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A COMPARISON OF MAGNETIC RESONANCE IMAGING AND CONE BEAM COMPUTED TOMOGRAPHY IN THE EVALUATION OF TEMPOROMANDIBULAR JOINT CHANGES IN RHEUMATOID ARTHRITIS PATIENTS

A THESIS SUBMITTED TO THE COUNCIL OF THE COLLEGE OF DENTISTRY, UNIVERSITY OF SULAIMANI IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN

ORAL AND MAXILLOFACIAL RADIOLOGY

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Dedication

This PhD thesis is dedicated to:

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Abstract

ABSTRACT

Background/ Aims: Changes in Temporomandibular joints(TMJ) occur in rheumatoid arthritis (RA) patients like other body joints. This study aimed at determining the occurrence and clinical and radiographic features of TMJ involvement in patients with RA and examining the association of radiographic changes with RA duration. By comparing the diagnostic efficacy of cone-beam computed tomography (CBCT) to magnetic resonance imaging (MRI) technique in identifying changes of TMJs, and to find out the correlation of laboratory tests with clinical symptoms of TMJs and correlations between condylar dimensional changes and the jaw movements in RA patients.

Patients and methods: This case-control study was performed on 40 patients previously diagnosed with RA classified into two groups according to their duration of the disease (group A with duration of 1-5 years and group B with duration of 6-10 years). At the same time, ten healthy adult individuals were enrolled as control cases (group C). Clinical examination of TMJs were carried out then laboratory tests were performed and CBCT and MRI of TMJs were done for participants and images interpreted by expert radiologist and the observed radiographic changes recorded.

Results: The frequency of TMJ involvement clinically in RA patients was 15% in Group A and 40% in Group B. The most frequently observed clinical symptom was facial pain (25%), and the slightest symptom was clicking (2.5%) during mouth opening. The frequency of TMJ involvement radiographically in RA patients using CBCT were (75% in group A and 90% in group B) and using MRI were (80% in group A and 95% in group B) and in the control group were 10% and 30%, respectively. No significant differences were seen in condylar length, width, and height between both RA groups and RA and

control cases. The common change in CBCT of RA patients was condylar head erosion (67.5%), and the less common change was articular eminence erosion (7.5%), while in controls was condylar head flattening (50%). The most frequent changes in MRI of RA patients were an osseous change of condylar head (80%), and the minor change was effusion (10%), while in controls were an osseous change of condylar head (30%) and condylar head flattening (10%). There was a positive correlation found between laboratory test results and facial pain and jaw pain and lock and joint clicking in RA patients. Positive correlation found between condylar dimensions (length, width and height) and vertical and horizontal jaw movements (mouth opening and lateral jaw excursion) There was a .positive correlation between ESR, RF, and Anti-CCP and osseous changes of TMJ.

Conclusion: Osseous changes occur in TMJs of RA patients with no/mild symptoms. The chronicity of RA affects the frequency of TMJ involvement MRI can be used as an efficient imaging modality for detecting changes in TMJ,. The elevated ESR, RF and Anti-CCP may indicate the presence of clinical symptoms and osseous changes of TMJs in RA patients and elevated ESR and Anti-CCP predict reduction in condylar dimensions. RA patients have limitation of jaw movements.

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List of Abbreviations

2D	Two Dimensional
3D	Three Dimensional
ACPAs	Antibodies to Citrullinated Protein Antigens
ACR	American College of Radiology
AP	Antero-posterior
APRs	Acute Phase Reactants
B0	Magnetic field strength
CBCT	Cone Beam Computed Tomography
CD	Compact Disc
CDAI	Clinical Disease Activity Index
CRP	C-Reactive Protein
CSF	Cerebrospinal fluid
CT	Computerized Tomography
DAS	Disease Activity Scoring
DICOM	Digital Imaging and Communication in Medicine
DMARDs	Disease-modifying Anti-rheumatic Drugs
ESR	Erythrocyte Sedmentation rate
EULAR	European League Against Rheumatism
F	Precessional Frequency
FID	Free Induction Decay
FOV	Field of view

FPD	Flat Panel Detector
G1	Grade I erosion
JAK	Janus kinase
JIA	Juvenile Idiopathic Arthritis
LT	Left
mGy	milliGray
MHz	Mega Hertz
ML	Medio-Lateral
MPR	Multiplanar Reconstruction
MRI	Magnetic Resonance Imaging
mS	millisecond
µSv	micro Sievert
Mz	Magnetization vector
N	Number
OA	Osteoarthritis
OS 1	Osseous change type I
PTML	Pterygomandibular ligament
RA	Rheumatoid Arthritis
RDC	Research Diagnostic Criteria
RF	Rheumatoid Factor
RT	Right
SD	Standard Deviation

SDAI	Simplified Disease Activity Scoring
SML	Sphenomandibular ligament
SNR	Signal-to-noise ratio
SPSS	Social Package for Statistical Sciences
STML	Stylomandibular ligament
T	Tesla
TE	Echo time
TMD	Temporomandibular Disorder
TMJ	Temporomandibular Joint
TR	Repetition time
US	Ultrasonography

Introduction

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease characterized by joint swelling, tenderness and destruction of synovial joints that leads to severe disability and premature mortality (Ruparelia et al., 2014). The TMJ is an important joint closely associated with masticatory and swallowing functions, and its damage severely reduces the quality of life. The Temporomandibular joint (TMJ) complaints in patients with RA were recorded to be higher than 50% from population (Cordeiro et al., 2016).

The Temporomandibular joint involvement in RA patients is excluded based on medical history, physical examination, radiographic findings, and laboratory test results. Therefore, a multidisciplinary approach is necessary (Sidebottom and Salha 2013). Common clinical signs and symptoms of TMJ involvement are bilateral pain, swelling, stiffness during mouth opening, weakness of the masticatory muscles with decreased bite force, joint noises, and restriction of jaw movements in the late phase of RA (Moen et al., 2005), ankylosis is more likely to occur (Aceves-Avila et al., 2013).

Rheumatoid Arthritis affecting the TMJ make a diagnostic challenge to the dentist in the initial stages of disease course (Chitroda, Katti and Ghali 2011). Accordingly, the importance of imaging diagnosis of RA in the TMJs should be emphasized, similar to that of other joints (Kretapirom et al., 2013).

Several imaging techniques have been used for the evaluation of the TMJ; among them, Magnetic Resonance Imaging (MRI) has significant advantages over them in its ability to depict soft tissue changes of the TMJ, but their diagnostic value for the detection of TMJ osseous abnormalities is still controversial (Navallas et al., 2017). Recently, Cone Beam Computerized Tomography (CBCT) has become widely used to diagnose abnormalities of the

dental region, and its reliability for detecting osseous abnormalities of the TMJ has been reported (Mupparapu et al., 2019).

The frequently observed radiographic changes in RA are joint-space narrowing and marginal erosions, while in the advanced stage are extensive osteolysis and even complete destruction of the condyle, however; ankylosis is rare; osteophytes may be observed but they are not a specific characteristic of RA (Sodhi et al., 2015).

Several studies has been conducted to evaluate TMJ changes in RA patients (Kretapirom et al. 2013, El-Melegy et al. 2017, Rehan et al. 2018, Yousef et al. 2020) however none of them characterize their radiological changes therefor the goals of this study were to determine the frequency and character of TMJ involvement in RA patients. Additionally comparing the diagnostic efficacy of MRI and CBCT in detecting radiographic changes of TMJs, and finally to find out the correlation between RA and clinical symptoms of the TMJ.

Aims and Objectives of the study

Aims of this study were:

1. To determine the frequency and characteristics of clinical and radiological involvement of TMJ in RA patients.
2. To find out if there is any correlation between duration of RA and clinical symptoms and radiographic changes of TMJ.

Objectives of this study were:

1. To Compare the diagnostic efficacy of two imaging modalities (MRI, and CBCT) for evaluation of TMJ involvement in RA.
2. To assess the condylar dimensional changes in rheumatoid arthritis patients.

Chapter One

Review of Literature

Chapter 1: Review of Literature

1.1 Temporomandibular Joint

The temporomandibular joint (TMJ) can be defined as a diarthrosis, or a ginglymoarthrodial joint (capable of both hinge-type movements and gliding movements). During wide mouth opening, the condyle rotates around a hinge axis and then translates as it glides, causing it to move beyond the anterior border of the fossa, which is identified as the articular eminence (Bender et al., 2018, Glick et al. 2021).

1.1.1 Anatomy

The TMJ is a complex joint comprised of bone, ligament, and an articular disc. The bony components include the mandibular condyle and the glenoid fossa of the temporal bone. The mandibular condyle forms the lower part of the bony joint and is generally elliptical in shape, although variations are common (Bordoni and Varacalo 2022).The articulation is formed by the mandibular condyle occupying a hollow in the temporal bone (the mandibular or glenoid fossa). The bony elements are enclosed and connected by a fibrous capsule (Figure 1-1) (Glick et al. 2021).

The fibrous joint capsule is lined with synovial tissue, a vascular connective tissue which extends to the boundaries of the articulating surfaces. The synovial membrane consists of macrophage-like type A cells and fibroblast-like type B cells identical to those in other joints (Glick et al. 2021).

The joint cavity is filled with synovial fluid. Synovial fluid is a filtrate of plasma with added mucins and proteins. Its main constituent is hyaluronic acid. Fluid forms on the articulating surfaces and decreases friction during joint compression and motion. Joint lubrication is achieved by mechanisms described as weeping lubrication and boundary lubrication. Weeping lubrication occurs as fluid is forced laterally during compression and expressed through the unloaded fibrocartilage. As the adjacent areas become loaded, the weeping lubrication aids in reducing friction. Boundary lubrication is a function of water that is physically bound to the cartilaginous surface by a glycoprotein (Glick et al. 2021).Collectively, the fluid dynamics depend on appropriate loading and

unloading of the joint through normal function in order to maintain continuous lubrication as well as maintenance of the tissue health (Koolstra et al. 2006).

Fibrocartilage, instead of the expected hyaline cartilage, covers the articulating surface of the joint. Fibrocartilage is less distensible than hyaline cartilage due to a greater number of collagen fibers including Type 1 collagen. The matrix and chondrocytes are decreased because of the larger irregular bundles of collagen fibers (Stocum and Roberts 2018).

The fibrocartilage found on the articulating surfaces of the TMJ is thought to provide more surface strength against forces in many directions while allowing more freedom of movement than would be possible with hyaline cartilage. This covering is thickest on the posterior slope of the articular eminence and on the anterior slope of the condylar head; these are the areas thought to receive the greatest functional load. The thinnest part of the fibrocartilage covering is on the roof of the mandibular fossa. Fibrocartilage has a greater repair capacity than hyaline cartilage which may affect how the TMJ responds to degenerative changes (Meikle 1992, Stocum and Roberts 2018).

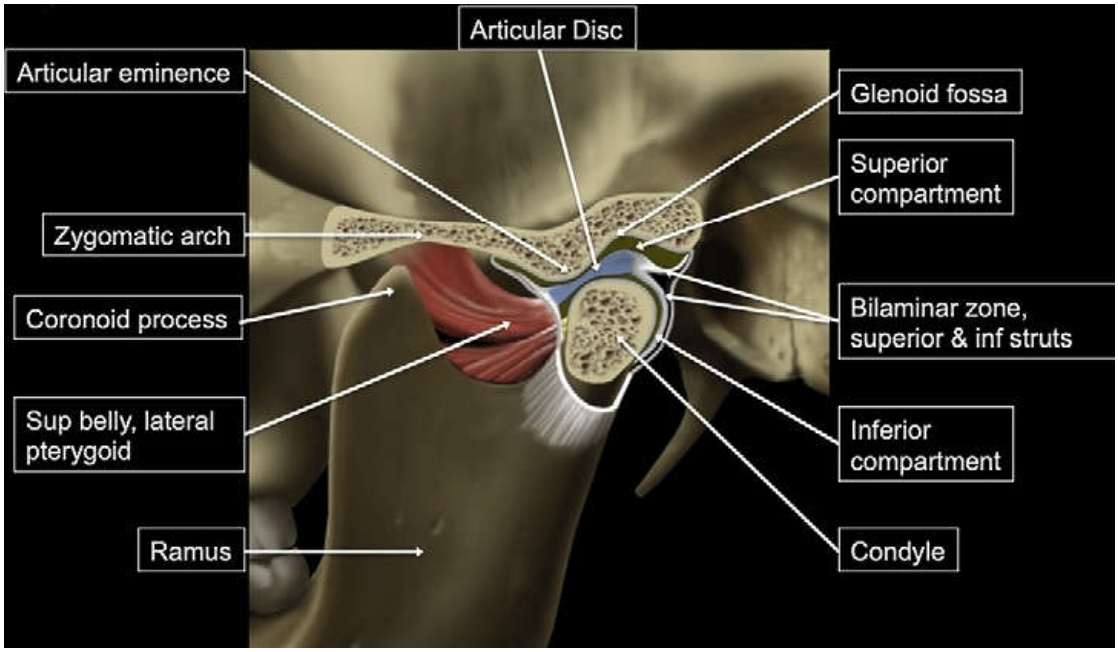


Figure (1-1): Different components of the temporomandibular joint. (Bordoni and Varacallo 2022).

1.1.2 Articular Disc

Dense fibrous connective tissue primarily made up of dense collagen of variable thickness is referred to as a disc and occupies the space between the fibrocartilage coverings of each of condyle and mandibular fossa (Glick et al. 2021).

The articular disc which covers the condyle and interposes below the glenoid fossa has a biconcave or oval shape; the cartilaginous disc has an anterior portion (about 2 mm) and posterior portion (about 3 mm), with a thinnest diameter in the middle. The anterior portion of the disk composed of a layer of fibroelastic fascia (superiorly) and a fibrous layer (inferiorly). The upper portion is in contact with the postglenoid process, and it prevent the disc from slipping during mouth opening. The lower portion of the disk has a function of avoiding excessive rotational movements of the disk relative to the mandibular condyle (Cuccia, Caradonna and Caradonna 2011).

The anterior portion of the articular disk is in contact with: the joint capsule; articular eminence; condyle; and upper area of the lateral pterysgoid muscle (Cuccia, Caradonna and Caradonna 2011).

The posterior portion of the articular disk relates to bilateral retro-disc tissue (behind the condyle), glenoid fossa; condyle; temporal bone (Cuccia, Caradonna and Caradonna 2011).

The medial and lateral aspects of the cartilaginous disc are attached to the condylar formation of the mandible. The edges of the disc partly fuse with the fibrous capsule surrounding the joint (Cuccia, Caradonna and Caradonna 2011).

1.1.3 Ligaments

There are Several ligaments that manage the forces of TMJ and send multiple proprioceptive afferents. The proprioception of the TMJ is provided by various components, such as the capsule, masticatory muscles, skin receptors and receptors within the periodontal ligaments. The tension that is perceived by the articular ligaments plays an important role in the function of TMJ (Cuccia, Caradonna and Caradonna 2011).

- The sphenomandibular ligament (SML) is a residue of Meckel cartilage. It is originated from the sphenoid spine (from which also the pterygospinous ligament originates) and it is inserted in the medial wall of the TMJ joint capsule. Through the petrotympanic fissure, it involves the malleus and forms some fibers of the anterior ligament of the malleus. It continues their descending path to attach to the lingula of the mandible (sphenoid, middle ear, jaw). The mylohyoid nerve and several vessels cross the ligament; has contacts with the pterygomandibular fascia. It is in a superior and lateral relationship with the lateral pterygoid muscle, the internal maxillary artery and the auriculotemporal nerve, the inferior alveolar nerve, and the medial meningeal artery. Its major task (function) is to protect the TMJ from an excessive translation of the condyle, after 10 degrees of mouth opening (Sencimen et al., 2008; Mérida-Velasco et al., 2012).
- The stylomandibular ligament (STML) arises from the styloid process of the temporal bone up to the posterior margin or the angle of the lower jaw. It is considered as a thickening of the deep cervical fascia (in particular of the parotid fascia). It acts to limit the excessive protrusion of the jaw. Its embryological derivation concerns the first and second

branchial arch, from which the middle ear stapes will derive (through the Reichert cartilage). Through its path, it covers the inner portion of the medial pterygoid muscle (Sencimen et al., 2008; Mérida-Velasco et al., 2012).

