para los pacientes afectados con artritis en la ATM, siguiendo los sistemas protocolarios establecidos en otros países europeos.

7.4 Resultados

En esta tesis se ha abordado, por primera vez en España, el problema de la afectación de la Articulación Temporomandibular (ATM) en pacientes con Artritis Idiopática Juvenil (AIJ).

Sabemos que la AIJ pertenece a un grupo de enfermedades inflamatorias sistémicas que resultan en la destrucción de los tejidos duros y blandos en una o varias articulaciones. En un número significativo de pacientes, una o incluso las dos articulaciones temporomandibulares pueden estar también involucradas. La importancia de esta enfermedad es su cronicidad en la población infantil. La patología presente en la ATM puede estar acompañada de dolor, hinchazón y limitación de la movilidad, así como retrognatismo mandibular, mordida abierta y asimetría. Por lo tanto, se hace importante el análisis y estudio de los síntomas de la AIJ en la ATM para evitar el dolor y los futuros daños en la estructura facial de estos pacientes.

En esta tesis se ha usado la imagen para observar y medir los cambios en el tiempo en una articulación afectada por la artritis.

A continuación se describen las principales aportaciones y conclusiones de este estudio en relación a este proceso:

1. A la hora de realizar la observación de la lesión, el uso de las nuevas tecnologías nos proporciona un efecto visual muy agradecido por el clínico para poder certificar el grado de dicha lesión presente en el área de estudio.

La ATM es una articulación de difícil acceso: en las otras articulaciones del cuerpo, las técnicas basadas en ultrasonidos son apropiadas para el uso clínico diario por el reumatólogo para la confirmación de inflamación; pero, en el caso de la ATM, la ecografía no se considera válida. Hasta la fecha, la Resonancia Magnética es la técnica más apropiada para la observación y detección de la inflamación en la ATM de los pacientes afectados con AIJ.

Aprovechando la disponibilidad y accesibilidad de la técnica de Cone-Beam Computed Tomography en odontología, se ha aprovechado esta ventaja para realizar este trabajo. En esta tesis se han utilizado avances en la generación de imágenes de tejidos articulares, con la incorporación de nuevas métricas que definen los cambios estructurales y espaciales en las mandíbulas de pacientes afectados con AIJ. Para analizar y observar los cambios producidos, se ha aislado el área de estudio del resto del cráneo mediante un proceso de segmentación manual.

Para realizar la segmentación y separación entre el tejido blando y el hueso se ha establecido un valor entre 500 y 700 unidades Hounsfield (HU). Esto resulta en una copia de la mandíbula que contiene los píxeles que representan solamente el hueso. De esta copia se generó el objeto tridimensional de las mandíbulas de estos pacientes. Gracias a este modelo tridimensional, se ha podido observar perfectamente cualquier grado de erosión en la morfología condilar y una posible alteración mandibular en una escala real. Por lo tanto, también se ha podido usar este objeto para comparar las diferencias (de cóndilo y mandíbula) entre pacientes con AIJ y las diferencias encontradas entre pacientes sanos y pacientes con AIJ.

2. Otra parte de esta investigación se ha centrado en el uso de la imagen tridimensional para el análisis métrico del cóndilo mandibular en pacientes afectados por la AIJ. Esto ha proporcionado datos cuantitativos sobre la adaptación del cóndilo en un proceso evolutivo de la enfermedad.

La metodología diseñada en este trabajo para poder realizar la superposición de los dos objetos tridimensionales de las mandíbulas obtenidas tras el proceso de segmentación nos ha permitido medir las diferencias, con el paso del tiempo, entre las mandíbulas pertenecientes al mismo paciente. Con los diferentes planos establecidos se han podido realizar mediciones, desde dichos planos medimos la distancia a puntos anatómicos mandibulares de referencia.

Este cálculo de las distancias indicó que el valor del desplazamiento vertical (VD en sus siglas inglesas usadas en esta tesis) fue significantemente más pequeño en el grupo con AIJ y, aunque con alguna variabilidad, en ambas ATMs. Es decir, en los niños con AIJ el cóndilo tiene menos actividad de crecimiento en sentido vertical que en los niños sanos.

Otro dato interesante del estudio es la obtención de los valores de la longitud de la rama mandibular (RL en sus siglas en inglés), siendo significantemente más pequeño en los pacientes con AIJ y en la ATM con artritis. Sin embargo, en los pacientes con AIJ, pero en el lado de la ATM sin artritis, el valor de RL es similar al valor del RL en los niños sanos. Este dato puede reforzar el uso de una férula de descarga (o distraction splint, DS) como tratamiento ortopédico en los niños con AIJ.

Con la superposición de ambas estructuras tridimensionales se calculó también la dirección del crecimiento de la mandíbula en los pacientes con AIJ (dentro de estos, en el lado afectado por la artritis y en el no afectado). Al disponer de un grupo control se ha podido realizar el mismo proceso, comparando así la diferencia en crecimiento mandibular entre los pacientes con AIJ y los pacientes sanos en un período de 2 años. Este análisis indicó que a nivel de la ATM, el crecimiento condilar es bastante diferente entre los dos grupos de niños. En los niños afectados de AIJ, el vector de crecimiento es mucho más pequeño que el vector en el grupo de los niños sanos. También la dirección de este vector es diferente en ambos grupos, presentado el grupo control una dirección de crecimiento condilar más vertical que el cóndilo de los niños con AIJ.

Con estos resultados podemos influir en las tomas de decisiones médicas en relación con el manejo de esta enfermedad. Por ejemplo en lo relacionado con el tratamiento. Partiendo de la realidad de que la inflamación se reduce con los fármacos apropiados, nuestros resultados sugieren que en los pacientes con AIJ, un tratamiento funcional (ortopédico) permite la remodelación del cóndilo, aunque la respuesta al tratamiento, en relación a este valor, se caracteriza por una gran variabilidad individual. Por tanto, la terapia de este aparato funcional, DS, es considerada una herramienta eficaz para el tratamiento de pacientes con AIJ y con artritis de la ATM, sobre todo en los afectados unilateralmente.

También se podría usar este análisis como prueba observacional en el seguimiento de cualquier tipo de tratamiento, ortopédico y sistémico. Con este objetivo se ha incluido en esta tesis el *anexo IV,* donde se pueden observar las diferencias entre algunos de los pacientes estudiados en esta tesis. Al ser un grupo reducido, no se han podido realizar correlaciones entre las distintas variables, pero sí se pueden observar diferencias visuales entre ellos. Esto introduce la necesidad de hacer más estudios clínicos para valorar los efectos en la ATM de los distintos tratamientos sistémicos utilizados en la AIJ.

3. Al usar en esta tesis un escáner tridimensional, se han podido realizar los cálculos de volúmenes del espacio articular. Esto ha permitido, además de un análisis morfométrico de la mandíbula, un análisis volumétrico de la ATM sobre imágenes de CBCT.

En lo referente al espacio articular, al revisar las diferentes técnicas publicadas de segmentación de imágenes y cálculo volumétrico, nos encontramos con la ausencia de la aplicación de estas técnicas en este espacio articular. Existen casos donde se ha calculado el volumen del espacio sinovial en articulaciones afectadas de artritis pero todavía, hasta la fecha, no se había intentado calcular el volumen del espacio articular en la ATM. En esta tesis se ha adaptado el método utilizado para el cálculo de volumen sinovial en rodillas de pacientes con artritis sobre imágenes de RM.

El análisis volumétrico del espacio articular mostró diferencias significativas entre el volumen encontrado en los pacientes con AIJ y el volumen encontrado en los pacientes sanos, siendo casi el doble en los pacientes con artritis.

Pensando en el volumen como un dato que cuantifique el volumen de líquido inflamatorio presente en la articulación, este método podría establecer diferencias entre las sinoviales de las ATMs correspondientes a niños con artritis y niños sin artritis.

Siguiendo esta idea, con la comparación de los datos, se ha calculado y establecido un umbral diferenciador de la enfermedad. Se pretende obtener un valor numérico que, a través del volumen, se traduce en un estado inflamatorio (por lo tanto enfermo), o en un estado sano de la ATM en niños con AIJ.

4. El último apartado de esta tesis se ha centrado en el estudio de las diferentes propiedades de las diversas técnicas de imagen utilizadas hasta la fecha para el manejo de la AIJ, con el objetivo de mejorar la calidad de dichas técnicas para un mejor uso de las mismas en el diagnóstico y control de la enfermedad.

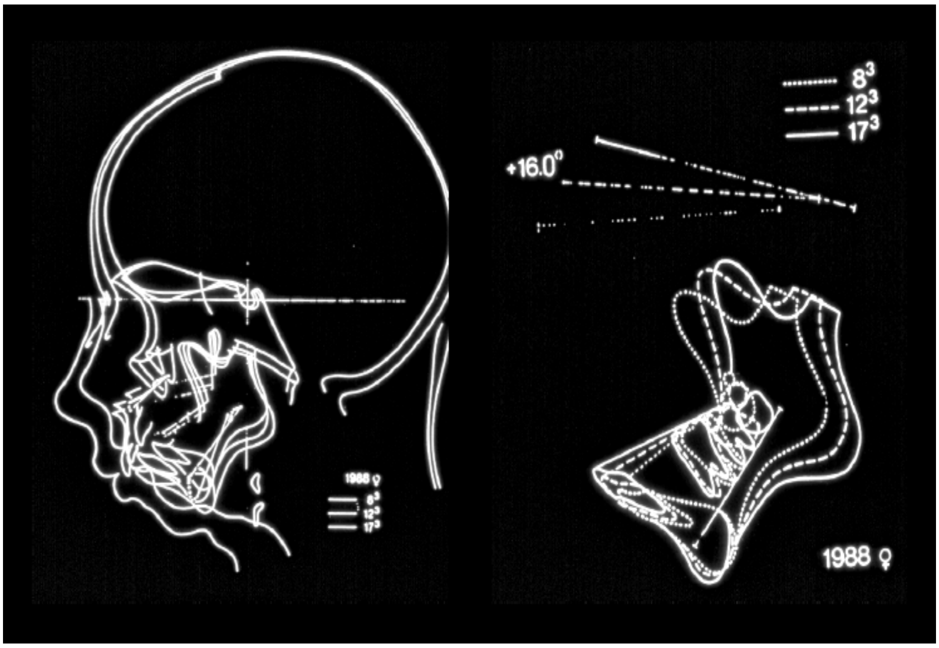
La AIJ es una enfermedad infantil y es importante detectar la enfermedad tan pronto como sea posible para evitar las complicaciones ligadas al crecimiento facial. Se conocen los signos patológicos relativos a la presencia de la artritis durante un tiempo en la articulación. Como se ha demostrado por Tomografía TC y RM son frecuentes, suelen ser bilaterales, y se caracterizan por deformidades en el cóndilo mandibular y los huesos temporales, la morfología anormal de disco y, con bastante frecuencia, la osteoartritis y la sinovitis leve.