- The pterygomandibular ligament or raphe (PTML) is a thickening of the buccopharyngeal fascia. It arises from the apex of the hamulus of the internal pterygoid plane of the skull up to the posterior area of the retromolar trigone of the mandibular bone. There are muscles in contact with PTML which are the buccinator muscle (anteriorly) and the pharyngeal constrictor muscle (posteriorly). Embryologically, this ligament derives from the mesenchymal connection of two branchial arches (first and second). PTML limits excessive jaw movements (Sencimen et al., 2008; Mérida-Velasco et al., 2012).
- Pinto or malleolomandibular or discomalleolar ligament. Embryologicaly derives from the tympanic portion. This ligament has two portions. The first includes the middle ear and the malleus relative to the anterior ligament of the malleus; the second involves the extra-tympanic area, the portion of the TMJ joint capsule, posterio-superior in contact with the retro-discal tissues (passing through the petro-tympanic fissure). The functions are twofold. For TMJ, it protects the synovial membrane with respect to the tensions of surrounding structures. For the middle ear, it seems to manage or influence adequate pressure for this area of the ear (Sencimen et al., 2008; . Mérida-Velasco et al., 2012).
- The collateral ligament consists of two bundles of symmetrical fibers that originate at the level of the intermediate fascia of the articular disk that

insert at the medial and lateral poles of the mandibular condyle. It serves to anchor the disk to the condyle (Sato et al., 1996; Bravetti et al., 2004).

1.1.4 Embryology

TMJ derives from the first pharyngeal arch which recognizes a mesodermal part (muscles and vessels) and mesenchyme (from neural crests) for bones and cartilages. The development of TMJ are divided into three stages: the blastemic stage; the cavitation stage and the maturation stage (Bender et al., 2018).

- Blastemic stage. starts from the seventh/eighth week of gestation where the formation of the glenoid fossa and condylar blastema happens (a group of cells that remain long undifferentiated and proliferating give rise to sketches of organs).
- Cavitation stage: at this stage, the formation of the lower joint space begins. The blastemis start to differentiate into multiple layers to form the lower synovial layer which will become the joint disk; this occurs between the ninth and tenth weeks of gestation.
- Maturation stage: the upper joint space starts to form at the eleventh week of gestation. TMJ will continue to form until the baby is born. Around 17 weeks, the joint capsule is formed, while at 19 to 20 weeks, the development of the cartilage inside the capsule can be recognized (Bender et al., 2018).
- The morphology of the glenoid fossa and the condyle will be influenced by the mechanical forces of the vessels and neighboring muscles. At birth, TMJ, in comparison to other types of synovial joints is not fully developed. The jaw will start to develop from the fourth week. TMJ develops with the ear simultaneously (Bender et al., 2018).

- Compared to adults, the child has a more obtuse mandibular arch, while adults have a more angular shape; in the baby, the glenoid fossa is looser and, the cartilage is not present yet, but there will be a fibrous connective tissue. In between 5 and 10 years of age, the condyles grow in a posterior, lateral and upward directions; the shape of the joint will be further managed by the mechanical forces of the teeth and the chewing muscles (Bender et al., 2018).

1.1.5 Blood Supply and Lymphatics

The arterial blood supply to TMJ is provided by the superficial temporal artery and the maxillary artery, and by the masseteric artery. Supply from other arterial branches are available , such as the posterior auricular artery and the ascending pharyngeal artery (derived from the external carotid artery), and from the ascending palatine artery (Figure 1-2) (Cuccia et al., 2013).

The venous drainage happen through the pterygoid plexus in the retrodiscal area, in conjunction with the internal maxillary vein, the sphenopalatine vein, the medial meningeal veins, the deep temporal veins, the masseterine veins, and the inferior alveolar vein (Bordoni and Varacallo 2022).

- Lymphatic drainage is not always the same to describe for all since in the case of TMJ disease, the number of lymph nodes increases. Usually, the lymphatic system related to TMJ comes from the area of the submandibular triangle (Bordoni and Varacallo 2022).

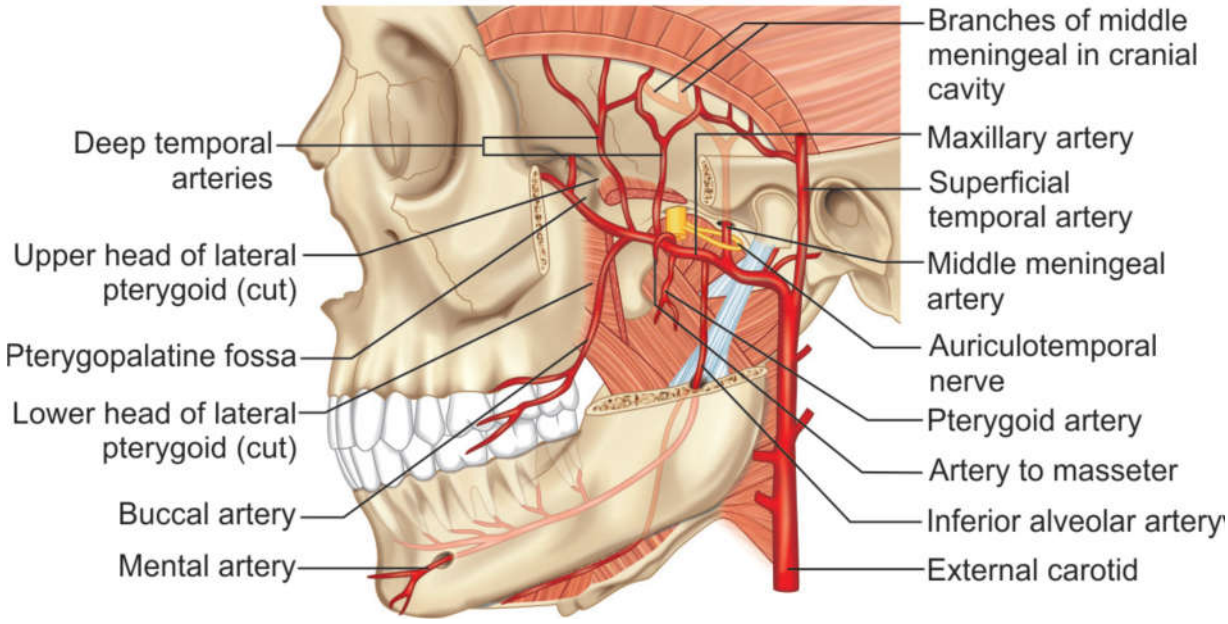


Figure (1-2): Blood supply of TMJ (Rawlani and Rawlani 2016)

1.1.6 Innervation

There are several proprioceptive receptors in TMJ, particularly in the parenchyma of the articular disk: myelinated and non-myelinated nerve fibers. The articular capsule in the anterolateral portion innervated by the masseteric nerve, which is a branch of the second branch of the trigeminal nerve. The lateral area of the capsule is innervated by the auriculotemporal nerve of the third branch of 5th cranial nerve (Figure 1-3) (Davison et al., 2003; Asaki et al., 2006).

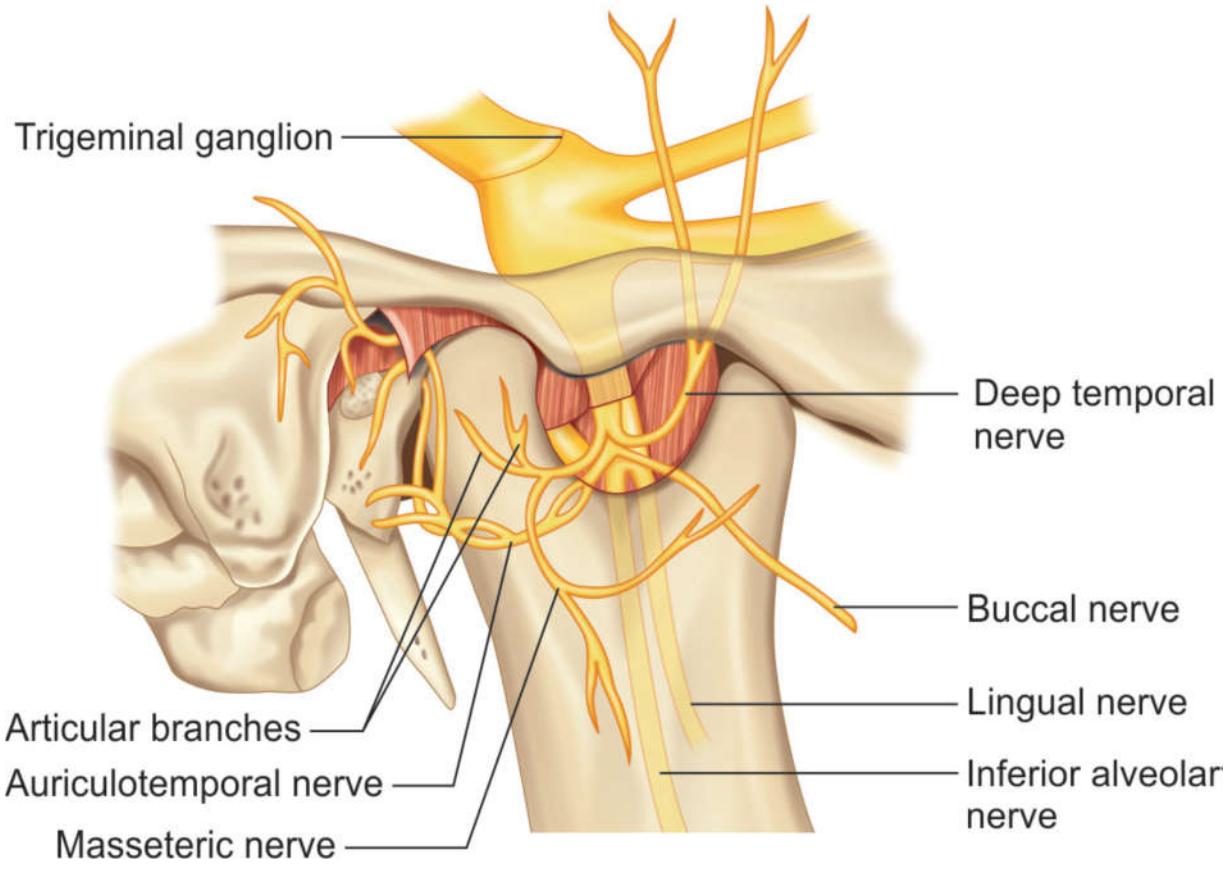


Figure (1-3): Nerve supply of TMJ (Rawlani and Rawlani 2016).

1.1.7 Muscles

TMJ is related to different muscles that have the function to move and protect the joint itself. The muscles that function to close the jaw are masseter, temporal, lateral or external pterygoid. The muscles that open the jaw are medial or internal pterygoid, geniohyoideus, mylohyoideus; digastric.

- The masseter muscle with its perimysium has direct contact with the articular disc on the front edge. It originates from the zygomatic arch with several muscular layers and inserts on the branch of the mandible (lateral surface) and the coronoid process (lateral surface).Its primary task is to elevate the jaw. The innervation of the muscle is through the masseteric branch of 5^{th} trigeminal cranial nerve).

- The temporalis muscle originates from the temporal fossa of the skull and the medial face of the zygomatic process; it inserts on the coronoid mandibular process. Like the previous muscle, the temporalis also makes contact with the articular disc anteriorly. It elevates the mandible. It receives innervation by the branches of the trigeminal, third branch (deep temporal nerves).
- The lateral or external pterygoid muscle consists of an upper head and a lower head. The upper bundle originates from the extracranial face of the large sphenoid wing to be inserted antero-medially to the joint capsule and/or the anteromedial face of the condyle neck in the upper portion of the pterygoid fovea. It contacts the disc at the anteromedial aspect. The inferior head originates from the lateral aspect of the lateral lamina of the pterygoid process of the sphenoid and inserts itself on the pterygoid fovea. Bilateral activation of the external pterygoid protrudes the mandible if activated unilaterally, it causes contralateral lateral deviation of the mandibular bone. The external pterygoid muscle pulls the condyle forward in the opening phase of the mouth; it pulls the disc antero-medially in the closing phase. The two upper and lower bundles are active in the early stages of opening and in the first stages of closing the mouth. The internal or medial pterygoid muscle originates from the pterygoid fossa, from the pyramidal process of the palatine and from the maxillary tuberosity, to terminate at the medial face of the angle and of the mandibular branch. Like the external pterygoid, the internal pterygoid is innervated by the mandibular branch of the trigeminal nerve. The internal pterygoid muscle elevates and protrudes the mandible (Bravetti et al., 2004).

1.1.8 Function

During mouth opening there is a combination of rotational movement of the discomandibular space and the translational action of discotemporal space; the rotation happen before the translation. The condyle can move laterally through a rotation then an anterior sliding of the same condyle happens, and an anterior translation/rotation in the medial direction of the opposite condyle occurs. One condyle can move backward while the opposite condyle slides forward. The bilateral or ipsilateral protrusion of TMJ happens by anterior sliding (Bordoni and Varacallo 2022).

The complex movements of TMJ allow multiple functions:

- Chewing
- Sucking
- Swallowing
- Phonation
- Facial expressions
- Breathing
- Protrusion, retrusion, lateralization of the jaw
- Opening the mouth
- Maintain the correct pressure of the middle ear (Bordoni and Varacallo 2022).

1.1.9 Physiologic Variants

An anatomical variant of TMJ is the Pneumatization of the articular tubercle . It consists of bone cavities/air cells in the root of the zygomatic arch / in the eminence or tubercle of the temporal bone. These cavities may be present only

unilaterally or bilaterally. Normally, these cavities are reabsorbed during puberty, but sometimes the reabsorption does not occur. This variability does not negatively affect the symptomatology or function of TMJ (Bichir et al., 2019).

1.1.10 Temporomandibular Disorders

Temporomandibular Disorders (TMD) are a heterogeneous group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joint complex, surrounding musculature and osseous components (Robert et al., 2015).

Temporomandibular Disorders (TMD) are characterized by pain in craniofacial region involving the joint, masticatory muscles, or muscle innervations of the head and neck. TMD is considered as a major cause of non-dental pain in the orofacial region. Population-based studies show that TMD affects 10% to 15% of adults, but only 5% seek treatment (Lim et al., 2010; Gonçalves et al., 2011).

The incidence peaks of TMD are between 20 to 40 years of age; in women it is twice common than in men and it carries a significant financial burden from loss of work. Symptoms can range from mild discomforts to debilitating pains, such as limitations of jaw functions (Maixner et al., 2011).

1.1.10.1 Etiology

The etiology of TMD is multifactorial which includes biologic, environmental, social, emotional, and cognitive triggers. Factors are consistently associated with TMD that include other pain conditions such as chronic headaches, fibromyalgia, autoimmune disorders, sleep apnea, and psychiatric illness (Scrivani, Keith and Kaban 2008; Lim et al., 2010) A prospective cohort study with more than 6,000 participants have shown a twofold increase in TMD in persons with depression (rate ratio = 2.1; 95% confidence interval, 1.5 to 3; $P < .001$) and a 1.8-fold

increase in myofascial pain in persons with anxiety (rate ratio = 1.8; 95% confidence interval, 1.2 to 2.6; P < .001) (Kindler et al., 2012).

1.1.10.2 Classification

TMD is categorized as an intra-articular (within the joint) or an extra-articular (involving the surrounding musculature) (Okeson 2007). Musculoskeletal conditions are the most common cause of TMD that account for at least 50% of cases (Stohler 1999; Reiter et al., 2012). Articular disk displacement involving the condyle–disk relationship (internal dearrangement) is the most common intra-articular cause of TMD (De Leeuw and Klasser 2013).

1.1.10.3 Diagnosis

The diagnosis of TMD is mostly based on history and physical examination findings. The TMD symptoms are often associated with jaw movement (e.g., opening and closing the mouth, chewing) and pain in the preauricular, masseter, or temple region. Another cause of orofacial pain should be suspected if pain is not affected by jaw movement. Unintended sounds of the jaw (e.g., clicking, popping, grating, crepitus) may occur with TMD, but also may happen in up to 50% of asymptomatic patients (Scrivani, Keith and Kaban 2008).

A large retrospective study (n = 4,528) conducted by a single examiner over 25 years that has been carried out, noted that the most common presenting signs and symptoms were facial pains (96%), ear discomforts (82%), headaches (79%), and jaw discomforts or dysfunctions (75%) (Cooper and Kleinberg 2007). Other symptoms may include dizziness or neck, eye, arm, or back pains. Chronic TMD can be defined by pains of more than three months' duration (Nassif 2001).

Physical examination findings that support the diagnosis of TMD may include but are not limited to abnormal lower jaw movement, decreased range of motion,

masticatory muscles tenderness , pains at dynamic loading, signs of bruxism, and neck or shoulder muscle tenderness. Clinicians should check for malocclusion (e.g., acquired edentulism, hemifacial asymmetries, restorative occlusal rehabilitation), which can contribute to the manifestation of TMD. Cranial nerve abnormalities should not be attributed to TMD. A clicking, crepitus, or locking of the TMJ may accompany a joint dysfunction (Scrivani and Mehta 2014).

A single click during mouth opening may be associated with an anterior disk displacement. A second click during mouth closure results in recapture of the displaced disk; this condition is referred to as disk displacement with reduction. When disk displacement progresses and the patient is unable to fully open the mouth (i.e., the disk is blocking translation of the condyle), this condition is referred to as closed lock. Crepitus is related to articular surface disruption, which often occurs in patients with osteoarthritis (Okeson and de Leeuw 2011).

Reproducible tenderness to palpation of the TMJ is suggestive of intra-articular derangement. Tenderness of the masseter, temporalis, and surrounding neck muscles may distinguish myalgia, myofascial trigger points, or referred pain syndrome. Deviation of the mandible toward the affected side during mouth opening may indicate anterior articular disk displacement (Emshoff et al., 2002).

1.1.8.4 Differential Diagnosis

Clinicians should be vigilant in diagnosing TMD in patients who have pains in the TMJ area. Conditions that sometimes mimic TMD include dental caries or abscess, oral lesions , conditions resulting from muscle overuse (e.g., clenching, bruxism, excessive chewing, spasm), trauma or dislocation, maxillary sinusitis, salivary gland disorders, trigeminal neuralgia, post-herpetic neuralgia, glossopharyngeal neuralgia, giant cell arteritis, primary headache syndrome, and pain associated with cancer (Okeson and de Leeuw 2011; Zakrzewska 2013).

The differential diagnosis and associated clinical findings are presented in Table (1-1) taken from (Okeson and de Leeuw 2011; Zakrzewska 2013). TMD symptoms can also manifest in autoimmune diseases such as systemic lupus erythematosus, Sjögren syndrome, and rheumatoid arthritis (Okeson and de Leeuw 2011).

Table (1-1): Conditions that may mimic Temporomandibular Disorders (Robert, Guaer and Michael 2015)

Condition	Location	Pain characteristics	Aggravating factors	Typical findings
Dental caries	Affected tooth	Intermittent to continuous dull pain	Hot or cold stimuli	Visible decay
Cratched tooth	Affected tooth	Intermittent dull or sharp pain	Biting, eating	Often difficult to visualize crack
Dry socket	Affected tooth	Continuous, deep, sharp pain	Hot or cold stimuli	Loss of clot, exposed bone
Giant cell arteritis	Temporal region	Sudden onset of continuous dull pain	Visual disturbance, loss of vision	Scalp tenderness, absence of temporal artery pulse
Migraine headache	Temporal region, behind the eye, cutaneous allodynia	Acute throbbing, occasionally with aura	Activity, nausea, phonophobia, photophobia	Often normal, aversion during ophthalmoscopic examination, normal cranial

				nerve findings
Glossopharyngeal neuralgia	Most often ear, occasionally neck or tongue	Paroxysmal attacks of electrical or sharp pain	Coughing, swallowing, touching the ear	Pain with light touch
Postherpetic neuralgia	Site of dermatomal nerve and its distribution	Continuous, burning, sharp pain	Eating, light touch	hyperalgesia
Trigeminal neuralgia	Unilateral trigeminal nerve	Paroxysmal attacks of sharp pain	Cold or hot stimuli, eating, light touch, washing	Pain with light touch
Sinusitis	Maxillary sinus, intraoral upper quadrant	Continuous dull ache	Headache, nasal discharge, recent upper respiratory infection	Tenderness over maxillary sinus or upper posterior teeth

1.1.11 TMJ imaging

A variety of imaging modalities can be used to image the TMJ. Those include non-invasive imaging modalities such as conventional radiographs, Transcranial and Transpharyngeal radiographs, ultrasound, Computed tomography (CT), Cone beam computed tomography (CBCT), MRI and an invasive imaging modalities such as arthrography. Each imaging modality has its uses (Bag et al., 2014).

A. Panoramic radiography

It demonstrates both upper and lower jaws and their associated structures, being a helpful imaging tool for the clinicians in diagnosing any periodontal or odontogenic causes for orofacial pain. Panoramic radiography does not include in the list of imaging techniques provided by RDC/TMD. Only the lateral part of the condyle can be assessed with panoramic technique, being limited in the use because of the superimposition of the zygomatic arch and the base of the skull (Ahmad et al., 2009).

High Panoramic radiography can be used in the evaluation of the following:

• Degenerative bone changes (only in late stages; it is inadequate for the early detection of osseous modifications);

• Asymmetries of the condyles (Figure 1-4);

• Hyperplasia, hypoplasia;

• trauma;

• tumors.

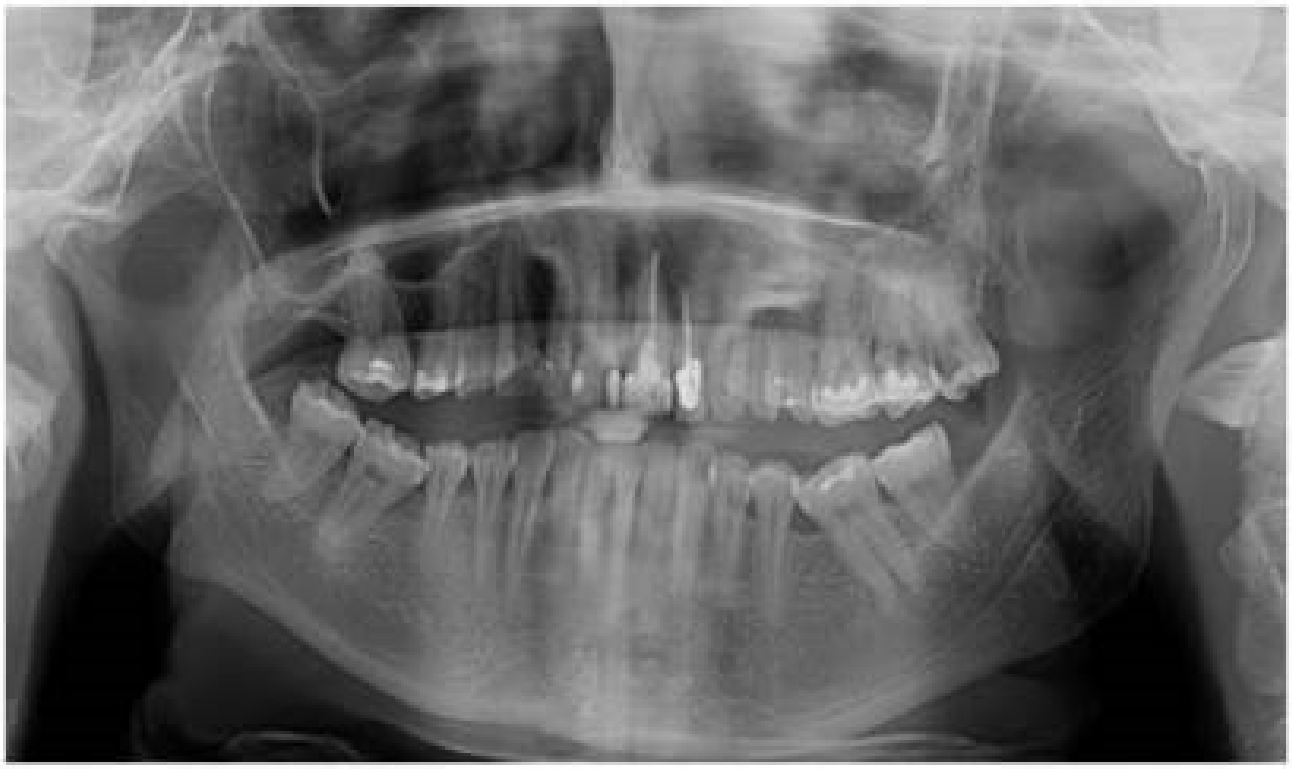


Figure (1-4): Panoramic radiography: important asymmetry between right and left mandibular condyle (Talmaceanu et al (a)2018).

The panoramic radiography does not show the functional status of the joint and has a relatively low specificity and sensitivity in comparison to CT (Ahmad et al., 2009, Poveda-Roda et al., 2015). Epstein, Caldwell and Black (2001) consider the clinical findings of greater importance than panoramic images for TMD patients. Nevertheless, some authors have proposed panoramic radiography as a good imaging modality for visualization of TMJ (Brooks et al., 1992). Although morphological abnormalities of the condyle can be assessed by panoramic radiography, they do not necessarily represent a sign of TMD (Crow et al., 2005).

B. Plain radiography

This consists of transcranial projection of TMJs. Different angulations are used to avoid the superposition of the temporal bone and the opposite TMJ: lateral oblique transcranial projections, anterior-posterior projections, submental-vertex

projection, transpharyngeal view (Brooks et al., 1997). Plain radiography is useful in depicting degenerative joint disease in advanced stages (Brooks et al 1997). The condyle position could also be assessed, but large variations of condyle position in the glenoid fossa were found, even in asymptomatic population (Figure 1-5) (Blaschke and Blaschke 1981; Pullinger et al., 1985).

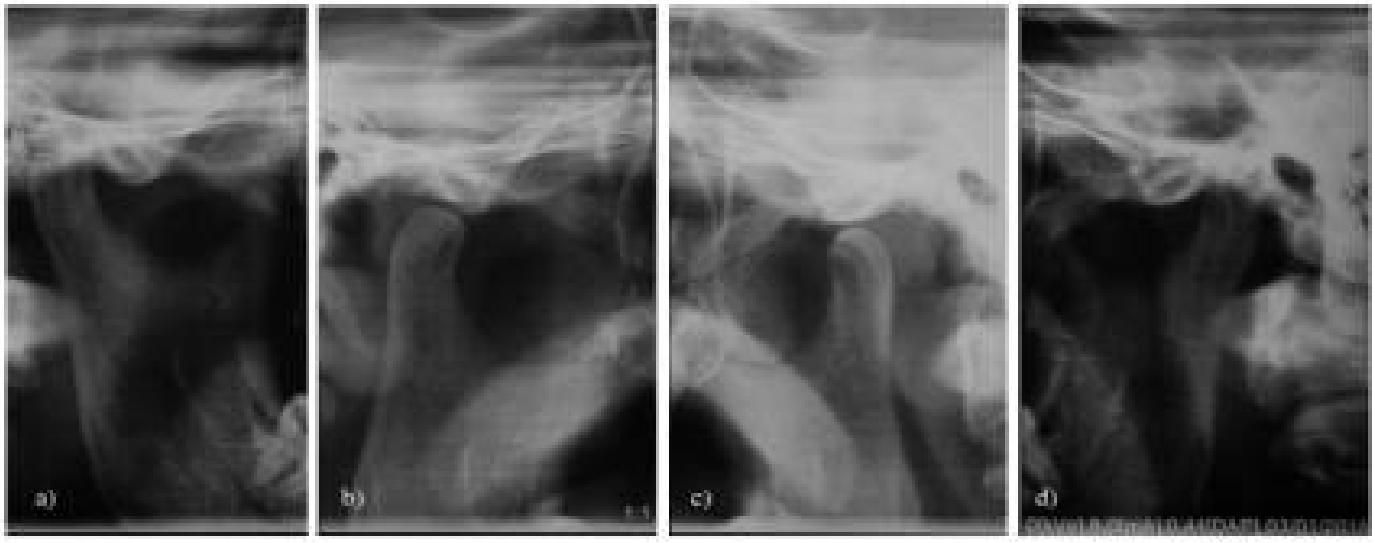


Figure (1-5): Comparative TMJ views obtained with a panoramic equipment: mouth-closed (a), (d) and mouth-opened (b), (c) (Talmaceanu et al. (a) 2018).

C. Computed Tomography (CT)

The first use of CT for TMJ evaluation was in 1980 (Baba et al 2016). It is considered as the best method for assessment of osseous pathologic conditions of TMJ. It allows a multi planar reconstruction (axial, sagittal and coronal) of TMJ structures, obtaining 3D images in both closed and opened-mouth positions. Degenerative changes in the joint, like surface erosions, osteophytes, remodeling, subcortical sclerosis, articular surface flattening can be evaluated by CT (Brooks et al., 1997).

Some scholars have revealed that the radiographic changes in the joint are not always be related to pain (Brooks et al., 1997; Sano et al., 2000; Bertram et al.,

2001). Some patients with osseous abnormalities may feel pain while others may not. Changes in the shape and location of the loading zone can also be detected on CT which is the main radiographic technique for evaluation of tumors, growth development anomalies and fractures (Figure 1-6) (Talmaceanu et al., 2018).

Autopsy studies done for the condylar abnormalities assessment showed better results for CT than MRI (Tanimoto et al., 1990).