La RM es el método de examen por imagen más fiable para la una detección temprana de la artritis en la ATM, pero tiene algunas desventajas, entre las que destaca su baja disponibilidad en la práctica clínica diaria. Este no es el caso para el CBCT, que es la modalidad de imagen generalmente disponible en la práctica de la clínica dental.

En esta tesis hemos presentado un nuevo enfoque para la generación de imágenes médicas en 3D mediante el uso de un CBCT. Hemos procesado la imagen original procedente del CBCT con una herramienta de mejora de contraste y que permite realzar los bordes que delimitan las diferentes estructuras de la ATM. Con esto mejoramos las capacidades del CBCT y proporcionamos también, con esta técnica, una prueba con valor clínico, ya que proporciona una nueva información sobre el paciente.

Además de las posibles aportaciones científicas, con esto se acelera el proceso de detección de enfermedad y se reduce el riesgo de solapar varias pruebas diagnósticas que se están haciendo para obtener un mismo resultado. Sin embargo se deben hacer otros estudios acerca de los parámetros que afectan a la calidad de imagen, con el fin de establecer un gradiente de observación para visualizar las diversas partes anatómicas de la ATM en imágenes procedentes de un CBCT.

Capítulo VIII: Modelo de propuesta



8.1 Tratamiento de esta patología en el sistema público español de salud

Tal y como se indica en los principios definitorios del sistema sanitario, la buena salud debe ser un objetivo en sí misma. No obstante, los sistemas sanitarios son complejos, abiertos e interrelacionados con factores determinantes de otros factores, como el sistema político, el fiscal o el educativo y deben cumplir, (para considerarse sistema sanitario de acuerdo con la OMS):

- ser universal, dando cobertura a toda la población.
- con atención integral, tanto higiene y salud mental, medicina preventiva, asistencia primaria, asistencia terciaria de todas las patologías agudas y crónicas.
- debe tener equidad en la distribución de los recursos.
- debe ser eficiente, es decir, aportar las mejores prestaciones y el mejor nivel de salud al menor coste.
- debe ser un sistema con flexibilidad, con objeto de poder adaptarse y responder de manera rápida a las nuevas necesidades.

La práctica clínica dentro de un sistema sanitario se adapta a la oferta disponible en cada zona y a las estrategias clínicas presentes en cada comunidad autónoma (CCAA) dentro de España. La mayoría de las CCAA incluyen las acciones encaminadas, fundamentalmente, a la salud buco-dental y a la prevención de caries infantil, con una denominación genérica dirigida, en general, a la población infantil de 6 a 14 años, sin especificar prestaciones dentro de dicho concepto. Sin embargo en relación a la población infantil tiene protocolizado realizar actividades de promoción y prevención, valorar las posibles alteraciones en la oclusión, hacer una detección precoz de caries, valorar de la administración de flúor, la realización de obturaciones simples y de sellados de fisuras.

En la salud buco-dental, no existe por parte del sistema sanitario público, una acción declarada para las enfermedades crónicas o específicas, como puede ser la AIJ.

La AIJ es la enfermedad reumática inflamatoria crónica más frecuente en la infancia. Hasta hace unos años no existía homogeneidad en los criterios de clasificación diagnóstica, por lo que la valoración de su incidencia y prevalencia resulta dificultosa. No existen estudios epidemiológicos de AIJ en España (hasta la fecha solo existen dos estudios, uno en Cataluña y otro en Asturias), por lo tanto no podemos saber con exactitud los niños españoles que pueden estar enfermos de AIJ. Según estudios europeos y americanos encuentran que en países desarrollados la incidencia de AIJ es 8-14 cada 100.000 niños y su prevalencia oscila entre 60-80 a 400 niños cada 100.000.

Existen en España tres Unidades de Referencia en reumatología pediátrica (Barcelona, Madrid y Valencia), en el resto de los centros hospitalarios pertenecientes a la sanidad pública la atención a estos pacientes con AIJ depende del sistema interno de gestión hospitalaria y de las medidas sanitarias de cada CCAA. En Galicia los niños afectados con AIJ son atendidos según la estructura asistencial del servicio sanitario de cada provincia .En Santiago, en el Servicio de Reumatología del Hospital Clínico, se ha creado la primera Unidad de Reumatología Pediátrica de Galicia, donde los niños son atendidos por un equipo multidisciplinar que forman un reumatólogo, un pediatra y un ortodoncista para evaluar la afectación de la enfermedad en todas las articulaciones del cuerpo, ya que hasta el día de hoy en España la observación y tratamiento de la ATM en estos niños está siendo infravalorada con respecto al protocolo sanitario existente en AIJ y en particular a la ATM en otros países Europeos.

Se adjunta en esta Tesis el anexo II donde se presenta una propuesta de protocolo Europeo, (un consenso entre diferentes especialistas internacionales) en la atención de estos pacientes con AIJ y en relación a la observación clínica de la ATM.

8.2 Propuesta de esta tesis

Durante el proceso de elaboración de este trabajo de tesis se ha detectado la ausencia de medios por parte del sistema sanitario y el desconocimiento por parte de la población en relación al tratamiento de la ATM afectada por la artritis.

Se ha añadido este apartado pensando en mejorar la calidad de la asistencia sanitaria, que es un valor muy apreciado tanto por los usuarios como por los profesionales de la sanidad. Una política de calidad del Sistema Nacional de Salud es un compromiso de las autoridades sanitarias en impulsar una serie de actuaciones que fomenten la mejora de los servicios sanitarios con los recursos disponibles. Pensando en esta definición se ha recogido en esta tesis un modelo de aplicación en asistencia sanitaria en enfermos con AIJ y en relación con la afectación de la ATM. Este modelo se ha adaptado del protocolo Europeo existente para el manejo de esta patología.

En el Norte de Europa existe un sistema sanitario flexible con cooperación entre profesionales que ha reforzado campos de investigación y ha generado grupos de trabajo y organizaciones como EuroTMjoint. Esta organización es una red interdisciplinar de especialistas europeos para la investigación, diagnóstico y tratamiento de las alteraciones craneofaciales en pacientes afectados con AIJ; donde el objetivo es unir esfuerzos para la obtención de un bienestar de salud dentro de un grupo poblacional.
Gracias a estas redes y equipos de investigación europeas se ha realizado un protocolo para el tratamiento de la ATM y de la alteración en el crecimiento facial de los pacientes afectados de AIJ.

En España existen también sociedades médicas relacionadas con este grupo poblacional y concretamente la SERPE está realizando grandes esfuerzos para actualizar y compartir los conocimientos sobre la AIJ, y restos de enfermedades reumáticas, con los diversos profesionales sanitarios para beneficiar así a estos pacientes. Este beneficio se traduce en una mejor atención por parte de los servicios sanitarios. Por supuesto que la aplicabilidad de este protocolo depende de la estructura del sistema sanitario y si se trata de un organismo público o privado.

Dentro del sistema nacional de salud existen diferencias a nivel individual, por ejemplo el sistema sanitario difiere de una Comunidad a otra, y por tanto puede ser más fácil la incorporación de nuevas técnicas o protocolos en diferentes áreas geográficas españolas. Por ejemplo en Galicia, teniendo en cuenta la propia estructura del complejo hospitalario, el sistema de salud concentra todas las especialidades en un mismo edificio, siendo entonces fluido el movimiento del paciente entre los distintos servicios y especialistas, por el contrario en Andalucía el sistema de salud estructura los servicios sanitarios por edificios, a este sistema se le conoce como Ciudad Hospitalaria. Esta gestión de estructuras puede afectar de alguna manera a la toma de decisiones en adaptación de nuevas técnicas. Sabiendo que la estructura del sistema de salud repercute en el paciente por la accesibilidad al medio, todo proyecto que surja para aumentar la fluidez de conocimientos sobre la AIJ entre los distintos departamentos y servicios ayudará tanto al paciente como al profesional a obtener un mejor resultado en el tratamiento.

Teniendo en cuenta los resultados obtenidos de nuestra investigación nos gustaría dejar plasmada una voluntad de trabajo y colaboración entre los diferentes profesionales dedicados al servicio y tratamiento de la AIJ, recogidos en una guía de recomendaciones.

A continuación se resumen los puntos de interés encontrados como carencia, en los sistemas sanitarios actuales, en la observación de la ATM en niños con AIJ según los resultados de este trabajo:

- Según nuestros resultados se debería incluir la observación de la ATM por los especialistas médicos en pacientes afectados con AIJ.

- Se debería tratar por un especialista la ATM que se encuentre afectada en estos pacientes, sobre todo en los casos donde se ha observado una notoria asimetría facial o dental para prevenir el progreso de la misma.

- Se podrían hacer reuniones o conferencias anuales para informar a los distintos servicios médicos sobre la afectación de la ATM por la AIJ. Ya existen reuniones educativas de los familiares de niños con AIJ, sería interesante también hacer reuniones de los diversos profesionales. Con esto se persigue involucrar más servicios médicos como maxilofaciales o radiólogos con el manejo de la ATM en niños afectados de AIJ.

- Se debería de hacer un buen uso de los recursos utilizados como pruebas diagnósticas.

- Se debería también seguir investigando para llegar a consensos en protocolos de observación y tratamiento, así como en el desarrollo de la tecnología aplicada en tratamiento de imágenes médicas.