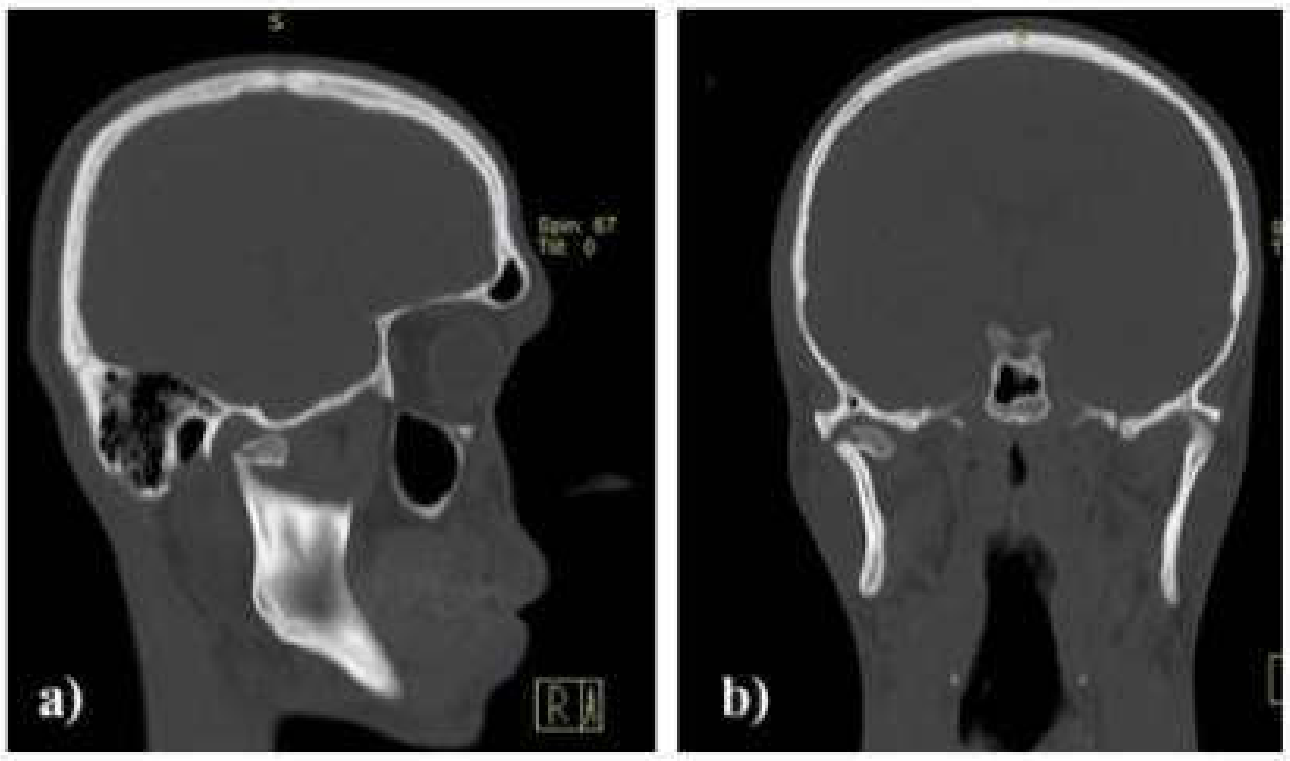


Figure (1-6): CT scan of an intracapsular fracture of the right TMJ. Sagittal plane (a), coronal plane (b) (Talmaceanu et al. (a) 2018).

Wesetesson et al. (1987) have found that the CT has a sensitivity of 75 % and a specificity of 100% for the diagnosis of condylar bony changes. CT cannot be used as a primary diagnostic tool for the visualization of the soft tissue components of TMJ (disc, synovial membrane, ligaments, lateral pterygoid muscle), The disc could be visualized on CT scans after injection of contrast

media into the joint (arthrography) which is a dynamic radiographic investigation, but it is not used widely due to their invasiveness, pain and possibility of allergic reactions of the contrast media (Maffe et al., 1988).

D. Ultrasonography

The Ultrasonography (US) was first used for TMJ exploration in 1991 by Nabeih et al. (1991), using a 3.5 MHz transducer. Although it is a non-invasive, dynamic, inexpensive procedure, it is not commonly used in TMJ exploration. Being a real time investigation, it provides information about disc position, during mouth opening (Talmaceanu et al., 2018). In the literature, contradictory levels of sensitivity and specificity were reported. These variable levels of sensitivity and specificity reported by the articles may be related to the different equipment used (different US frequencies). The use of high-resolution US (transducer at least 7.5 MHz or higher) significantly increases the diagnostic value of this technique (Manfredini and Guarda-Nardini 2009; Kundu et al., 2013).

The US examination is useful in depicting disc displacement and effusion. The disc is normally situated between two hyperechoic lines represented by the mandibular condyle and the articular eminence. If the disc is displaced in the closed-mouth position, the diagnosis is disc displacement. If the disc returns to its normal position during opening, the diagnosis is disc displacement with reduction (Figure 1-7). If not, the diagnosis is disc displacement without reduction (Figure 1-8) (Jank et al., 2001; Jank et al., 2005; Habashi et al., 2015; Talmaceanu et al., 2018). Regarding degenerative changes of the TMJ, US is still not recommended (Emshoff et al., 2003). One difficulty of US is the possibility to obtain clear images, especially in the opened-mouth position due to the overlying osseous structures. Another limitation of US is that the medial part

of the disc cannot be visualized (Jank et al., 2001; Emshoff et al., 2003; Jank et al., 2005; Manfredini and Guarda-Nardini 2009; Kundu et al., 2013; Habashi et al., 2015; Talmaceanu et al., 2018).

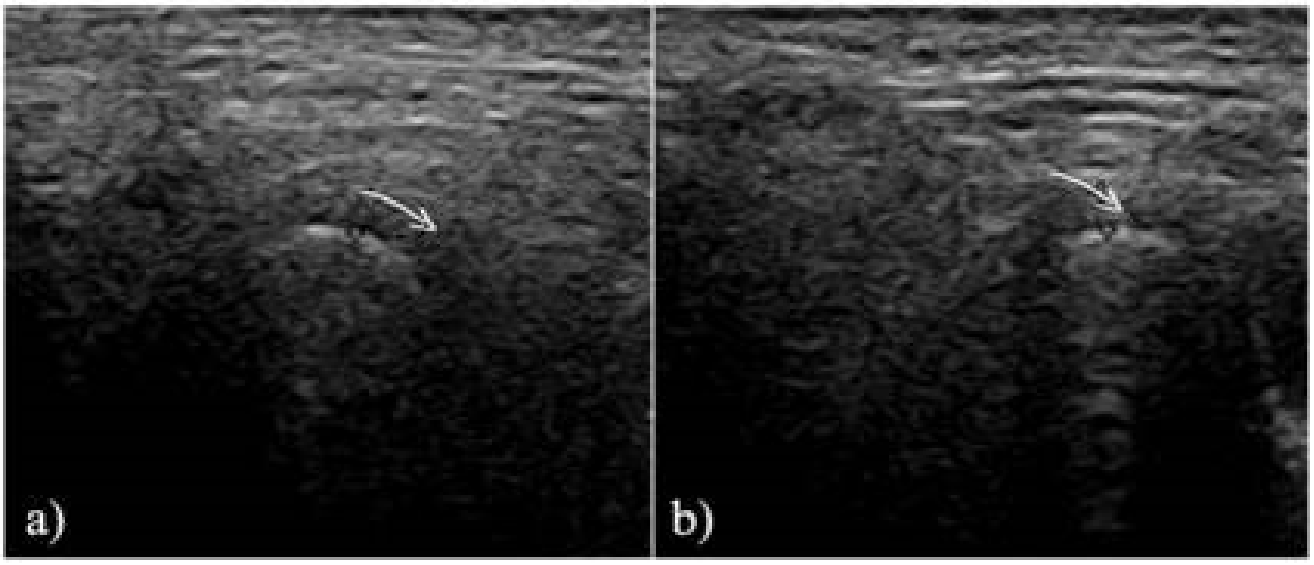


Figure (1-7): High resolution US of an anterior disc displacement with reduction: mouth-closed (a), mouth-opened (b). The arrow shows the displaced disc (Talmaceanu et al. (a) 2018).

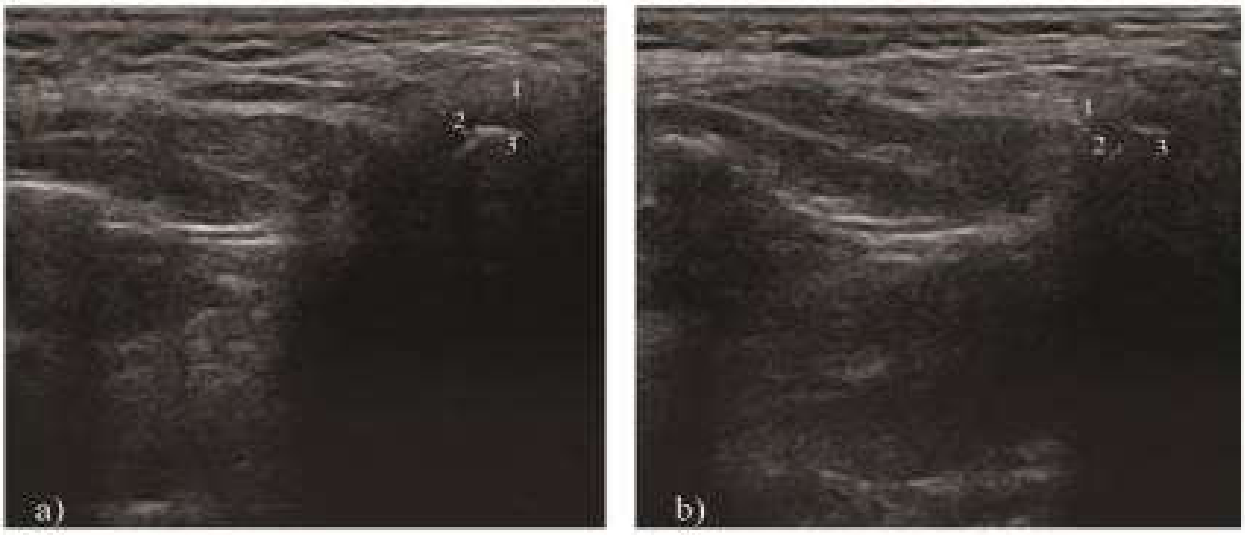


Figure (1-8): High-resolution US of an anterior disc displacement without reduction: mouth-closed (a), mouth-opened (b). 1 - articular eminence; 2 – articular disc; 3 - mandibular condyle (Talmaceanu et al. (a)2018).

1.2 Cone Beam Computed Tomography (CBCT)

CBCT is a medical imaging technique in which a cone-shaped X-ray beam centered on a two dimensional (2D) receptor to produce a series of 2D images. The reconstruction of these images in a 3 dimensional (3D) data set is done using the modified Feldkamp algorithm. (Gupta et al., 2005; Miracle and Mukherji (a) et al., 2009). Hence data can be reformatted in a volume rather than a slice thereby giving 3D information (Figure 1-9).

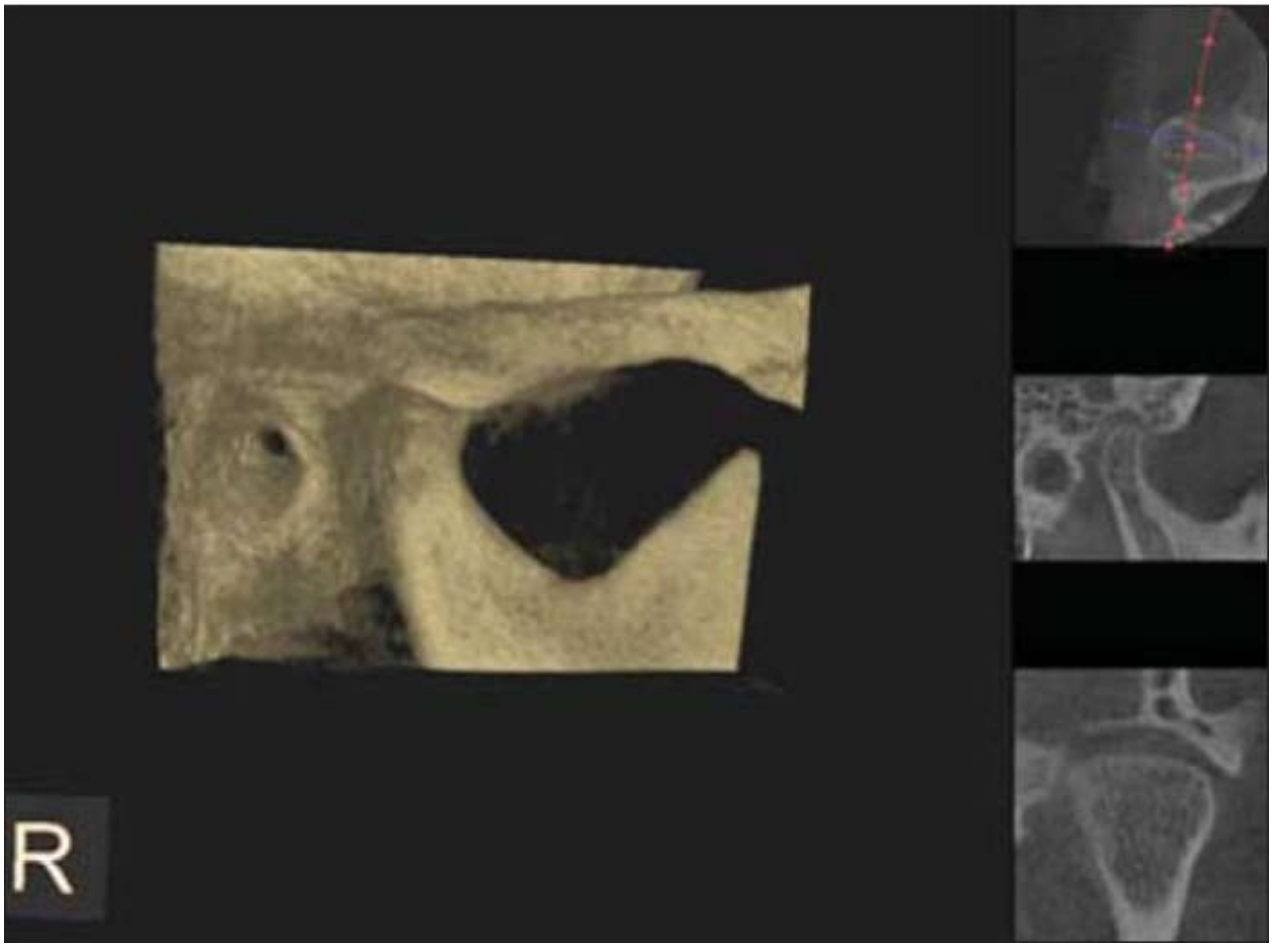


Figure (1-9): CBCT image showing the right TMJ with 3 dimensional (3D) reconstruction (Krishnamoorthy, Mamatha and Kumar, 2013).

CBCT allows Multiplanar reformation (MPR) i.e., 2D images in 3 main planes which are axial, coronal, sagittal and even oblique or curved image planes

(Figures 1-10, 1-11 and 1-12) taken from (Scarfe et al., 2006). Advancements in production of flat panel detector (FPD) technology (digital FPDs which enable direct conversion of x-ray energy into a digital signal with high spatial resolution), improved computing power and relatively low power requirements of x-ray tubes in CBCT have resulted in an exponential use of CBCT (Miracle and Mukherji (a) 2009).

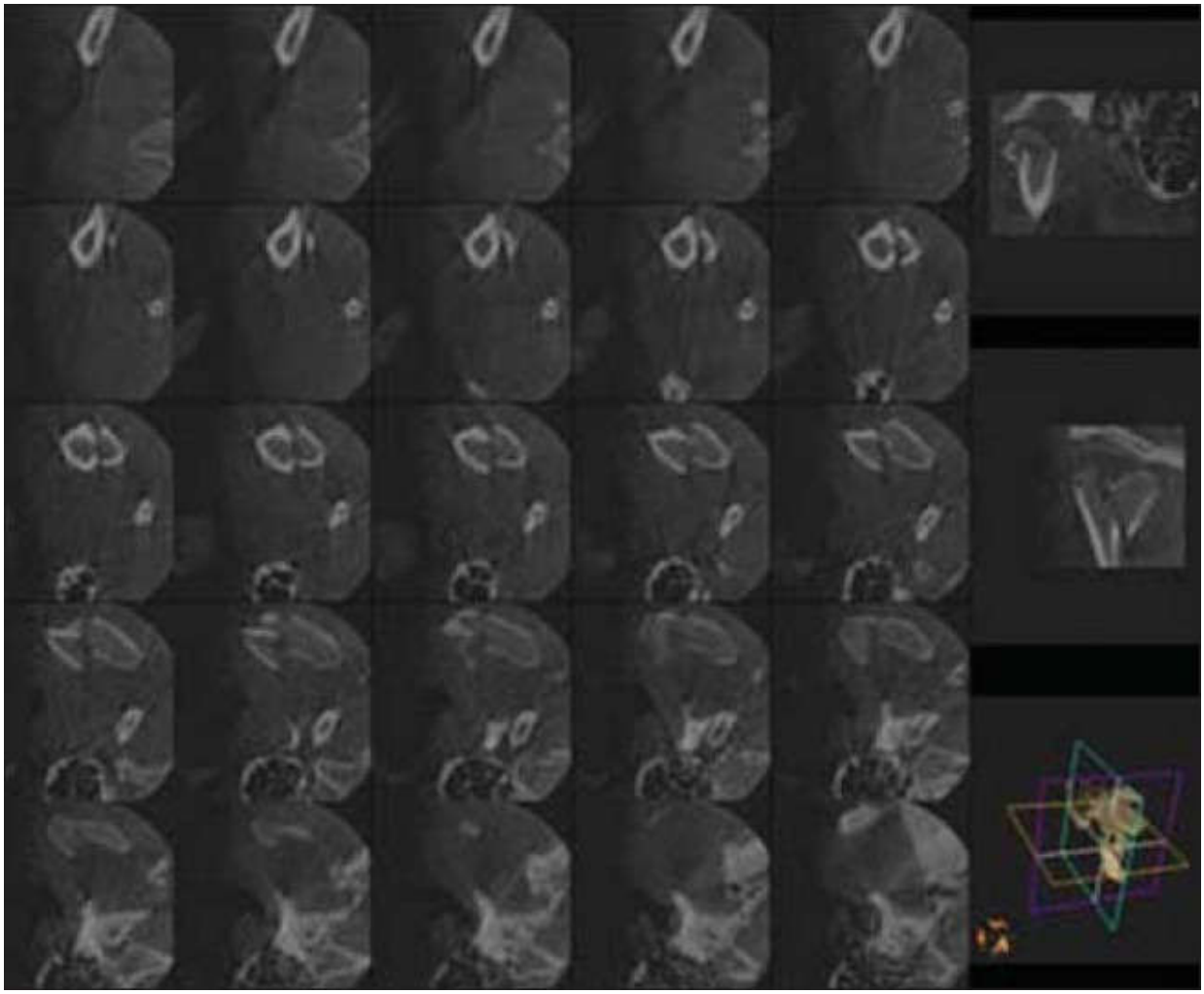


Figure (1-10): Axial sections of the right TMJ as seen on a CBCT image (Krishnamoorthy, Mamatha and Kumar, 2013)

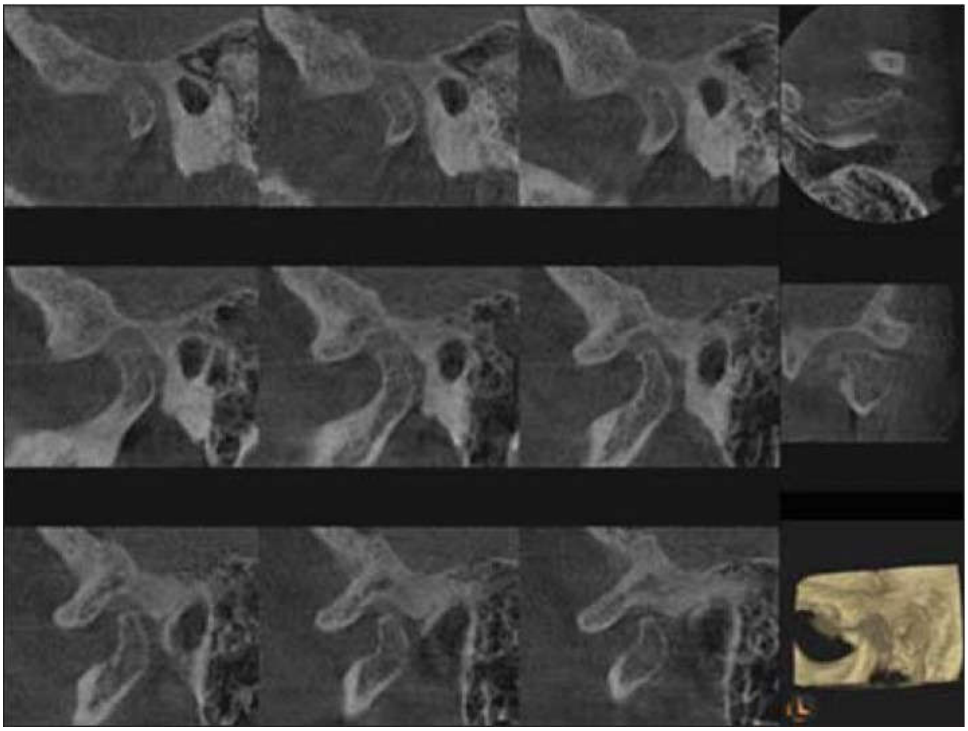


Figure (1-11): CBCT image of the coronal sections of the right TMJ (Krishnamoorthy, Mamatha and Kumar, 2013)

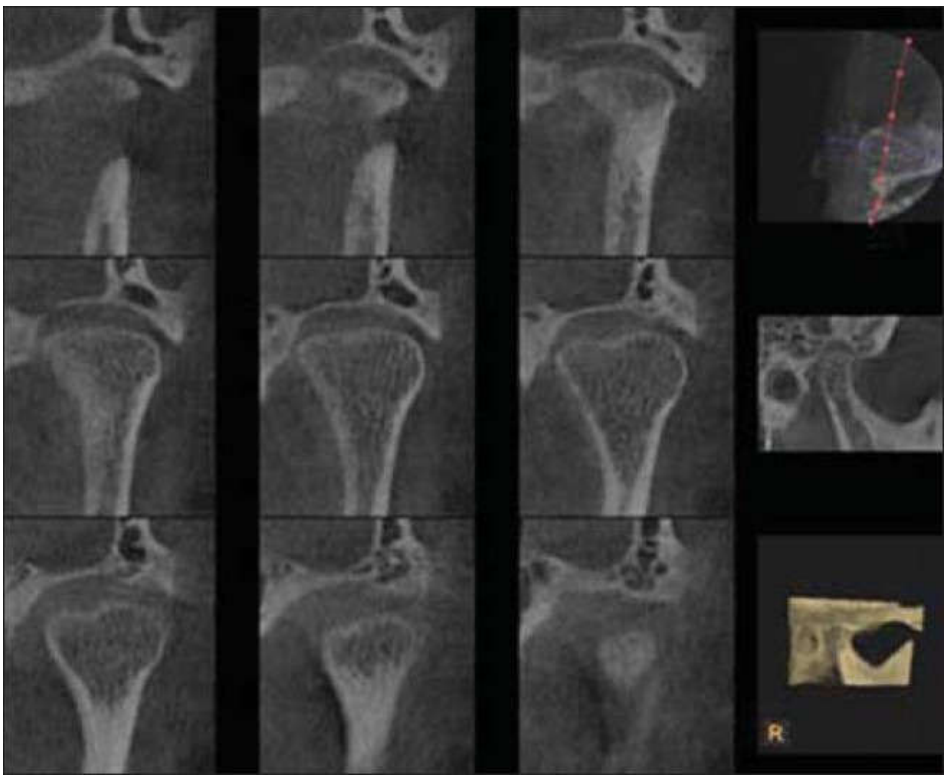


Figure (1-12): Sagittal slices of the left TMJ taken on a dedicated head and neck CBCT scanner (Krishnamoorthy, Mamatha and Kumar, 2013).

A large number of systems are available in the market which have application-specific exposure parameter protocols, with field of view (FOV) designed to capture the area of interest and minimize exposure to adjacent structures (Miracle and Mukherji (a) 2009).

CBCT scanners can be classified according to the type of detector, patient position during the procedure (sitting, standing or supine), field of view and use of fixed radiation settings or user controlled settings. A CBCT machine can also be either a dedicated or hybrid scanner (Dahlstrom and Lindvall 1996).

The CBCT has great advantages over CT in the imaging of the maxillofacial region. The CBCT of the head and neck can be adjusted to image small regions for specific diagnostic purposes by efficient limitation (collimation) of the primary x-ray beam. Thereby the irradiated area size is significantly reduced. CBCT provides high diagnostic quality of images. This is due to the isotropic (equal in all 3 dimensions) voxel resolutions which produces sub-millimeter spatial resolution ranging from 0.4mm to as low as 0.125mm. A short scan time which ranges from 10 to 70 seconds is another great advantage of the CBCT as it acquires all basic images in a single rotation (Scarfe et al., 2006).

Another important attraction of the dentomaxillofacial CBCT is the low effective dose which is reported to be 30-80 μSv (Miracle and Mukherji (b) 2009).This indicates that the radiation dose is noticeably reduced by up to 98% when compared to the conventional CT and amounts to 4-15 times the dose of a panoramic radiograph. Unique display modes and reduced image artifacts enable the clinicians to perform chair-side image analyses, Multiplanar reconstruction (MPR) and volume reconstructions. All these features have potentially enhanced the use of CBCT in the various fields of dentistry (Scarfe et al., 2006).

A major advantage of TMJ imaging by CBCT is that it allows accurate measurements of the surface and the volume of the condyle. These measurements are extremely helpful in clinical practice for treating TMJ dysfunctions (Tecco et al., 2010).

Osteoarthritis of the TMJ is an age – related degenerative change seen in almost 40% of patients above the age of 40. It causes osseous changes in the TMJ like flattening, sclerosis, formation of osteophytes, erosion, resorption of the condylar head, erosion of the mandibular fossa and reduced joint space. Flattening (59%) and osteophyte (29%) are the most common degenerative changes seen on CBCT (dos Anjos Pontual et al., 2012).

Many radiographic studies on cadavers have discovered the importance of CBCT in evaluating bony defects and osteophytes. Erosive bony changes in the TMJ are most efficiently diagnosed using CBCT with small FOV (6 inch) as compared to the large FOV (12 inch) (Librizzi et al., 2011). Alexiou, Stamatakis and Tsiklakis (2009) have evaluated the degenerative changes by CBCT for evaluation and they have found that patients in older age groups have more frequent and more severe bone changes than the younger patients.

Alkhader et al. (2010) have performed a comparative study between CBCT and MRI. According to them, CBCT is better than MRI in detecting changes in shape (flattening, osteophyte formation or erosion) rather than changes in size. They concluded that this was probably because MRI has limited spatial resolution and has increased slice thickness (>3mm) in clinical use. Other problems such as the presence of fibrous tissues inside the TMJ, proximity of lateral pterygoid muscle to the articular surface of the condyle and the presence of air spaces in the temporal bone can impede the accuracy in the interpretation of MRI. However, there is a poor correlation between condylar changes observed on CBCT images

and clinical symptoms seen in patients with TMJ osteoarthritis (TMJOA) (Palconet et al., 2012).

CBCT has an important role in diagnosing early stages of juvenile idiopathic arthritis (JIA) in children when undetected that can lead to damages of facial development and growth alterations. According to Farronato et al. (2010), CBCT can be used to volumetrically quantify the TMJ damages in those patients by measuring condylar and mandibular volumes.

Condylar asymmetry is rather common in children with JIA, CBCT shows a wide variety of condylar destruction patterns which could be small erosions within the cortex to almost complete deformation of the head of the condyle (Huntjens et al., 2008).

1.3 Magnetic Resonance Imaging (MRI)

Magnetic Resonance (MR) imaging is an exciting diagnostic imaging tool that uses strong magnets and low-energy radiofrequency signals such as those found in radios and televisions to gather information from certain atomic nuclei within the body. Therefore, MR does not require ionizing radiation to obtain images (Heiken and Brown, 1991; Stark and Bradly, 1992; Rinck 1993; Rayan 1997).

A correct description of what happens when tissue is subjected to a magnetic field relies on quantum mechanics. Fortunately, all the theories necessary for MRI can be based on a simple classical model which certain nuclei to spin around their own axes behave like small magnets. For clinical imaging, hydrogen is the most frequently used nucleus, but other possible nuclei are carbon-13, sodium, and phosphorus. Under normal circumstances, these tiny magnets are randomly distributed in space, the magnetic moments cancel each other, and thus the net magnetic vector is zero (Figure 1-13A). However, when the patient is

submitted to a strong external magnetic field (B0), the nuclei adopt one of two possible orientations: parallel or antiparallel to the external field (Figure 1-13B) (van Geuns et al., 1999).

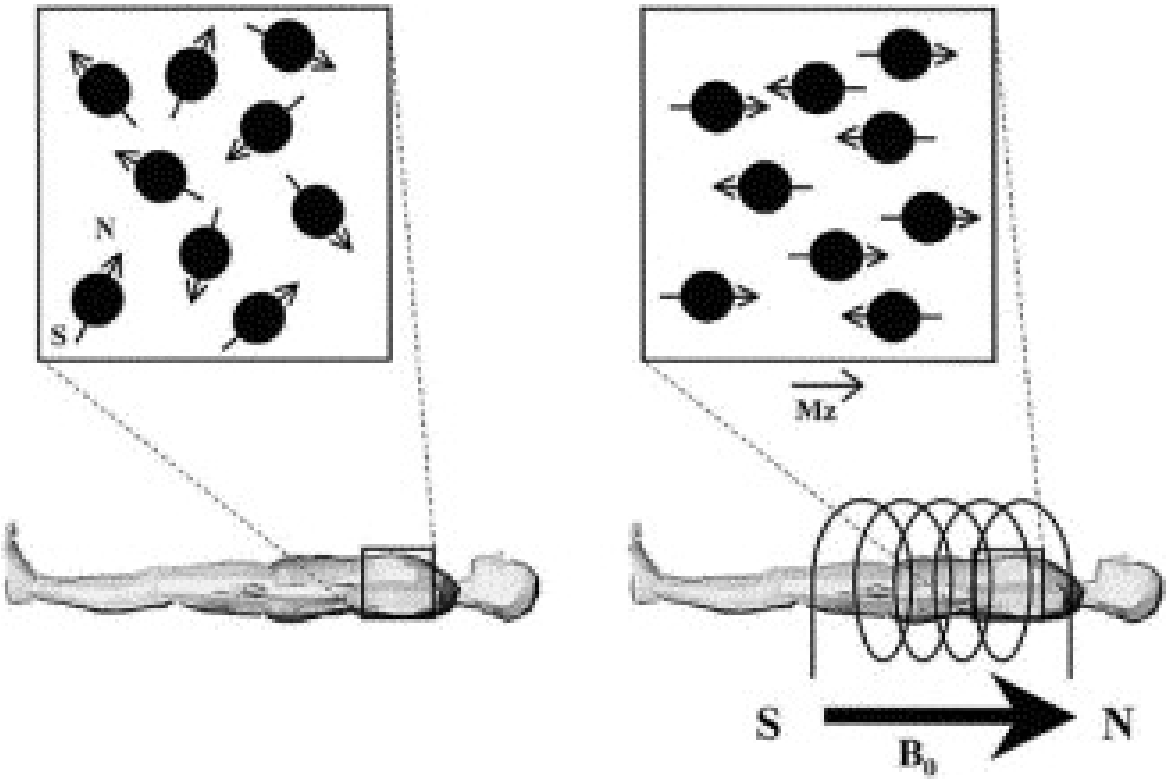


Figure (1-13): Magnetic momentum of nuclei (A) Without a magnetic field the magnetic moments of the nuclei are distributed at random and thus the net magnetization factor is zero. (B) When there is a strong external magnetic field the spinning nuclei align parallel or antiparallel to the external field (B0) with a few more parallel than antiparallel. This results in a net magnetization vector (Mz) parallel to the external magnetic field (van Geuns et al., 1999).