A consecuencia de esta carencia se ha elaborado, en esta tesis, una guía como modelo de observación y tratamiento de la ATM afectada con artritis para uso de la misma por los profesionales sanitarios. Este modelo de propuesta ha sido adaptado según protocolos Europeos y se justifica su necesidad con la definición de dicho modelo. También se explica a continuación la aplicabilidad de este modelo dentro de los servicios sanitarios:

8.2.1 Definición del modelo

La presente guía se aplica en niños con AIJ diagnosticada en base a los criterios de la ILAR (International League of Associations for Rheumatology) con presencia de artritis en la ATM y/o que presentan inflamación en la ATM acompañada de alteraciones dentofaciales relacionadas con la artritis.

Se ha descrito con anterioridad en esta tesis que los pacientes con AIJ tienen riesgo de desarrollar alteraciones en al crecimiento dentofacial debido a la artritis en la ATM. Si no se llega a tratar este anormal patrón de crecimiento se va a afectar o comprometer la función cranio-mandibular, así como a la estética facial del paciente.

8.2.2 Organización de los servicios de salud

Estos pacientes se encuentran en edad pediátrica, por lo tanto serán examinados y diagnosticados en las unidades de reumatología pediátrica. Se recomienda que todos los pacientes diagnosticados de AIJ se refieran o sean examinados por un ortodoncista para la evaluación de la posible afectación de la ATM por la artritis.

El propósito de este examen es registrar todas las posibles desviaciones en el crecimiento dentofacial de estos niños.

El examen clínico incluye también una prueba de imagen de la ATM. Se utilizan pruebas como la RM o CBCT. Siendo la ecografía la técnica más utilizada en el resto de las articulaciones del cuerpo para la temprana detección de la inflamación, en la ATM no se considera una técnica apropiada.

Se hace entonces importante para tratar a estos pacientes la existencia de una comunicación fluida o de una buena colaboración entre los distintos servicios sanitarios implicados.

8.3 Propuesta de guía clínica

8.3.1 Diagnosis

El diagnóstico de la artritis en la ATM se basa en el examen clínico, el análisis funcional y la prueba de imagen.

En el análisis clínico se debe anotar la presencia de asimetría facial y las posibles alteraciones dentofaciales relacionadas con una oclusión defectuosa como puede ser una mordida abierta o un resalte llamativo de los dientes superiores.

En el análisis funcional se debe de incluir una valoración subjetiva y objetiva por parte del profesional. En la valoración subjetiva se registrará la información dada tanto por el propio paciente como la información dada por los padres, en relación a la masticación y a la deglución del paciente.

La valoración objetiva del análisis funcional abarca:

- El registro del rango de movilidad de la mandíbula tanto en apertura, como lateralidad y protusión.
- La detección de una posible desviación en la apertura bucal
- El examen de la translación de los cóndilos durante la apertura
- El registro de la presencia de sonidos articulares.

Para la prueba de imagen, la RM con contraste, es hasta ahora, la única prueba utilizada por los servicios médicos para verificar la inflamación presente en el ATM. Para la observación de los cambios estructurales se puede usar tanto el CBCT como la RM.

El análisis del paciente (clínico y funcional) en el que ha sido diagnosticada la presencia de artritis en la ATM, se debe de realizar regularmente para registrar la evolución de la enfermedad. En este caso se debe controlar al paciente utilizando el mismo protocolo de seguimiento que se hace durante la fase de activación de la enfermedad, por parte del servicio de reumatología. En el caso de que la ATM no presente signos de artritis cuando se realiza el examen, se repetirá este en un período de frecuencia entre los tres y doce meses. El período de frecuencia depende del subtipo de artritis y de la severidad de la enfermedad, (si se encuentra en un período activo o en un período de remisión).

A destacar en este examen es la importancia de detectar la presencia de las alteraciones en el crecimiento dentofacial de estos pacientes. Esto es así para realizar un correcto plan de tratamiento para estos pacientes que perdure en el tiempo, (hay que puntualizar que se están tratando pacientes en edad o período de crecimiento). Se debe de tener en cuenta la edad del paciente en la elaboración del plan de tratamiento; las edades importantes en relación al crecimiento dentofacial y que pueden ayudar en la toma de decisiones de un determinado tratamiento son los seis años, los once años y los quince. Entre los 15 y 16 años las posibilidades de éxito de un tratamiento ortopédico son muy escasas. A partir de esa edad y si estamos ante un paciente con asimetría funcional y estructura se debe orientar el tratamiento hacia la ortodoncia o cirugía según el caso.

8.3.2 Indicaciones de tratamiento

- Tratamiento de la ATM con artritis:

La infiltración local con corticoides (0.5 ml de triamcinolonehexacatonide a 20mg/ml mezclado con 0.5ml de lidocaína a 5mg/ml) es la primera elección de tratamiento ante la presencia de artritis aguda o activa en la ATM. Este tratamiento se puede repetir 1-2 veces en un período de seis meses, pero se debe tener especial cuidado en niños pequeños debido al posible efecto negativo del corticoide en el crecimiento mandibular a largo plazo. Se ha encontrado relación entre este tratamiento y la reducción en la actividad inflamatoria con la posterior mejora de la función mandibular (1)(2).

La segunda elección de tratamiento en esta patología es el MTX; se recomienda iniciar el tratamiento con MTX y si el paciente ya está en tratamiento se recomienda entonces subir la dosis de la medicación o debatir la posibilidad de uso de otro posible tratamiento como son los fármacos biológicos.

Existe la posibilidad de administrar el corticoide sistémico, pero no se ha encontrado evidencia científica para esta vía de tratamiento en relación a esta patología.

- Tratamiento del crecimiento dentofacial patológico o alterado:

La artritis en la ATM puede causar, aunque con un rango de variabilidad, cambios en el crecimiento del cóndilo mandibular. Un desarrollo atípico del cóndilo se traduce en un crecimiento anormal de la mandíbula, del área dento-alveolar y por lo tanto repercute también en el desarrollo del maxilar superior.

Se ha observado una remodelación condilar en algunos pacientes con AIJ, se cree que puede ser debida a los períodos o picos de crecimiento que presentan los niños. Es durante estos períodos donde los tratamientos funcionales u ortopédicos pueden tener un efecto positivo o beneficioso en esta estimulación del crecimiento condilar. De todas formas antes de realizar este tipo de tratamiento se recomienda hacer un plan de tratamiento individual para cada paciente afectado con AIJ. Este plan de tratamiento se basa en el análisis funcional de la articulación, análisis de crecimiento del paciente, así como la de la morfología de los maxilares y del pronóstico.

El tratamiento ortopédico se realiza con el llamado DS (distraction splint). La fabricación y uso de este aparato se ha descrito por Pedersen et al en 1995. El principio de acción de este aparato ortopédico es aumentar gradualmente la dimensión posterior vertical del paciente manteniendo los contactos anteriores. Idealmente se busca conseguir la erupción de los molares posteriores para el desarrollo de un plano oclusal no patológico.

Existe una segunda línea de tratamiento usado en caso de que el estado de remodelación condilar no alcance un nivel aceptable. En esta segunda línea se combinarían ambos tratamientos, la distracción osteogénica y el DS para poder llegar a normalizar el desarrollo mandibular.

- Tratamiento de la alteración dentofacial después del cese del crecimiento:

En los casos donde el cese crecimiento está ya establecido, se necesitará tratamientos combinados de ortodoncia y cirugía ortognática. La distracción osteogénica (DO) suele ser una buena opción ante casos severos donde los tejidos blandos se ven comprometidos.

Se deben tener en cuenta las posibles recidivas postquirúrgicas que se dan en la insuficiente elasticidad de los tejidos blandos y posibles futuras alteraciones en los cóndilos con artritis. A la hora de elaborar un plan de tratamiento se debe tener en cuenta el riesgo de la actividad presente en la ATM después de la cirugía. En muchos casos para evitar estas complicaciones el paciente necesita pasar por varios procedimientos quirúrgicos.

Brevemente y como recordatorio dejamos plasmados, a continuación, en una tabla los puntos más importantes a tener en cuenta a la hora de realizar un análisis clínico de la ATM en pacientes con AIJ:

Valoración clínica de la ATM afectada con artritis	
Diagnosis	
	Análisis de la ATM con artritis
	Evaluar la función de la ATM y el desarrollo dentofacial
**En el caso de no presencia de artritis en la ATM de los pacientes con AIJ; se debe hacer un segundo examen a los 3/6 meses en pacientes con riesgo elevado de padecer artritis y anual en los pacientes con riesgo bajo*	
Tratamiento de la artritis de la ATM, en fase aguda	
	Infiltraciones de corticoides
	Reevaluación de la medicación sistémica
	Reorientación del crecimiento dentofacial y la función de la ATM con ortopedia funcional
Tratamiento de la alteración en el desarrollo dentofacial	
	Hacer un plan de tratamiento y pronóstico en relación a la edad, severidad de la enfermedad y el estado de desarrollo
	Dentro de los diversos tratamientos; ortopedia funcional, ortodoncia, distracción ósea y cirugía ortognática.

8.3.3 Bibliografía

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Capítulo IX: Aplicabilidad de los resultados obtenidos

Dado que las aportaciones tecnológicas desarrolladas en el transcurso de esta tesis doctoral podrían ser susceptibles de un aprovechamiento clínico, se ha estimado oportuno añadir el presente capítulo.
El uso de la imagen como arma diagnóstica ya está siendo evaluada desde hace tiempo. En los últimos años incluso se intenta a través de la investigación la realización de protocolos clínicos para el uso de la imagen. Concretamente, en relación a nuestro campo, ha habido proyectos en diferentes países para evaluar el uso de la RM en la detección temprana de la AIJ en la ATM a través del cálculo de la inflamación. Se han llegado a establecer parámetros para definir la presencia de sinovitis y por lo tanto, de enfermedad, en las demás articulaciones afectadas por AIJ; pero todavía no se ha conseguido lo mismo en la ATM.

La ventaja del CBCT es su accesibilidad y frecuencia de uso por parte de los especialistas dentales. Esto hace del CBCT una tecnología multifactorial. La investigación desarrollada se ha centrado en estudiar la mejora de esta aparatología para aumentar su uso clínico.

Concretamente se ha trabajado en la mejora de la imagen desde ambos aspectos: cuantitativa y cualitativa.