Parallel alignment is the lower energy state and is thus the preferred alignment, whereas antiparallel alignment is the higher energy state. The energy difference between the two states is very small: the population ratio is approximately 100,000 to 100,006. A net magnetization vector (Mz) aligned to the external

magnet results from the difference between the two populations. Individual nuclei do not actually line up with the magnetic field but wobble or precess around the direction of the external field (Figure 1-14A). The frequency of this precession is given by the Larmor equation:

F =yB0/2∏

where F is the precessional frequency, B0 is the strength of magnetic field, and y is the gyromagnetic ratio of the nucleus. This frequency is also called the Larmor frequency. In the frequently used commercial systems of 1.5 Tesla (T), the Larmor frequency will be 63.75 MHz for hydrogen. It is noted that the phase of precession around the axis of the magnetic field is different for each individual nucleus (Figure 1-14B) (van Geuns et al., 1999).

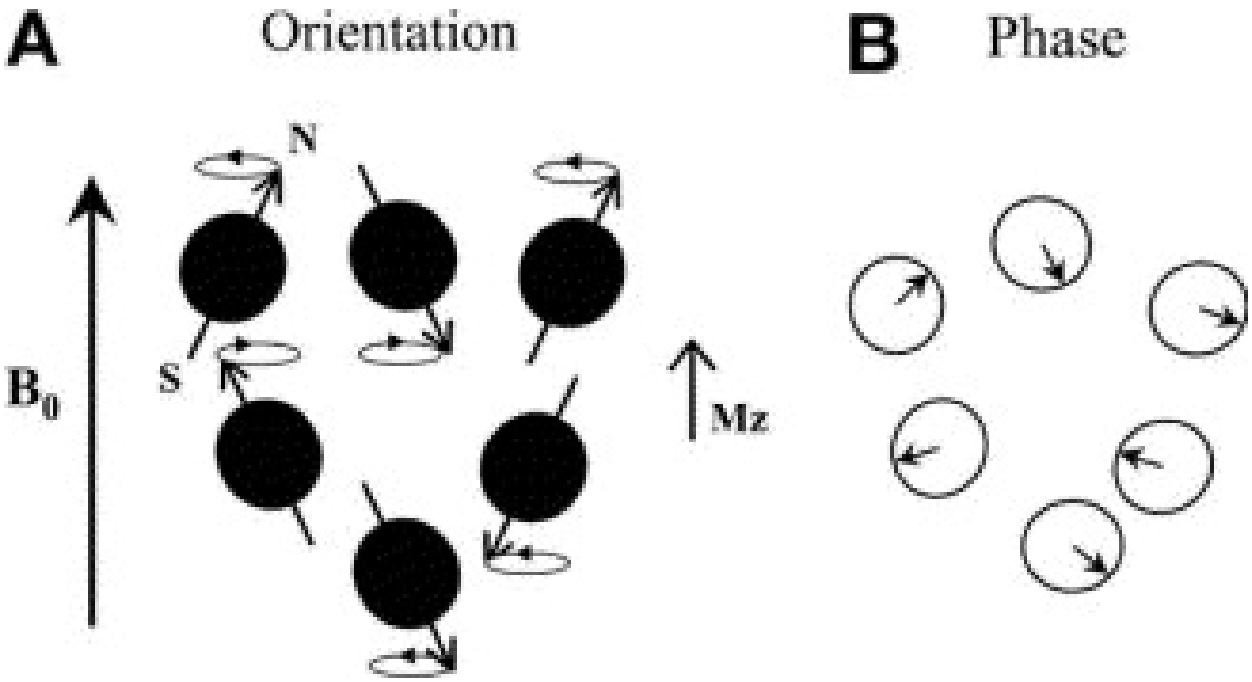


Figure (1-14): Nuclei precession (A) in more detail the individual nuclei spin around their own axes and wobble or precess around the direction of the external field (B0). (B) The phase of the precession around the axis of the external magnetic field is for each individual nucleus. van Geuns et al., 1999.

Nuclei that possess spin can be excited within the static magnetic field, B_0, by application of a second radiofrequency (RF) magnetic field B_1, applied perpendicular to B_0. The RF energy is usually applied in short pulses, each lasting microseconds. The absorption of energy by the nucleus causes a transition from higher to lower energy levels and vice versa on relaxation. The energy absorbed (and subsequently emitted) by the nuclei induces a voltage that can be detected by a suitably tuned coil of wire, amplified and displayed as the "free-induction decay" (FID). In the absence of continued RF pulsation, relaxation processes will return the system to thermal equilibrium. Therefore, each nucleus will resonate at a characteristic frequency when placed within the same magnetic field (Westbrook et al., 2011).

The energy required to induce transition between energy levels is the energy difference between the two nuclear spin states. This depends on the strength of the B_0 magnetic field the nuclei are subjected to . Application of an RF pulse at the resonant frequency generates a FID. In practice, multiple RF pulses are applied to obtain multiple FIDs, which are then averaged to improve the signal-to-noise ratio (SNR). The signal-averaged FID is a time-domain signal. It will be made up of contributions from different nuclei within the environment being studied (e.g. free water and ^1H bound to tissue). The signal-averaged FID can be resolved by a mathematical process known as Fourier transformation, into either an image (MRI) or a frequency spectrum, providing biochemical information (Figure 1-15) (Westbrook et al., 2011).

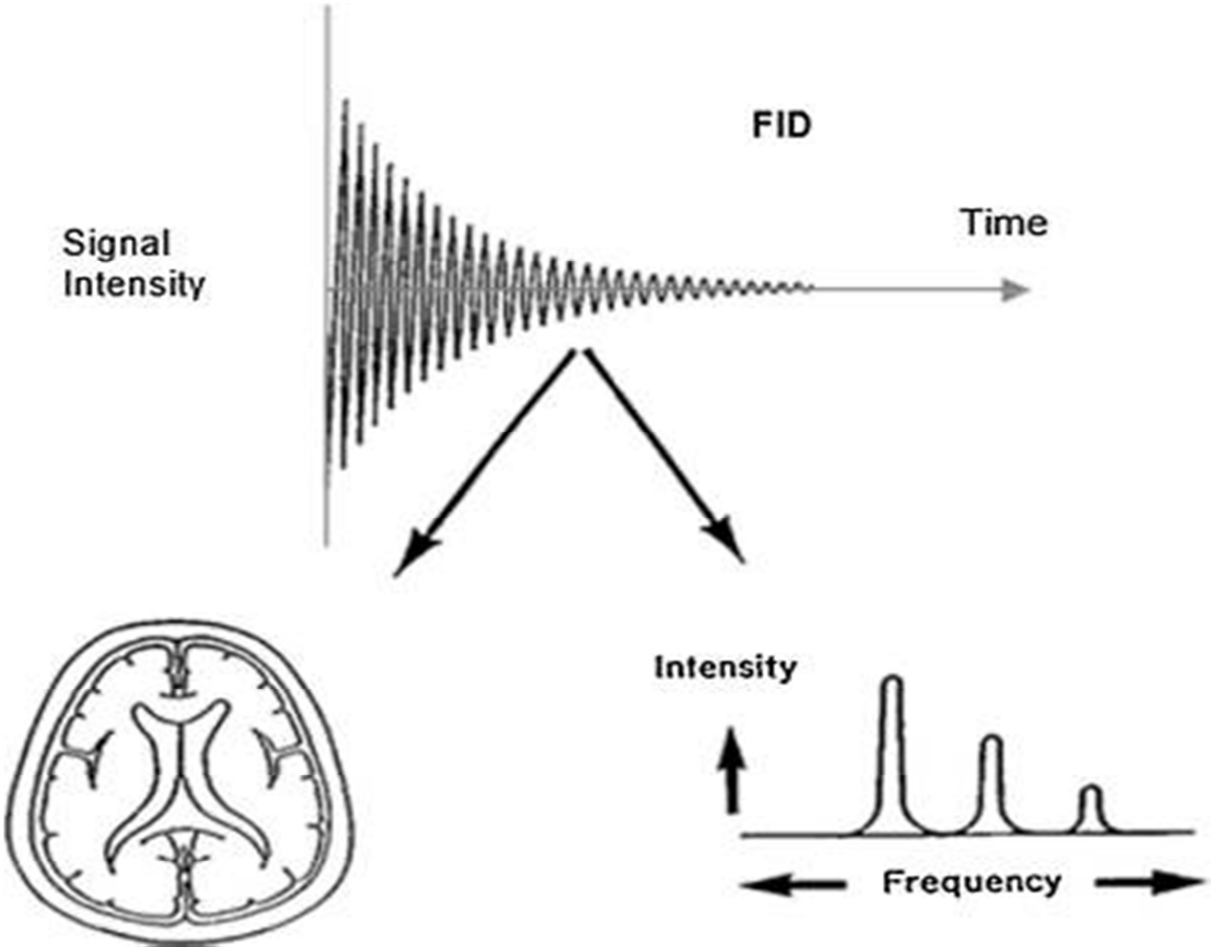


Figure (1-15): The free induction decay (FID) and Fourier transformation to generate MR images or MR spectra (Grover et al., 2015).

Relaxation is the term used to describe the process by which a nuclear "spin" returns to thermal equilibrium after absorbing RF energy. There are two types of relaxation, longitudinal and transverse relaxations, and these are described by the time constants, T_1 and T_2, respectively (Westbrook et al., 2011).

T_1 is also known as "spin-lattice relaxation", whereby the "lattice" is the surrounding nucleus environment. As longitudinal relaxation occurs, energy is dissipated into the lattice. T_1 is the length of time taken for the system to return 63% toward thermal equilibrium following an RF pulse as an exponential function of time. T_1 can be manipulated by varying the times between RF pulses,

the repetition time (TR). Water and cerebrospinal fluid (CSF) have long T_1 values (3000–5000 mS), and thus they appear dark on T_1-weighted images, while fat has a short T_1 value (260 mS) and appears bright on T_1-weighted images (Westbrook et al., 2011).

Relaxation processes may have redistribute energy among the nuclei within a spin system, without the whole spin system losing energy. Thus, when a RF pulse is applied, nuclei align predominantly along the axis of the applied energy. On relaxation, there is dephasing of nuclei orientations as energy is transferred between the nuclei and there is reduction in the resultant field direction, with a more random arrangement of alignments. This is T_2, termed transverse relaxation, because it is a measure of how fast the spins exchange energy in the "xy" plane. T_2 is also known as "spin-spin" relaxation (Figure 1-16) (Westbrook et al., 2011).

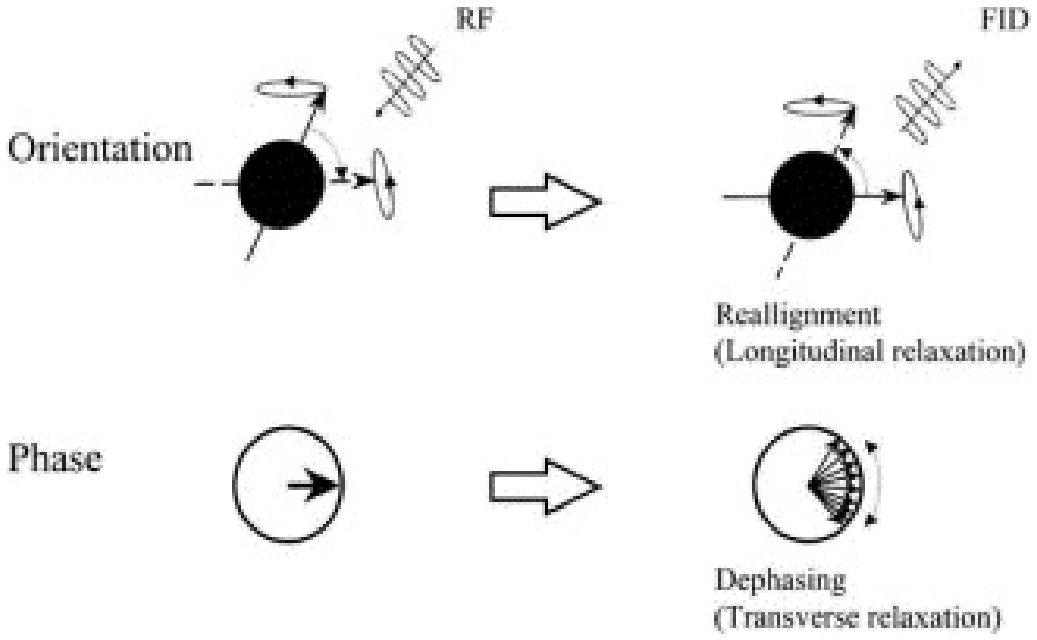


Figure (1-16): Relaxation phases of nuclei. Longitudinal relaxation (upper row) is the realignment of the net magnetization to the external magnetic field. Transverse relaxation is the dephasing of the precessing spins (lower row) (van Geuns et al., 1999).

In digitized imaging, such as MRI, pictures are composed of a matrix of elements, called picture elements or pixels. The image matrix defines the number of pixels used to construct an image that is determined by the number of frequency encodings (128 or 256 on the x-axis) and the number of phase-encoding steps used (128 or 256 on the y-axis) for a certain FOV. Therefore, the FOV, the matrix size used, and the slice thickness determine the volume of each pixel. In practice the resolution is determined by the pixel size (the smaller, the higher the resolution), but the signal-to-noise ratio is the limiting factor if the pixels become too small and do not contain enough spinning protons to produce a measurable signal (van Geuns et al., 1999).

1.4 Rheumatoid Arthritis (RA)

1.4.1 Definition

Rheumatoid arthritis (RA) is a systemic disease characterized by chronic inflammation, joint swelling, joint tenderness, and destruction of synovial joints (Jameson 2018). Overall, the prevalence of RA is 0.5-1% in the general population (Almutairi et al., 2020).The disease affects women more than men and occurs at any age with peak incidence in the sixth decade of life (Myasoedova et al., 2010).

Previously, RA was lead to disability, inability to work, and increased mortality rate. Recently, improvement in outcomes has been achieved through a better understanding of pathophysiology of RA and development of better outcome measures and therapies (Aletaha and Smolen, 2018).

1.4.2 Pathophysiology

The RA is characterized by infiltration of the T cells ,B cells, and monocytes within synovial membrane in multiple joints. This process is preceded by

activation of endothelial cells. Growth of new blood vessels(neovascularization) is another hallmark of RA synovitis. Expansion of synovial fibroblast-like and macrophage-like cells leads to a hyperplastic synovial lining layer. This expanded synovial membrane, often termed “pannus,” invades the periarticular bone at the cartilage-bone junction and causes bony erosions and cartilage degradation (Figure1-17) (Wallach 2016).

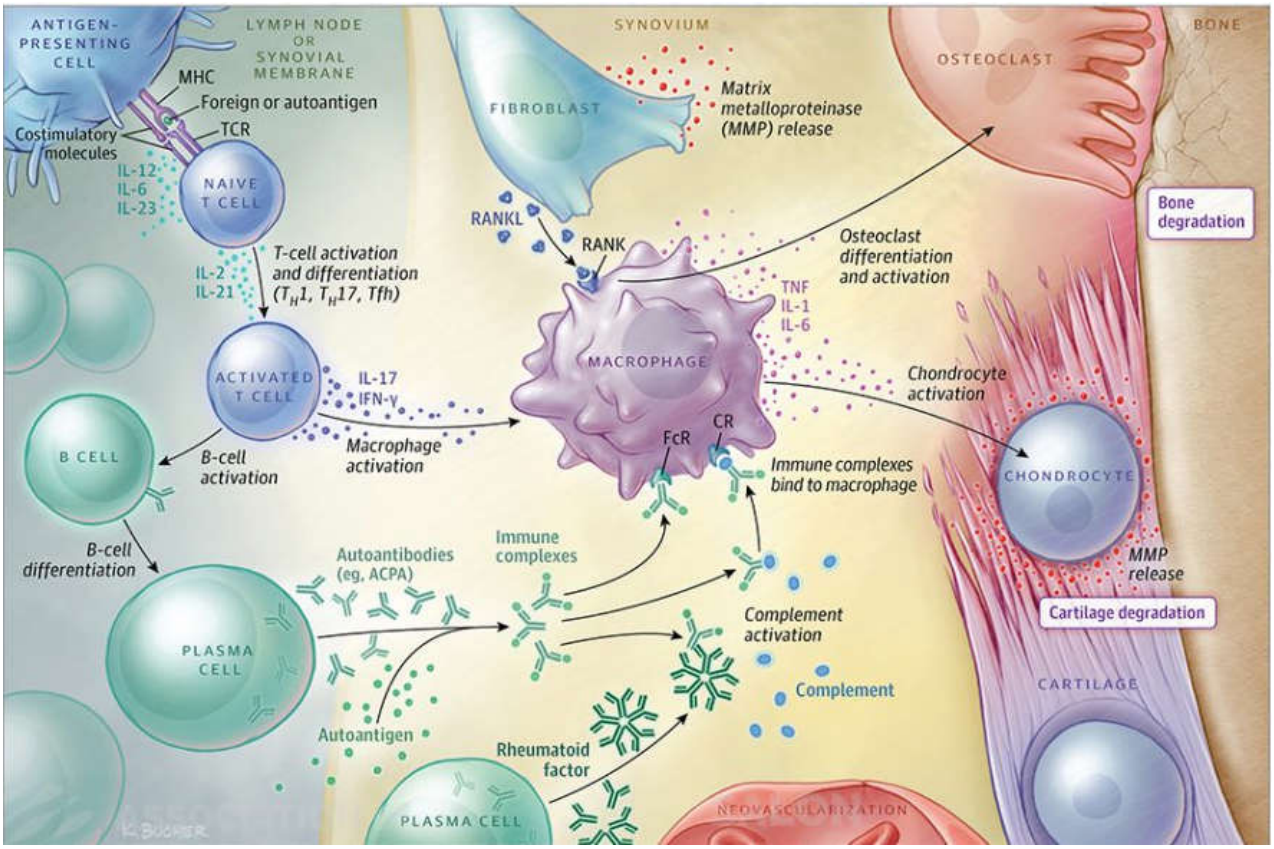


Figure (1-17): Pathogenic Aspects of Rheumatoid Arthritis (Aletaha et al., 2011).

1.4.3 Etiology

The RA cause is unknown. However, both genetic and environmental factors contribute to the development of RA. Many gene loci are associated with RA (Viatte and Barton 2017). However, certain HLA class II antigens, such as

HLA-DRB1*01 and HLA-DRB1*04, contain the “shared” epitope—a stretch of 5 amino acids in the region responsible for antigen presentation to T lymphocytes and are most closely associated with RA (Gregersen et al., 1987). Genes with weaker associations may also contribute, especially by gene-gene and gene-environment interactions (Raychaudhuri 2010).

The environmental risk factors for RA include smoking, periodontitis, and characteristics of the microbiome of the gut, mouth, and lungs, as well as viral infections (Scher et al., 2013; Tan and Smolen 2016). Regarding the microbiome, Prevotella species which are expanded in the gastrointestinal tract in early RA, and Porphyromonas gingivalis, which is associated with periodontitis, may play a role in pathogenesis (Wegner et al., 2010).

New data suggest that bacteria may translocate from the gut to tissues causing inflammation and autoimmunity (Manfredo Vieira et al., 2018).

The relationship between genetics and environment is evident based on recent observations that HLA-DR molecules of patients with RA present peptides of auto antigens having sequence homology with epitopes from proteins of commensal bacterial species present in RA (Pianta et al., 2017). The similarity between amino acid sequences of autoantigens and bacterial or viral proteins has been described (Alam et al., 2014).

Epstein-Barr virus infection has also been implicated. It is supported by recent observations that transcription factor EB nuclear antigen 2 (EBNA2) binds preferentially to genetic loci associated with RA and other autoimmune diseases (Tan and Smolen 2016; Harley et al., 2018).

Autoantibodies develop before the occurrence of the symptoms, this stage is called “pre-RA” and can last between less than 1year and more than 10 years. The length of time before appearance of RA symptoms is related to the

autoantibody profile. People who only express ACPAs develop symptoms 5 to10 years after the auto antibody appearance, whereas people who develop ACPAs and RF and also increased C-reactive protein(CRP) levels develop symptoms within a few months after the appearance of third factor (Nielen et al., 2004).

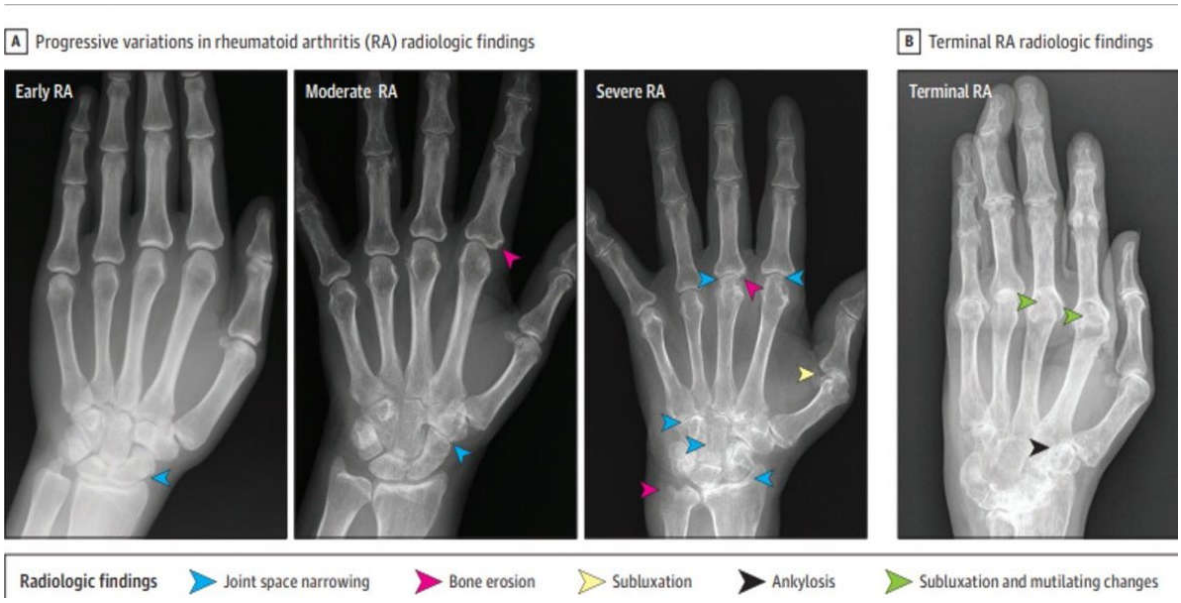
Subtle inflammatory changes in the synovium have been noted in some patients with pre-RA, even in established RA, overt inflammatory changes identified by histology are not always accompanied by clinical signs and symptoms (deHair et al., 2014).

1.4.4 Clinical presentation

RA is a polyarticular symmetric disease that involves multiple joints bilaterally. A patient with RA typically presents with pain and swelling in the joints of the hands and feet. The swelling is primarily in the wrists and meta carpophalangeal, metatarsophalangeal, and proximal interphalangeal joints. This is accompanied by morning joint stiffness lasting more than 30 minutes and usually up to several hours. The swelling is typically “soft” because of synovitis and effusion in contrast to the “hard”(bony) swellings of osteoarthritis. When the fingers are involved, swelling centers around the joint (fusiform) rather than involving the whole digit (“sausagedigit”),as seen in psoriatic arthritis. Both small and large joints can be involved; although the distal interphalangeal joints are rarely affected. Small joints include the metacarpophalangeal, metatarsophalangeal, proximal interphalangeal, and wrist joints. Large joints include ankles, knees, elbows, and shoulder joints (Aletaha and Smolen, 2018).

The early manifestations of RA range from mild arthritis with few involved joints to severe poly-articular disease and from a state of negative autoantibodies to multiple positive autoantibodies. Very early disease does not exhibit structural

damage, whereas later stages are characterized by erosive disease or joint space narrowing as an indicator of cartilage degradation. If not adequately treated, RA progresses into a more homogeneous destructive disease (Figure1-18) (Aletaha and Smolen, 2018).



Figure(1-18): Structural Phenotypes of Rheumatoid Arthritis (Aletaha, Funovits and Smolen, 2011).

If RA is insufficiently treated, extra-articular manifestations may develop. The most frequent ones are rheumatoid nodules (firm subcutaneous lumps near bony prominences such as the elbow).A more serious manifestation is rheumatoid vasculitis, a necrotizing inflammation of small or medium-sized arteries, mostly involving the skin, vasa nervorum, and occasionally arteries in other organs (Aletaha and Smolen, 2018).

The RA patients may be affected by multiple co-morbidities. Cardiovascular disease is a common consequence of chronic inflammation and the primary cause of death in people with RA. The cardiovascular disease in RA patients is

more closely associated with disease activity rather than with traditional cardiovascular risk factors (Crowson et al., 2018).

Treatment with targeted biologic agents reduces cardiovascular risk (Low et al., 2017). Interstitial lung disease may be a manifestation of RA or may be a complication of RA therapies, such as methotrexate and leflunomide (Bongartz et al., 2010).

RA interferes with physical functioning, work productivity, and quality of life (Sokka et al., 1999). If insufficiently treated, 80% of patients will have malaligned joints and 40% will be unable to work within 10 years from disease onset (Wolfe 1996; Sokka et al., 1999).

Quality of life as assessed by the 36-Item Short Form Health Survey, is similar to or worse than that associated with cardiovascular disease and diabetes (Matcham et al., 2014). RA affects all activities of daily life (Radner et al., 2011). In long-standing, insufficiently treated disease, accumulation of joint damage which is irreversible in RA, leads to disability; patients who sustain irreversible joint damage will never recover nor mal-physical function, even if clinical remission (i.e., absence of signs of inflammation such as joints swelling and elevated CRP levels) is subsequently attained. Even the most effective therapies will not reverse joint damage (Aletaha et al., 2008). The evolution of radiographic findings ranges from joints with minimal abnormalities to severe destructive changes seen as bony erosions and joint space narrowing, reflecting cartilage changes since cartilage is radio-translucent, changes can only be seen indirectly (Figure1-15). Cartilage damage contributes more to irreversible disability than bony damage (Aletaha, Funovits and Smolen, 2011).

1.4.5 TMJ Involvement

The clinical findings in the TMJ affected by RA include pain, swelling, movement impairment and crepitation; moreover, in advanced stages, malocclusion of the teeth and anterior open bite may occur (Scutellari and Orzincolo, 1998). There is sensitivity or preauricular pain during joint movement, probably due to compression of retrodiscal tissue, stretching of the joint capsule and synovitis. There is also morning stiffness usually lasting more than 30 minutes and decreased masticatory force. In children, it may result in disturbance in mandibular growth, facial deformity and ankylosis, generally found in the later stages of the disease, but it is a rare finding (Sodhi, Naik, Pai and Anuradha, 2015). The presence of morphologic alterations on conventional radiographs of the TMJ in RA patients varies from 19% to 86% (Delantoni et al., 2006). The main changes are flattening, spiked deformity or pencil-like condylar head, cortical erosion, gradual decrease in joint space due to granulation, deossification, and sub cortical cysts (Goupille et al., 1992, Helenius et al., 2005). The use of the drugs can be associated with adverse events in the oral cavity, such as changes in mucous membranes and other symptoms different from patient to patient (Ahola et al., 2015). About half of the patients with RA (51.5%) complain from xerostomia and, consequently, difficulties in swallowing and phonation, sensation of burning mouth, increased thirst, loss of taste, unpleasant taste and odor and dental sensitivity (Chamani et al., 2017).

1.4.6 Diagnosis and Assessment

In the early disease, RA may involve only 1or a few joints. At the same time or even earlier, tendon inflammation (tenosynovitis) develops. The presence of tenosynovitis, (e.g., at the flexor carpi ulnaris tendon) and subclinical synovial inflammation can be detected by color Doppler sonography or gadolinium-

enhanced magnetic resonance imaging, which demonstrate expansion of intra-articular soft tissue or hyper vascularization of the synovial membrane (Aletaha and Smolen, 2018).

No diagnostic criteria exist for RA. However, the 2010 classification criteria, although primarily developed for identification of homogenous patient populations in clinical studies of RA may help physicians establish a diagnosis (Aletaha et al., 2010; Radner et al., 2014).

The classification of RA requires presence of at least 1 clinically swollen joint and at least 6 of 10 points from a scoring system (Table1-2) (Aletaha et al., 2010).

Table (1-2): Rheumatoid Arthritis Classification and Follow-up

Classification	**points**
Joint distribution (0-5 points)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (≥ 1 small joint)	5
Serology (0-3 points)	
Negative RF and negative ACPA	0
Low positive RF and negative ACPA	2
High positive RF and high positive ACPA	3
Symptom Duration (0-1point), weeks	
< 6	0

≥ 6	1
Acute Phase Reactants (0-1 point)	
Normal CRP and normal ESR	0
Abnormal CRP and abnormal ESR	1

*** Abbreviations: ACPA, anti-citrullinated peptide antibodies; CRP,C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.**

Involvement of joint based on physical examination or imaging by ultrasound or magnetic resonance imaging contributes up to 5 points; elevated levels of RF, ACPAs, or both provides 2 additional points (or 3 points with levels>3 times the upper limit of normal); and elevated acute phase reactant (APR) response, such as increased CRP level or erythrocyte sedimentation rate, and duration of symptoms (6 weeks) provide 1 additional point each. These 2010 criteria have a sensitivity of 82% and specificity of 61%. Sensitivity of the new classification criteria was 11% greater and specificity 4% lower compared with the 1987 criteria (Radner et al., 2014).

Early diagnosis and treatment prevents progression of joint damage in 90% of patients with RA (Goekoop-Ruiterman et al., 2005). It is important to diagnose patients with RA as soon as possible. Specific symptoms that may indicate possible RA include articular pain and swelling in metacarpophalangeal joints, metatarsophalangeal joints, or both, morning stiffness of finger joints lasting for 30 minutes or longer, and positive autoantibody (Emery et al., 2002).

Initial patient assessment requires joints examination with serologic testing for autoantibodies and APRs. For follow-up, joint assessment, evaluation of APRs, and evaluation of patient reported outcomes such as patient global assessment of disease activity and evaluation of physical function are important. Composite measures that include joint counts, number of tender and swollen joints,

constitute the best way to evaluate RA disease activity in practice (and in trials), since they capture the most important disease aspects in a single score. These scores, namely the clinical disease activity index (CDAI), the disease activity score using 28 joint counts (DAS28), or the simplified disease activity index (SDAI), correlate with outcomes such as damage progression and functional impairment (van der Heijde et al., 1992; Aletaha et al., 2005).