En el aspecto de imagen cuantitativa se ha conseguido:

1. Utilizar el poder de la imagen tridimensional para analizar la evolución temporal de una estructura anatómica y poder así medir los cambios producidos por la enfermedad o bien por un determinado tratamiento a una escala real.

2. Adaptar al CBCT las metodologías usadas en otras técnicas estudiadas durante años para la detección de artritis en las articulaciones a través del cálculo de volúmenes. Es la primera vez que se realiza una

volumetría en el espacio sinovial de la ATM con imágenes procedentes de un CBCT.

En el aspecto de la imagen cualitativa y con el objetivo de proporcionar al clínico una mejor visión de la afectación, se ha mejorado un software desarrollado en la Universidad de Santiago para su uso sobre imágenes procedentes de un CBCT. Con este proceso se ha intentado conseguir protocolizar el uso del CBCT para observar una lesión en la ATM. Se han obtenido así imágenes con una calidad visual tan aceptable (incluso mayor en algunos casos) como en la RM para casos donde la imagen ha sido clave como apoyo a la sospecha clínica de artritis en la ATM de pacientes con AIJ. Hasta ahora el CBCT solamente se usaba para la observación del tejido óseo y la RM para observación del tejido blando. Con este trabajo quizás el CBCT se empiece a usar para la observación de ambos tejidos en la ATM.

Como explicación visual de lo relatado anteriormente añadimos en este texto varias figuras donde se puede apreciar el papel de un buen registro gráfico para un uso clínico, tanto en diagnóstico como en pronóstico.

A continuación se presentan algunas imágenes de pacientes con AIJ pertenecientes a las muestras utilizadas en esta tesis:

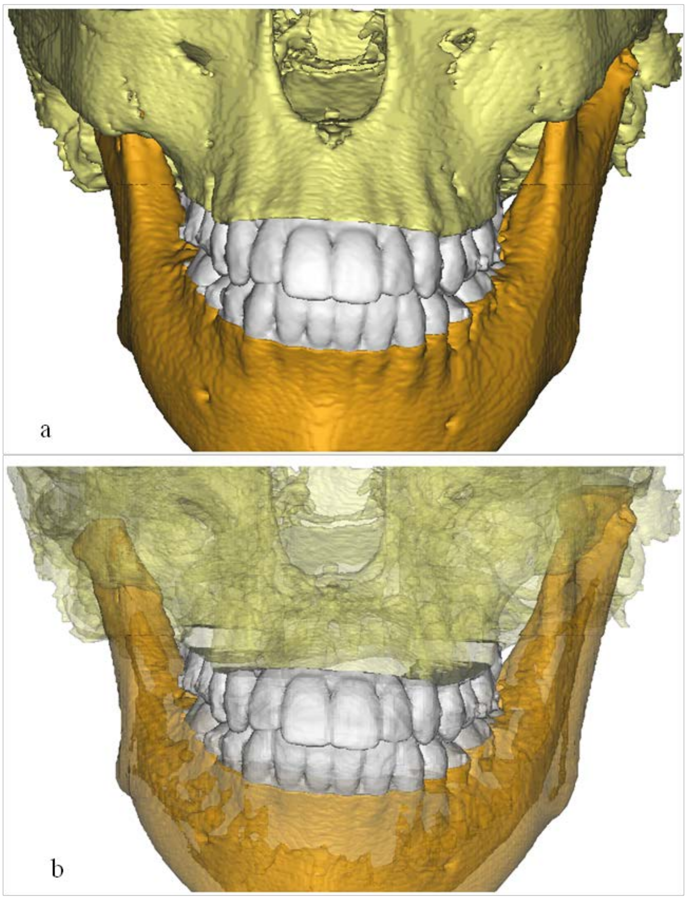

Figure 7.1.Representación de la asimetría facial de uno de los pacientes incluidos en este estudio. Para obtenerla se ha partido de los cortes axiales obtenidos mediante CBCT y se ha realizado un "renderizado" volumétrico. Con ello se obtiene una representación tridimensional del cráneo del paciente. Con las herramientas del software podemos transparentar la parte anatómica del malar para poder observar mejor el daño en la zona condilar, como se observa en la imagen b.

Después de la observación, si se necesita medir el grado de afectación condilar se puede realizar mediante un proceso de segmentación, para así poder aislar la mandíbula del resto del cráneo. En la figura 7.2 se muestra uno de los pacientes pertenecientes al Servicio de Reumatología del Hospital Clínico de Santiago. En este paciente se observa la presencia de asimetría dental y mandibular. Este grado de asimetría prácticamente se observa en todos los pacientes afectados de AIJ (tanto en la muestra danesa como en la muestra la gallega). En este caso hemos aislado las figuras de ambos cóndilos del resto del cráneo en el objeto tridimensional. De esta manera se puede calcular el volumen óseo de cada cóndilo y observar con detalle cualquier alteración o desgaste en la zona condilar.

Figura 7.2 Fotografía y escáner del mismo paciente de la muestra. Se representa tanto en la fotografía como en el objeto tridimensional la presencia de asimetría dental. La paciente refiere en clínica dolor en la articulación temporomandibular izquierda, para ello se han aislado los dos cóndilos para observación de posible daño óseo y cálculo de volumen.

Durante el desarrollo de este documento se ha mencionado la importancia dual de la imagen para su uso en diagnóstico y evaluación de un tratamiento. En las figuras 7.3 y 7.4 se plasma el proceso evolutivo de un paciente con AIJ que ha sido tratado con cirugía ortognática. Este paciente ha sido diagnosticado de AIJ y ha llegado a una edad adulta con afectación de la ATM derecha y ha desarrollado una marcada asimetría facial con acortamiento de la rama mandibular de su lado derecho.

En esta tesis se ha plasmado el problema existente de la patología (artritis), en la ATM de los niños con AIJ. Se ha registrado la existencia de asimetrías faciales en estos pacientes y se ha llamado la atención sobre el deber de tratar la ATM de estos niños para evitar complicaciones en el crecimiento facial.
Teniendo en cuenta los resultados obtenidos de nuestra investigación nos gustaría defender una voluntad de trabajo y colaboración entre los diferentes profesionales dedicados al servicio y tratamiento de la AIJ.

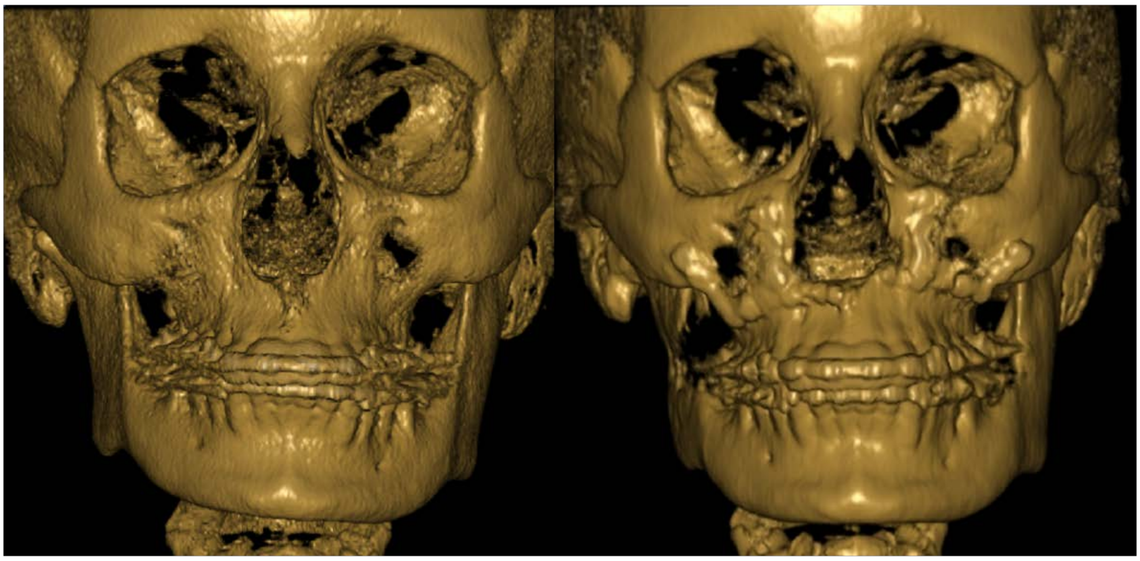

Figura 7.3 En esta figura se representa la imagen tridimensional del cráneo de un paciente de 20 años diagnosticado de AIJ. En la figura de la izquierda (pre-operatorio) se puede apreciar la asimetría mandibular. En la foto de la derecha se puede apreciar la nueva posición mandibular después de la cirugía.

Figura 7.4 Fotos clínicas de la misma paciente de la figura 7.3. Se puede observar la similitud, en términos de asimetría facial, entre las imágenes del escáner y las fotos clínicas. La imagen de la izquierda pertenece al inicio del tratamiento de ortodoncia y la imagen de la derecha es una foto tomada después de la cirugía ortognática y al mismo tiempo que el escáner post-operatorio de la figura previa.

Anexo I: Los factores que afectan a la calidad de una imagen médica

Existen factores o valores que afectan a la calidad de una imagen independientemente de la tecnología a usar. Estos factores se deben tener en cuenta al querer alterar de alguna manera la calidad de una imagen médica y son:

- La densidad del tejido: El ordenador va a generar una imagen en una escala de grises, donde la densidad de tejido se indica por tonos de gris. Estos van desde negro que indica la densidad del aire a blanco que representa la densidad del hueso más duro. Sin embargo, la diferencia de densidad entre las diferentes estructuras de tejido blando no es grande y por lo tanto, puede ser difícil distinguir entre los diferentes órganos adyacentes en una imagen de TC. Para solventar este problema, agentes de contraste que absorben energía de los rayos X pueden ser introducidos en el cuerpo, lo que hace que algunas estructuras se realcen más.

- La distancia de corte: Las imágenes de TC se generan como una imagen de píxeles en escala de grises. Las imágenes resultantes de un escaneo con un CT se dividen en un gran número de píxeles (normalmente una matriz de 512x512). Cada pixel es una sombra de gris que se traduce como la densidad del tejido en ese lugar escaneado. Las imágenes resultantes son, por lo tanto, una aproximación de las formas de tejido original de acuerdo con su densidad. El problema surge cuando se trata de visualizar dos estructuras con densidades similares. Si el límite entre dos estructuras diferentes cruza un píxel determinado, este no puede representar ambas densidades. Lo que hace el pixel es coger un valor medio entre las dos densidades. La distancia entre los cortes axiales es un valor que influye en la calidad de la imagen. Algunos escáneres pueden recortar esta distancia hasta 0,5 mm, lo que da excelentes resultados, pero esto debe equilibrarse con el aumento de la dosis de rayos X.

- El campo de visión o field of view (FOV): Alterando el FOV se altera el tamaño de píxel en la imagen axial. Por lo general, se utiliza un FOV lo suficientemente grande como para capturar toda la sección transversal de la anatomía. Sin embargo, cuando se requieren pequeñas áreas específicas de la anatomía, el FOV puede ser reducido para capturar sólo esa área. Esto resulta en un tamaño de píxel más pequeño, lo que aumenta la exactitud física de la exploración.

- El ruido: este valor es especialmente frecuente en los tejidos densos. Aunque estas imágenes pueden ser visualmente aceptables, no son prácticas por ejemplo, para una reconstrucción tridimensional. A tener en cuenta también que se intensifica el efecto del ruido en los bordes de las estructuras con diferentes densidades, como el hueso y el tejido blando.

Es decir, debemos de tener este factor muy presente a la hora de trabajar con imágenes de articulaciones.

Hoy en día, el software de los escáneres modernos ya permite utilizar diferentes Kernels (filtros digitales). Estos filtros modifican los datos para dar mejores reconstrucciones tridimensionales y ayudan a reducir el ruido. Por lo general, las opciones van desde 'sharp' a 'smooth'. Los Kernels aumentan la nitidez de contornos, realzando así la diferencia entre estructuras contiguas, pero a costa de aumentar el ruido de la imagen.

Anexo II: Modelo del protocolo europeo para el manejo de la ATM afectada de AIJ

Treatment of the temporomandibular joint and related growth abnormality in patients with juvenile idiopathic arthritis – A European consensus practice.

Definition

The present protocol involves children with Juvenile Idiopathic Arthritis (JIA) diagnosis based on the ILAR criteria (1) and with temporomandibular joint (TMJ) arthritis or chronic TMJ changes and dentofacial alterations related to JIA and TMJ arthritis.

Patients with JIA are at risk of having disturbances in dentofacial development caused by TMJ arthritis. The dentofacial development evolves into a complicated abnormal growth pattern which untreated may lead to compromised craniomandibular function, dentofacial morphology and esthetical appearance (2-4).

This protocol addresses diagnosis, indications and treatment of TMJ arthritis and related growth disturbances in the dentofacial region.

Organization

Patients are examined and diagnosed with JIA in the pediatric rheumatology clinic. It is recommended that all newly diagnosed JIA patients are referred for further TMJ examination performed by experts in growth and development of the dentofacial region and TMJ function. Furthermore a specific training and expertise in TMJ arthritis related to JIA is mandatory. The purposes are to screen for TMJ arthritis, to register possible growth disturbances and related malocclusions, to assess the risk for TMJ involvement and to outline a long term individual treatment plan concerning dentofacial growth and development. It is important to have close collaboration with the pediatric rheumatology clinic.

The examination includes imaging of the TMJ. Magnetic resonance imaging (MRI) is considered an optimal method for detecting arthritis and even early inflammatory changes without structural deformation of the joint components. Ultrasound examination has been considered as an option for this purpose but is not as accurate as MRI (5). Tomography or cone beam computed tomography (CBCT) reveals osseous alterations and condyle – fossa relation. More detailed description of imaging methods will be given by the EUROJOINT group on diagnostics, examination and imaging.

Patients at risk for TMJ involvement are identified as patients with early on-set JIA especially with high ESR, polyarticular subtype, polyarticular course, arthritis in the upper extremities and female gender (6-8). In this context, the facial growth type of the patient will influence the degree of potential growth deviation. The severity of JIA arthritis affects the risk of TMJ involvement.

TMJ high-risk patients including children with severe JIA with a polyarticular course without clinical signs of TMJ affection should be seen every 3 - 6 months depending on age, dental stage, type of facial morphology, dentofacial development and activity level. Low-risk patients can be scheduled for examination depending of their dentofacial and dentoalveolar development or by the request of the rheumatologist, usually with a frequency of 1-3 years. Current examination by a pediatric rheumatologist is implied.

If TMJ arthritis is present, treatment initiation is aimed at 1) specific TMJ inflammation and 2) potential changes in the dentofacial development.

Treatment related to 1) will concentrate on the medication administrated locally, considering intra-articular (ia) corticosteroid injections as well as modification of systemic treatment with remission- inducing agents (MTX, biological). Treatment related to 2) will depend on the experience at the center in question. In general, an orthopedic treatment with a functional appliance is planned in order to support normal growth and avoid dentoalveolar compensations until growth arrests. If acceptable jaw relations have been obtained with this treatment, an orthodontic treatment may be needed to correct the occlusion. The TMJ should be examined on a regular basis during the treatment of the TMJ arthritis and the dentofacial anomaly and required adjustments done.

In case of inadequate jaw relations an orthognathic surgical treatment will be indicated. The surgical procedure will in most cases be surgery in both jaws supplied with a chin augmentation. In severe or asymmetric cases distraction osteogenesis

(DO) is an option in order to plan limited surgery in two or more steps. DO is also a method for the correction of asymmetries and increase of mandibular bone length at an earlier phase than conventional surgery. In contemporary orthognathic surgery transplantation of rib graft does not seem to play a major role. Joint prosthesis may be the treatment of choice when the TMJ is extensively destructed, with extreme deteriorated function or presence of ankylosis, but only when the patient has definitively stopped growing.

Diagnosis

Diagnosis of TMJ arthritis is based on functional status, clinical examination and imaging.

Functional examination includes a subjective and an objective assessment. History given by both patient and parents gives information about chewing and eating disabilities, TMJ pain, TMJ sounds and restricted mouth opening. The objective functional examination covers the range of movement of the lower jaw (opening capacity, latero – and protrusion), deviation on mouth opening of the lower jaw, translation of the condyles during opening, joint sounds and end-feel. The clinical examination describes facial asymmetry, dentofacial deformations and related malocclusions (open bite, increased overjet).

To verify TMJ inflammation contrast enhanced MRI is the only imaging method (9). Changes in bony structures can be confirmed by MRI but also CBCT can be used for that purpose. The advantage of using CBCT is an additional possibility for types of images describing craniofacial morphology at the same time. CBCT scanning is therefore currently taken on indication to describe morphological TMJ changes and dentofacial growth deviations. Orthopantomograms do not give enough information to be used for diagnostic purposes (10). Differential diagnosis such as temporomandibular disorders (TMD), TMJ hypermobility and muscular pain and tenderness should be considered. These conditions are relatively common in children and can likewise be seen in children with JIA. TMD might be followed by morphological changes of the TMJ condyle (osteoarthritis or osteoarhthrosis) similar to the changes seen in JIA patients. The role of radiographic imaging of the osseous changes in relation to differential diagnosis is not significant since this is not a specific finding for JIA, osteoarthritis or degenerative changes.

Since early diagnosis of TMJ arthritis activity is essential for an optimal treatment course routine examinations are recommended. Examination including evaluation of facial growth and dentoalveolar development has to be carried out on a regular basis supported by joint imaging. It is recommended to conduct the dentofacial examination of the patient at time of the primary JIA diagnostics. The clarification of the JIA diagnosis will also be supported by the TMJ and facial examination. In case of no TMJ involvement the examination is repeated with a frequency of 3-12 month dependent on arthritis type, severity and present activity as mentioned earlier. In patients with TMJ involvement and dysmorphic dentofacial growth it is important to outline the long-term treatment plan where the important ages for decision are: age 6 years (1. molar eruption, vertical control of the occlusal plane and secondary effect on the development of the maxilla), 11 years (time for planning distraction osteogenesis and additional orthopedic treatment, 2. molar eruption) and 15 years (growth is ceasing). At the age of 15 – 16, no further possibility for orthopedic treatment is available and evaluation of the severity of malocclusion and facial malformation is done for the outline of a possible orthodontic and surgical treatment related to the individual variation in skeletal and dental maturation. Assessment of treatment options of dysmorphic dentofacial appearance will be focused on functional/orthopedic treatment, orthodontics, osseodistraction or orthognathic surgery.

Details on diagnosis and imaging are described by the Euro^{TM}Joint working group related to these subjects.

Indications for treatment

Treatment of TMJ related problems falls into two categories:

1) TMJ Inflammation

2) Growth disturbances of the condyle, the dentofacial area, jaw relations and the dentoalveolar development.

Acute TMJ inflammation and related pain can be treated with intra-articular (ia) corticosteroid injections and adjustment of the general medication.

A registration and evaluation regarding the dentofacial growth should be carried out and based on this, a prognostic evaluation and an individual treatment plan is outlined for the patient.

Treatment of TMJ arthritis

Ia corticosteroid injection is the first choice for the treatment of acute TMJ arthritis in addition to adjustments in general medication. At present, it has been found that corticosteroid in the TMJ's can reduce inflammatory activity and improve the function (11). However, no studies have described whether the dentofacial growth disturbances are affected negatively or positively by treatment with steroids in humans. Animal studies indicate a negative effect of ia corticosteroids injections on the mandibular development (12). Therefore, precautions (controlling dentoalveolar development with orthopedic appliance) must be taken in order to support dentofacial development according to individual evaluation and treatment planning. Differential diagnosis with other temporomandibular disorders has to be considered as mentioned above.

For corticosteroid injections triamcinolonehexacetonide 20 mg/ml or triamcinoloneacetonide 40 mg/ml can be used together with local anesthesia ex. lidocain. The two components can be mixed for simultaneously injection in the joint, ex. 0.5 ml triamcinolonehexacetonide 20 mg/ml mixed with 0.5 ml lidocain 5 mg/ml. 1-1.5 ml can be injected under sterile conditions depending on weight of the patient (10-15 mg triamcinolonehexacetonide). Triamcinolonehexacetonide has been demonstrated to be more efficient in other joints than the TMJ (13) and could be considered efficient in the TMJ as well.

The injection is placed in the upper joint compartment with the mouth open. The needle is inserted approximately 10 mm anterior to tragus, directed anterior and cranial. The needle is placed in the temporal fossa posterior to the forwarded condyle. Aspiration is done to secure extra vascular position. Position of the needle is important and difficulty in judging the optimal position before injection is a vital clinical issue. Ultrasound or CT-guided injection has been reported (14;15) and also CBCT could turn out to be useful for this purpose.

Ia corticosteroid can be repeated 1-2 times in a 6 months period but caution is recommended especially in younger children. In terms of functional improvements repeated injections have shown minimal effect (16). Second line treatment such as MTX should be considered when ia corticosteroid is needed also to avoid need for additional ia injections. If the patient is already on MTX dose can be increased or addition of biologics can be the treatment of choice. Systemic steroids have also been suggested as an option for treating acute TMJ arthritis. However, this administration form lacks scientific evidence.

Treatment of developing dentofacial anomaly

TMJ arthritis may cause changes of the condylar growth with a large individual variation. A deformity of the condyle was earlier interpreted as a “resorption” and described as a “flattening”. Contemporary understanding of condylar deformity is now more towards a growth deviation of the condyle due to a chronic state of the arthritis and with possible independence of general arthritis activity. There has been reported spontaneously condylar remodeling (17;18) although a dysmorphic development of the mandibular complex still can be seen. A developing condylar deformity impacts the overall development of the mandible, the dentoalveolar area and secondarily the maxilla (19). In human craniofacial development, periods with high growth rate occur including growth of the condyle. Since spontaneously remodeling of the condyle in JIA patients are seen, these periods may be beneficial to support normal growth and dentoalveolar development. Remodeling of the condyle is a possible expression of growth more or less similar to normal growth. In these periods functional, orthopedic appliance could be expected have an effect. In periods with affected growth unbeneficial dentoalveolar compensations can be avoided by the use of such an appliance. Orthodontics serves as an additionally treatment to orthopedics and aims to establish an acceptable, functional occlusion. Prior to the initiation of a functional/orthopedic treatment, a thorough individual treatment plan is recommended to be carried out based on analysis of the joint function, growth, maxillofacial morphology and prognosis. There is low evidence on the orthopedic treatment efficacy although there might be a beneficial outcome related to mandibular retrognathia and pain (20). A few reports exist (21-23), but the optimal treatment procedure and the effectiveness of these types of appliances are unknown and will need the organization of multi-center studies designed for the purpose of comparing different types of treatments.

Orthopedic treatment can address both the vertical dimension of the posterior face or the sagittal position of the mandible.

Distraction splint treatment aims to gain control of the occlusal plane in order to avoid posterior rotation and to keep posterior distance between the upper and lower jaw in periods with delayed condylar growth. The treatment goal is to avoid a collapse of the posterior face height which may be an obstacle for further vertical condylar growth.
The fabrication and use of the distraction splint has been described by Pedersen et al. 1995 (24). The principle of the splint is a graduate increase of posterior height without preventing the patient to occlude in the impressions on the splint. The splint is initially made as a flat splint and provided with an occlusal relief soon thereafter. In an articulator mounting the articulator condyle can be lowered with a small distance to the articulating surface (0.25-1.00 mm) keeping a constant distance between the upper and lower incisors. This opens up a wedge-shaped space between the splint and the occluding teeth which is filled out with acrylic material i.e. increasing the posterior vertical height of the splint. Every 6-8 weeks this procedure is repeated. In case of unilateral affection increase in splint height is only taking place on the affected side (23). The splint has to be replaced according to the dental development and a change can be made from the lower to the upper jaw during tooth sheading. Ideally, the distraction splint will tend to open the bite posteriorly and eruption of the posterior upper teeth is favored in order to control the inclination of the occlusal plane. This can take place by grinding the splint selectively or to change to an activator to allow the upper posterior teeth to erupt and correct sagittal discrepancies. Alternatively, in the deciduous dentition composite material can be used to build up the deciduous molars creating the same effect as the distraction splint. Lower permanent molars must be anchored to the deciduous molars for separately eruption of the upper permanent molars.

Type of activator treatment in JIA patients has not been specifically described in the literature but different clinical experiences exist. Most commonly used are conventional activators basically designed for advancing the mandible with a controlled eruption of the teeth, adjusting the occlusal plane according to individual development. Using a conventional activator, clockwise rotation of the mandible can be the result why this treatment is not favorable in all facial types. Supplying the activator with a high-pull headgear can be a solution but will also tend to steepen the occlusal plane even further. A combination of an activator and the distraction splint is recommended based on clinical experience either used as two appliances in two phases (22) or as one appliance (24).

Distraction osteogenesis (DO) is indicated where dysmorphic mandibular and maxillary development takes place and remodeling does not reach an acceptable level. In growing individuals this option provides a possibility for a “catch-up growth” which in combination with orthopedic treatment can lead to a normalization of the mandibular development. The sequence and course in a combined orthopedic appliance/distraction osteogenesis treatment is described by Pedersen and Nørholt 2011 (25).

Treatment of the dentofacial anomaly after cessation of growth

Combined orthodontics and orthognathic surgery is required in case of severe dentofacial growth deviations in adolescence or adulthood. DO should be considered for the mandible in case of extended facial dysmorphic development including soft tissue insufficiency. It is not known whether DO results in a more stable outcome compared to conventional orthognathic surgery performed as a bilateral split osteotomy with anterior rotation of the mandibular corpus. However, counterclockwise rotation of the occlusal plane is necessary in case of short posterior face height (short mandibular ramus) and steep occlusal plane in order to achieve an acceptable result. This can be attained by both options. Mandibular asymmetries are often seen likely to originate from a difference in TMJ arthritis onset between the two sides. Obtaining symmetry is possible from both surgical methods described. Obviously, both techniques are associated with different technical difficulties which are important to consider in the treatment planning.

Post-operative relapse is a well-known complication after orthognathic surgery in arthritis patients mainly reasoned by two important issues: soft tissue insufficiency and further condylar alteration followed by worsening of the intermaxillary relations. Care should be taken to avoid extensive surgical movements beyond soft tissue limitations. Planning should be characterized by a thorough conceived balance in the different movements of the bony segments addressing the soft tissue envelope. The risk for further activity in the TMJ followed by shift in mandibular position should be considered. DO may be beneficial in relation to the soft tissue insufficiency and if performed early the patient will benefit from the immediate changes. In case of post – DO relapse, this can be corrected with a minor surgical correction of the maxilla when growth has ceased. It will be a challenge to reach evidence in this field which will be an assignment for multicenter research. At present, it seems to be most effective, in severe cases, to divide the surgical processes into two or three procedures including DO.

Alloplastic joint replacement is the final solution in rare cases of total functional loss or ankylosis. However, the replacement requires that the patient is definitively out of growth.

Brief list of the TMJ procedures in JIA

<u>At diagnosis:</u> Examination for TMJ arthritis
Evaluation of the dentofacial development and TMJ function

If no TMJ arthritis: examination of high-risk patients every 3-6 month, other patients 1-3 years depending of severity, type of JIA and stage of maturity.

<u>Treatment of acute or subacute inflammation in the TMJ:</u>

- Ia corticosteroid
- Moderation in general medication
- Evaluation of the dentofacial development and TMJ function.
- Support normal growth and dentoalveolar development with functional/orthopedic appliances.

<u>Treatment of dentofacial dysmorphic development:</u>

- Treatment planning and prognostic evaluation according to age, severity of disease and stage of development
- Treatment plan includes: functional/orthopedic treatment, orthodontics, osseodistraction and orthognathic surgery.

This protocol is written with contributions from:

Torino, Italy
Riga, Latvia
Zurich, Switzerland
Tampara, Finland
Copenhagen, Denmark
Toronto, Canada
Helsinki, Finland
Aarhus, Denmark
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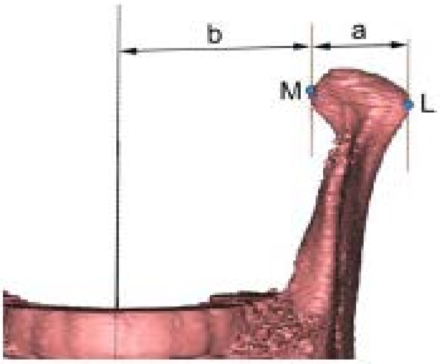
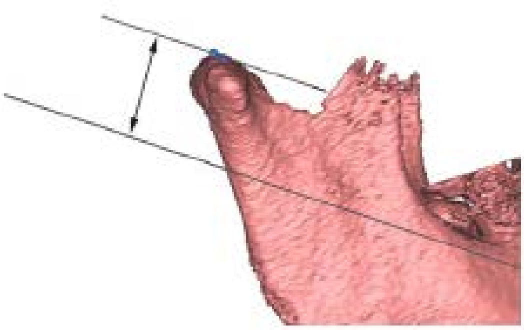
Anexo III: Metodología del análisis mandibular

AIII.1 Análisis condilar

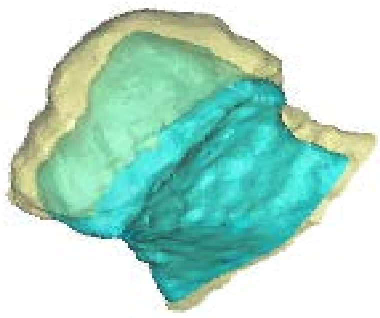
AIII.1.1 Ancho condilar (CW): Se mide desde el punto anatómico L (lateral) al punto anatómico M (medial). Nos da una medida a la que llamamos distancia *a*, para diferenciarla de la distancia *b*. La distancia *b*, que va desde el punto M al plano interno de la mandíbula nos representará la distancia transversal en el espacio del cóndilo en el momento de la intervención.



AIII.1.2 Altura vertical condilar (CVD): Representa la distancia desde el punto anatómico superior del cóndilo al plano basal de la mandíbula.



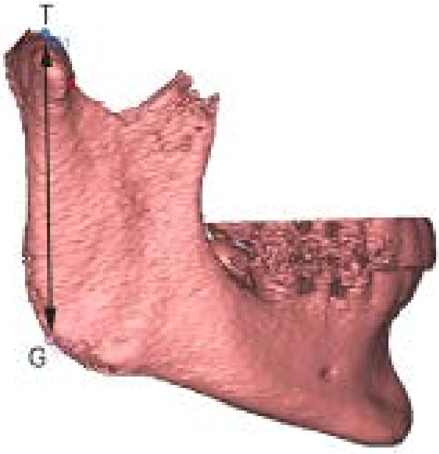
AIII.1.3 Volumen condilar (CV): Se obtiene automáticamente por medio del software una vez aislado el cóndilo.



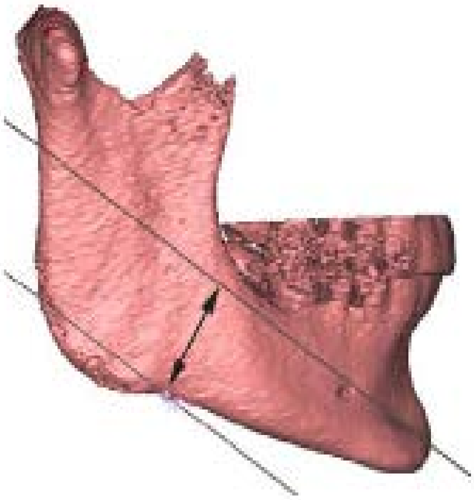
AIII.1.4 Posición distal (DP): Representa la distancia desde el punto anatómico posterior del cóndilo al plano transversal de la mandíbula.

AIII.2 Análisis mandibular:

AIII.2.1 Longitud de la rama mandibular (RL): Se representa con la distancia existente entre los puntos anatómicos superior del cóndilo al punto más inferior de la rama mandibular definido como Gonium.



AIII.2.2 Escotadura antegonial (ND): Donde se representa y mide la deformidad antegonial existente en los pacientes con AIJ descrita en la literatura. Se mide la distancia desde el punto más profundo de la curvatura antegonial hasta el plano basal.



AIII.3 Análisis del espacio articular:

Se representa visualmente y numéricamente la diferencia entre las articulaciones mandibulares estudiadas en todos los pacientes con AIJ que pertenecen al estudio. Con esto se pueden observar las diferencias en afectación de la ATM a nivel óseo e inflamatorio.

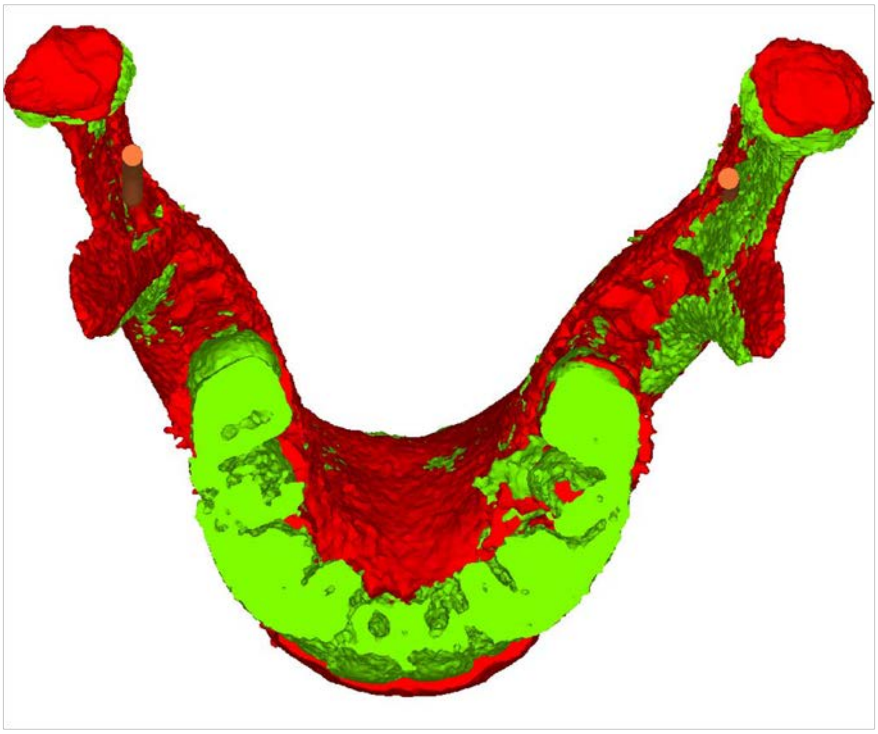
Anexo IV: Representación visual del crecimiento mandibular en pacientes con AIJ que han sido tratados con diferentes fármacos

En este anexo se representan las diferencias entre algunos pacientes con AIJ.

Se han escogido al azar algunos pacientes del grupo con AIJ, se han superpuesto las dos mandíbulas, la primera mandíbula substraída del escáner realizado al principio del tratamiento (color verde o amarillo) y la segunda mandíbula substraída del escáner realizado a los dos años (rojo). Se han coloreado con el software médico para observar fácilmente las diferencias del crecimiento condilar. Al ser un número reducido y no teniendo acceso a toda la historia clínica del paciente no se pueden hacer correlaciones estadísticas pero se puede observar diferencias marcadas entre los casos aquí representados.

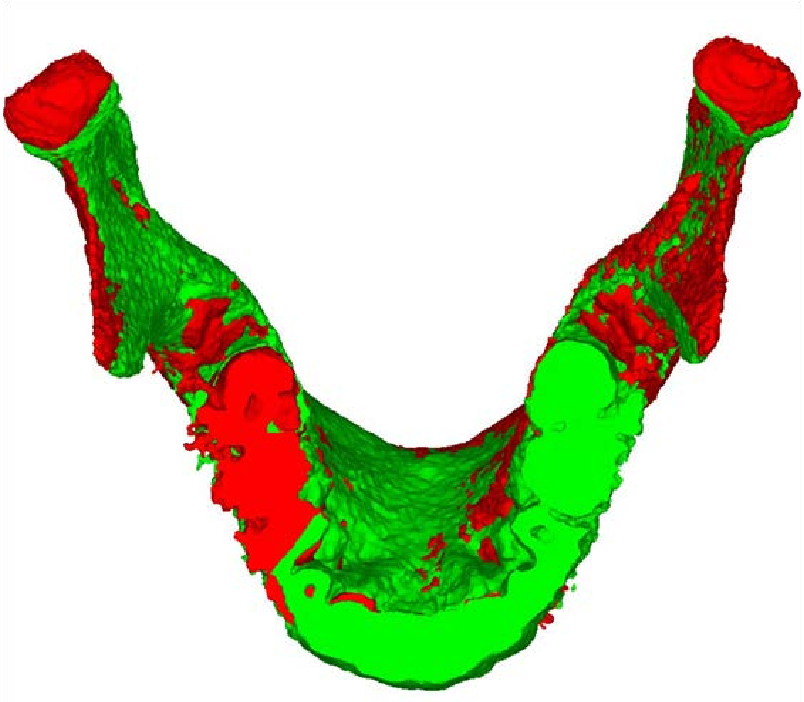
A continuación se exponen en este anexo estos casos:

AIV.1 Pacientes tratados con Enbrel (Etanercept):

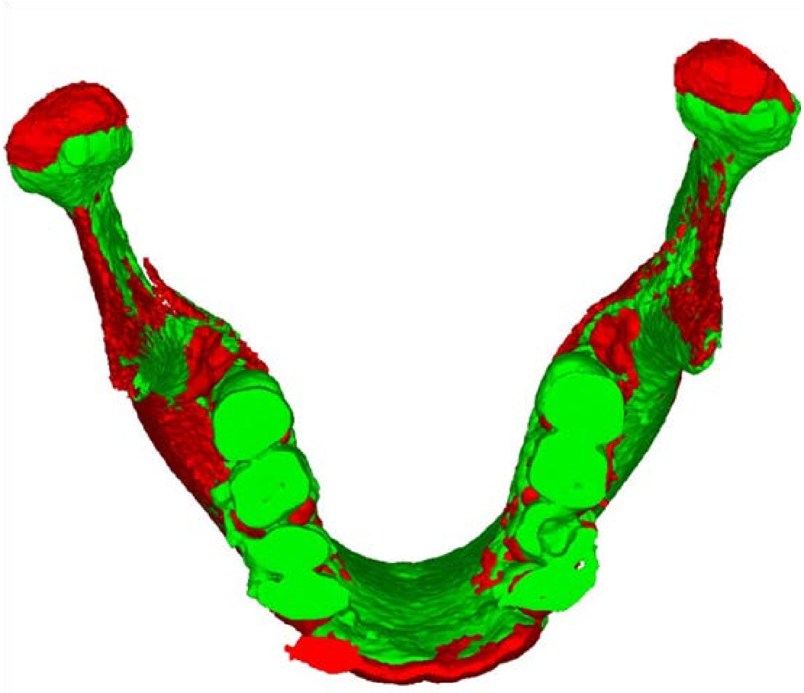


Paciente 1. Niña de 11,5 años con AIJ y tratada con DS. Tratamiento sistémico enbrel. En este caso se puede apreciar un buen crecimiento ambos cóndilos mandibulares, si bien el crecimiento vertical condilar en este caso es mayor que el crecimiento distal condilar.

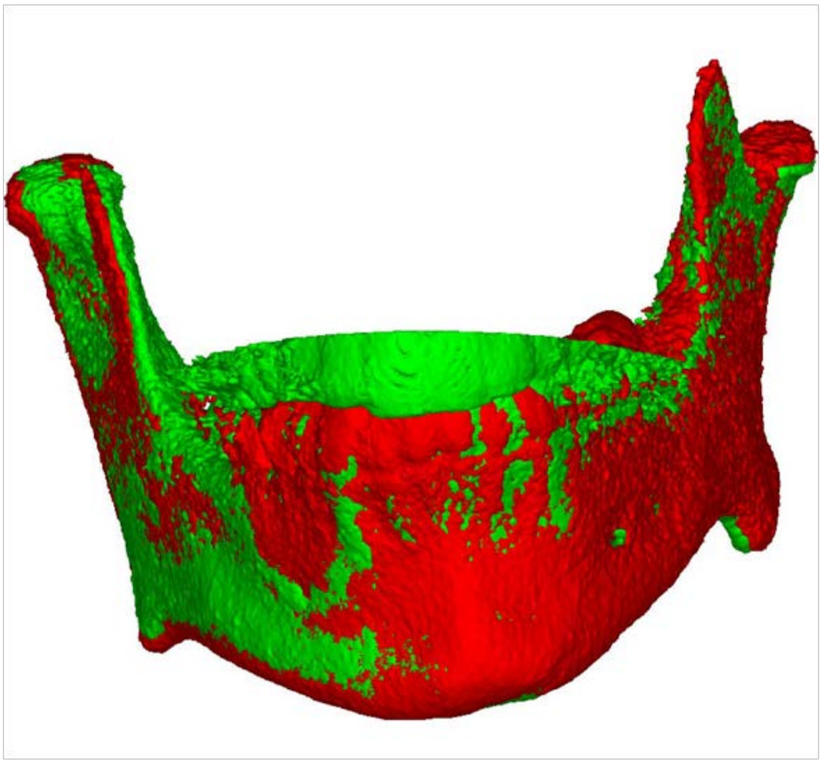
AIV.2 Pacientes tratados con MTX (metotrexato):



Paciente 2. Niña de 8,5 años con AIJ y tratada con DS. Tratamiento sistémico MTX. Se puede apreciar un buen crecimiento en ambos cóndilos, tanto en vertical como en distal.

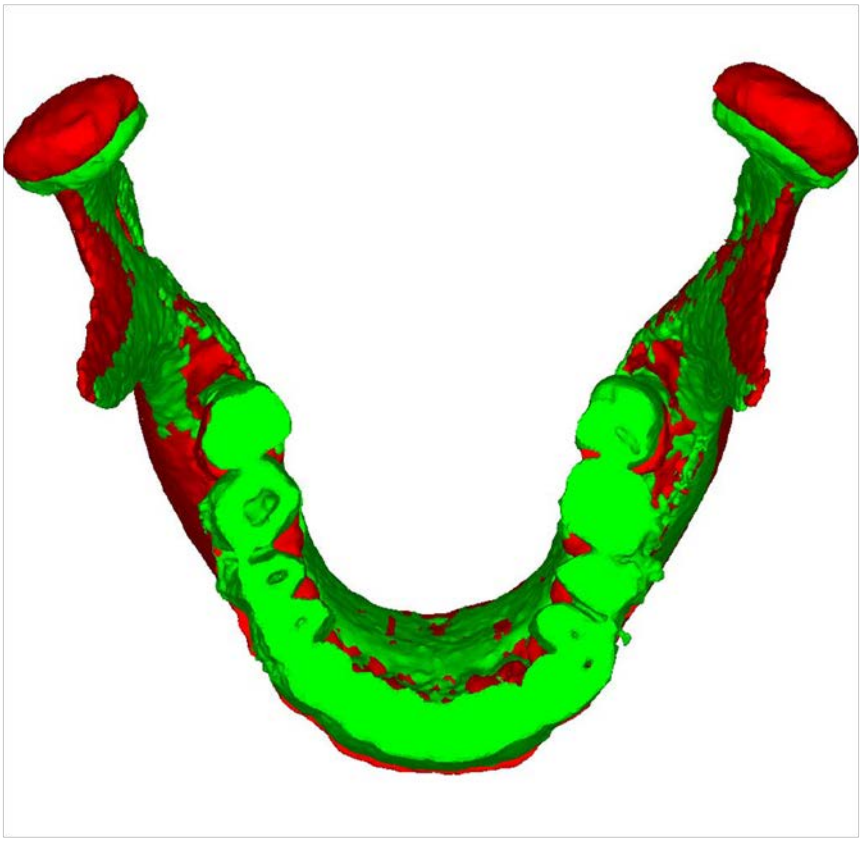


Paciente 3. Niña de 11,7 años con AIJ y tratado con DS. Tratamiento sistémico MTX. Se puede apreciar un buen crecimiento en ambos cóndilos, pero en este caso el crecimiento distal del cóndilo es ligeramente mayor que el crecimiento vertical.



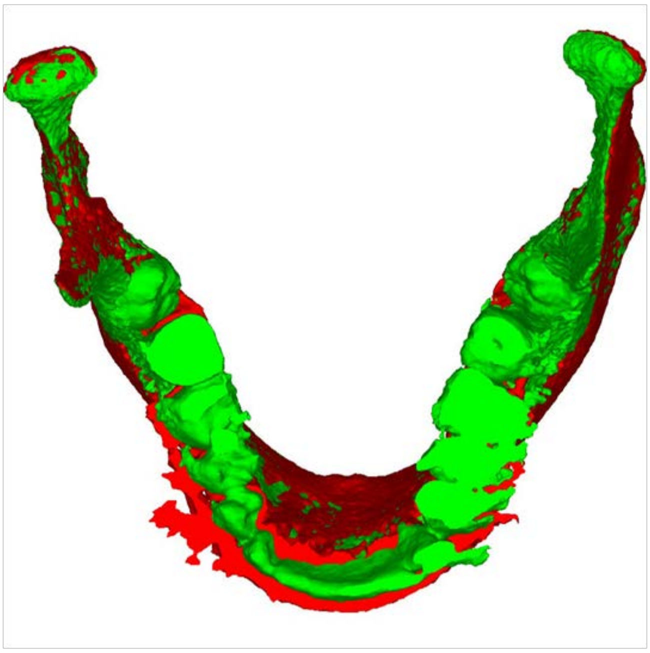
Paciente 4. Niña de 12 años con AIJ y tratada con DS. Tratamiento sistémico MTX. Este paciente presenta una gran asimetría de la mandíbula. Puede apreciarse un bajo patrón de crecimiento; el cóndilo derecho no presenta ningún crecimiento vertical condilar y el cóndilo izquierdo presenta un ligero aumento vertical.

AV.3 Pacientes tratados con Remicade (infliximab):

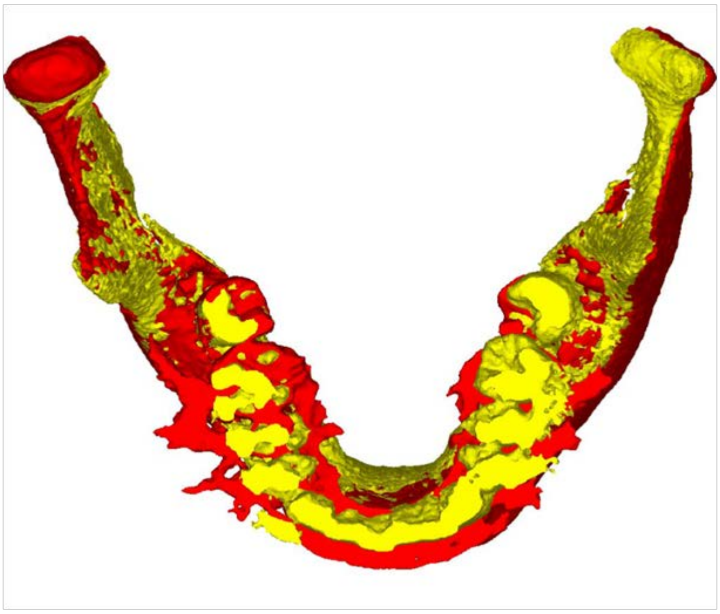


Paciente 5. Niña de 12 años con AIJ y tratada con DS. Tratamiento sistémico infliximab. Este paciente presenta un muy buen crecimiento de ambos cóndilos. El crecimiento es bastante simétrico en ambos cóndilos tanto en sentido vertical como distal.

AV.4 Pacientes no tratados con fármacos sistémicos (solo AINES durante períodos de dolor):



Paciente 6. Niña de 16 años con AIJ y tratada con DS. Nunca ha sido tratada con fármacos, solamente con AINES para dolor. No existe presencia de crecimiento en ambos cóndilos. Solamente se puede observar un ligero cambio en la parte distal de ambos cóndilos. Se trata de una niña de edad casi adulta donde el crecimiento general del paciente puede estar consolidado.



Paciente 7. Niño de 13,8 años con AIJ y tratado con DS. Nunca ha sido tratado con fármacos, solamente con AINES para dolor. En la historia clínica el paciente siempre refiere dolor en el cóndilo izquierdo. En este caso solamente se observa un buen crecimiento en el cóndilo derecho, (tanto en sentido vertical como distal). En el cóndilo izquierdo solamente se aprecian cambios en sentido distal.

COMUNICACIONES Y PUBLICACIONES DERIVADAS DE ESTA TESIS

Comunicaciones a congresos:

1. F. Otero, P. G. Tahoces, A. Mera, J. Mira

"Assessment of soft tissues within the TMJ by software processing of Cone Beam Computed Tomography data enhancing image contrast"

91th Congress of the European Orthodontic Society
Venecia (Italia), 13-18 de junio de 2015

2. F. Otero, A. Mera, A.Souto, M. López, E. Cervantes

"Grado de afectación de la articulación temporomandibular en la artritis idiopática juvenil estableciendo un umbral radiológico diferenciador entre estados sano y enfermo"

XI Congreso de la SERPE
Sevilla, 26-28 de noviembre de 2015

3. F. Otero, A. Mera, P. G. Tahoces, J. Mira

"Medical Imaging in JIA"

EuroTmjoint 7th Congress 2016
Milan (Italia), 26-28 de septiembre de 2016

Publicaciones:

1. M.F. Otero, T.K. Pedersen, M. Dalstra, T. Herlin, C. Verna

"3D evaluation of mandibular skeletal changes in juvenile arthritis patients treated with a distraction splint: A retrospective follow-up"

Angle Orthodontist DOI: 10.2319/081715-549.1 (2016)

2. M. F. Otero, P. G. Tahoces, A. Mera, M. Dalstra, C. Verna, T. K. Pedersen, T. Herlin, J. Mira

"Quantification of temporomandibular joint space in patients with juvenile idiopathic arthritis assessed by cone beam computerized tomography"

(enviado a European Journal of Orthodontics)

3. M. F. Otero, P. G. Tahoces, A. Mera, J. Mira

“Assessment of TMJ soft tissues by enhancing image contrast of cone beam computed tomography data”

(enviado a American Journal of Orthodontics and Dentofacial Orthopedics)