These measures allow quantification of disease activity which is based on specific cut points of these indices that have been defined to help guide treatment. Treatment goals include remission, defined as no disease activity, and low disease activity, corresponding to mild residual activity with low risk of damage progression; these 2 states are contrast with moderate and high disease activity states, which signify uncontrolled disease associated with progression over time (Smolen et al., 2006). Among all available indices, the CDAI is rather easy to perform. It is a simple numerical summation of 4 variables: swollen and tender joints (using 28 joint counts), patient global assessment, and evaluator global assessment, both on a 10-cm visual analogue scale. The CDAI ranges from 0 to76 (higher scores worse, Aletaha et al., 2005).

Clinical remission as indicated by CDAI or SDAI is a state in which physical function is maximally improved and progression of joint damage is halted (Aletaha and Smolen, 2011).

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have recently defined remission criteria based on a Boolean approach or based on indices, namely the SDAI and CDAI (Felson et al 2011). Therapy should be titrated to achieve clinical remission according to the definition by these indices and not according to the improvement in the subclinical inflammations measured by ultrasound, for example. There is no

evidence that treatment beyond clinical remission, as defined by ACR and EULAR index or Boolean criteria, improves outcomes; therefore, it should not be pursued (Dale et al., 2016).

1.4.7 Treatment

1.4.7.1 Disease-Modifying Anti-rheumatic Drugs

Although RA is incurable, modern therapeutic approaches allow achievement of excellent disease control. Patients with RA must be treated with disease-modifying anti-rheumatic drugs (DMARDs). A DMARD is defined as a medicine that interferes with signs and symptoms of RA, improves physical function, and inhibits progression of joint damage. Therapies that only improve symptoms, such as non-steroidal anti-inflammatory drugs or pain medications, do not prevent damage progression and irreversible disability. These drugs are not DMARDs and should only be used as adjunctive, symptomatic therapy or during the short phase until a diagnosis is established (Aletaha and Smolen, 2018).

DMARDs are categorized into synthetic (small chemical molecules given orally) and biologic (proteins administered parenterally) agents (Smolen et al., 2014).

Among the empirically developed conventional DMARDs, methotrexate is the most important. Although methotrexate has been used in treatment of RA for more than 50 years (Hoffmeister 1983), the optimal dose of 25 mg weekly was more identified. Patients who cannot tolerate this dose because of adverse effects (<10%) may improve with a lower dose. Fewer than 5% of patients have to stop methotrexate because of adverse events (van Ede et al 2001).

Methotrexate is important for several reasons. First, a large proportion of patients (25%-40%) significantly improve with methotrexate monotherapy, and in

combination with glucocorticoids almost half of patients can attain low disease activity or remission in early RA, a rate similar to that achieved with biologic DMARDs (Nam et al., 2014; Emery et al., 2015). Second, its adverse events are well known such as nausea, hair loss, stomatitis, and hepatotoxicity, can be prevented by prophylactic use of folates (folic acid at 1 mg/d or 10 mg/wk) (van Ede et al., 2001). Third, targeted DMARDs, biologic and synthetic, have less efficacy as mono therapies than when combined with methotrexate (Nam et al., 2017).

Other conventional synthetic DMARDs include sulfasalazine (3-4g/d) and leflunomide (20mg/d with or without a loading dose of 100mg/d for the first 3 days). In some patients, lower doses (1.5-2g of sulfasalazine or 10mg of leflunomide daily) are used because of intolerability of higher doses. Hydroxychloroquine (400mg/d) is another conventional synthetic DMARD, but its efficacy is lower than that of other agents (van der Heijde et al., 1990).

EULAR recommends instantly treating every newly diagnosed patient using methotrexate combined with short-term glucocorticoids and a treat-to-target approach (Smolen et al., 2017). The ACR guidelines are similar (Singh et al., 2016). Glucocorticoids should be prescribed for short term (up to 3-4 months) use only, because prolonged use is associated with adverse events (Chatzidionysiou et al., 2017). There are no advantages of prescribing combinations of conventional synthetic DMARDs over methotrexate monotherapy. These combinations are associated with more adverse events and drug discontinuation (Smolen et al., 2017).

If the treatment target is not reached with methotrexate and glucocorticoids, patients should be categorized using prognostic markers. Poor prognostic markers such as the presence of auto-antibodies, early joint damage, and high

disease activity are associated with rapid disease progression that can be halted or slowed by adding a biologic DMARD or targeted synthetic DMARD (JAK inhibitor) rather than another conventional synthetic DMARD (Smolen et al., 2006, Vastesaeger et al., 2009).

All biologic DMARDs and targeted synthetic DMARDs have greater efficacy when combined with methotrexate or other conventional synthetic DMARDs, compared with prescription alone (Emery et al., 2015; Burmester et al., 2016; Kaneko et al., 2016; Fleischmann et al., 2017). Therefore, EULAR recommends using biologic DMARDs and targeted synthetic DMARDs combined with methotrexate or other conventional synthetic DMARDs. However, compared with anti-TNF monotherapy (e.g., adalimumab), monotherapies of IL-6 receptor antibodies (sarilumab, tocilizumab), and perhaps also JAK inhibitors (e.g., baricitinib), have better clinical efficacy (Gabay et al., 2013;, Burmester et al., 2016). If all conventional synthetic DMARDs are poorly tolerated or contraindicated, then IL-6R antibodies and JAK inhibitors are more efficacious than other agents (Smolen et al., 2017).

1.4.8 Prognosis

With the availability of effective therapies and treatment strategies, remission or low disease activity can be achieved in about 75% to 80% of patients (Aga et al., 2015). Patients in remission, but also those with low disease activity, can continue normal participation in social and work activities and have normal life expectancy (Listing et al., 2015).

However, about 20% to 25% of the patients in the industrialized world and many more in less affluent countries do not reach low disease activity. For some patients, poor access to optimal care precludes better outcomes. For other patients, causes of refractory disease have not been identified, but delaying

prescription of effective therapy and higher disease activity at treatment onset appear to be important factors contributing to resistance (Putrik et al., 2014).

Chapter Two

Patients and Method

Chapter 2: Patients and Methods

2.1 Study Design

The following flowcharts describe the study design and number of cases and procedures used in this study (Figure 2-1).

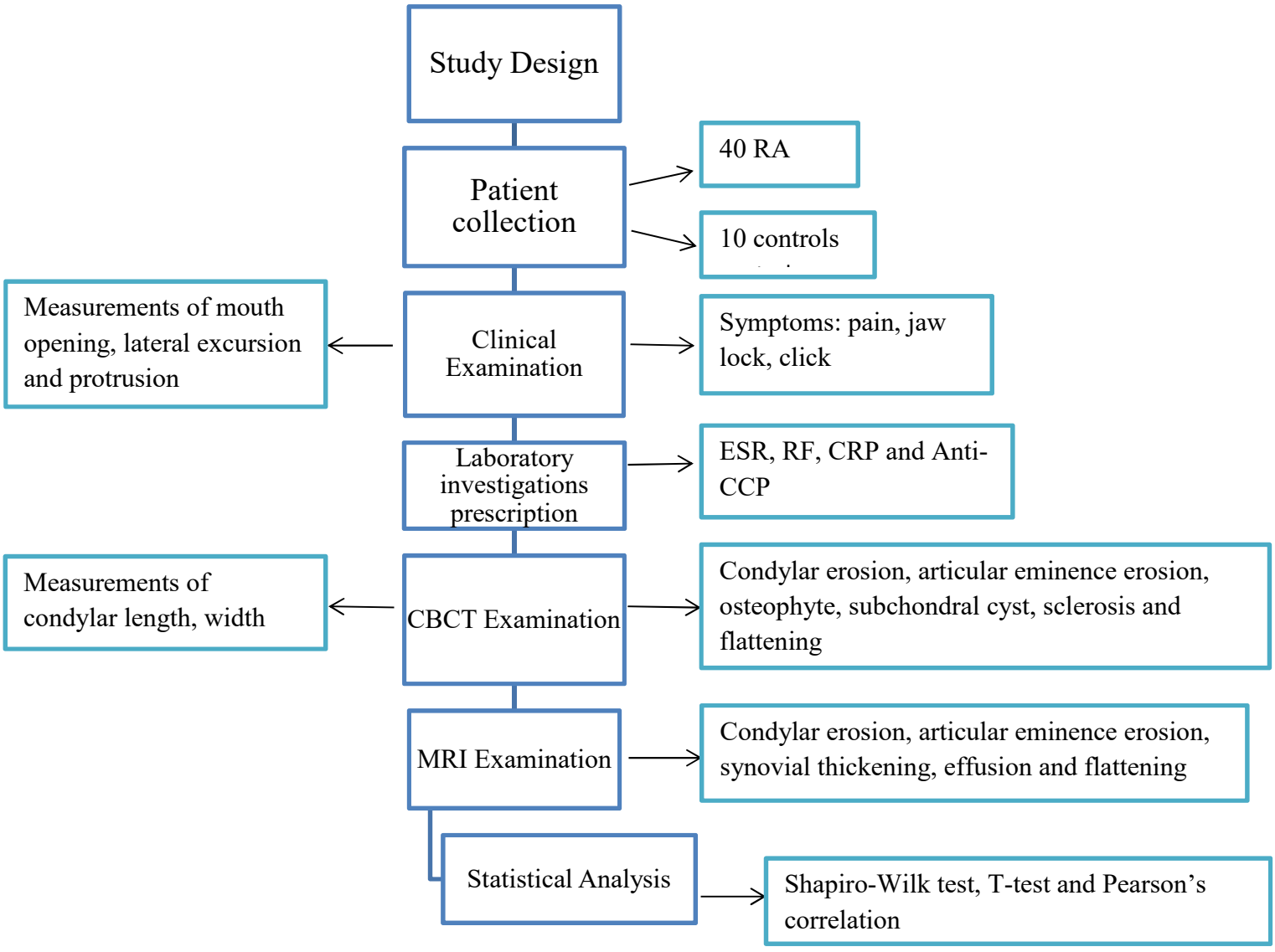


Figure (2-1): Flow chart of study design

2.2 Patients

Forty patients previously diagnosed as having RA by a rheumatologist were used in this study, They were 38 females (95%) and 2 males (5%). The sample were divided into 2 equal groups according to the duration of their disease. Group A included 20 patients (1-5 years duration) and group B included 20 patients (6-10 year duration). Both groups were on treatment under care of the rheumatologist. Group C consisted of Ten healthy persons (all females) without any chronic disease and no TMD signs and symptoms was included in the study and used as control group (Figure 2-2).

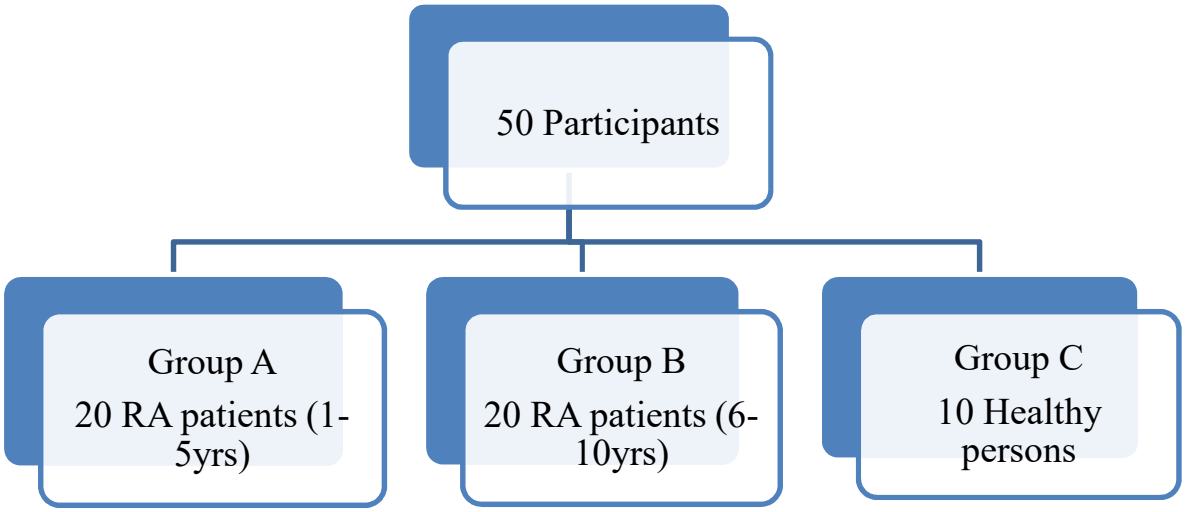


Figure (2-2): Sample size distribution

TMJs of all groups examined clinically and radiographically at time of inclusion to the study. The TMJs of all participants (100 TMJs) were evaluated by magnetic resonance imaging (MRI) and cone beam computerized tomography (CBCT).

2.2.1 Inclusion criteria of the study:

1. Patients who have been diagnosed with RA (1st year or longer duration).

2. Patients without any other systemic diseases

2.2.2 Exclusion criteria of the study:

1. Patients with psoriatic arthritis, osteoarthritis

2. Patients with history of juvenile rheumatoid arthritis

3. Pregnant women

4. Patients contraindicated to MRI (bullets, metallic objects, cardiac pacemaker, insulin pump biostimulator, neurostimulator, cochlear implant, Intracranial aneurismal clips and hearing aids).

2.3 Research registration and approval

Proposal of this PhD project was submitted to scientific committee of College of Dentistry and has approval from university of Sulaimani by formal letter of no.(7/5/10570) at (2nd of September 2019).

A confirmation of the approval was done at postgraduate department of College of Dentistry by no. (7/29/1159) and approval of the University of Sulaimani ethical committee obtained at (8th of September 2019).

Ethical approval was obtained from the Ethics Committee of College of Medicine and obtained ID (no.7) at (27th of January 2020).

This study was registered at Scientific Committee of College of Dentistry and obtained ID (no.394) at (7th of January 2020).

This thesis was registered in German Clinical Trails Register (DRKS) site belonging to WHO clinical trial registration official sites and obtained no. (DRKS00024167)

2.4 Methods

2.4.1 Patient collection

Patient collection started in Rheumatology and Rehabilitation center/ Sulaimani City after bringing the formal letter from the Dean of college of Dentistry, the approval from manager of Rheumatology center with help of Rheumatologist for patient selection.

Each patient received alone in a room in this center for privacy and details of research methods explained for each patient with the possibility of TMJs involvement as other body joints by RA and the changes that might happen in TMJs to the patients with types of radiographs that be taken for patients and the necessary laboratory test which prescribed for them.

All participants were informed that all clinical examinations and radiographs that are taken for them will be free of charge and their participation is voluntary, most of patients accepted to participate.

After that an appointment arranged for each patient for visiting a private dental center located at Perot medical building for clinical examination and taking Cone Beam Computed Tomography (CBCT).

Each patient once came to the center his/her RA hand book were checked. A pre-designed case sheet including demographic characteristics and social information, duration of RA illness, information on medication used, smoking and alcohol consumption (appendix1) were used for recording the given information.

A designed patient information consent in Kurdish language were given to each patient to be read and signed to accept participation (appendix 3 &4).

2.4.2 Clinical Examination

After registering patients data and signing consent, a clinical assessment of Temporomandibular joint was done following the Research Diagnostic Criteria for TMJ. The following signs and symptoms were recorded: sound over TMJ: (click, crepitus), tenderness over TMJ, tenderness over muscles of mastication, pain during jaw opening, maximal mouth opening, lateral excursion and protrusion of the mandible (appendix 2) (Schiffman et al., 2014).

2.4.3 Laboratory investigations

The rheumatologist prescribed a set of laboratory blood tests for each patient for diagnosis and for determining progress level of the disease. The tests include the following:

a. Erythrocyte Sedmentation Rate (ESR) which measure the ability of erythrocytes to fall through the blood plasma and accumulate together at the base of container in one hour (Harrison 2015).

The normal value of ESR in men is age (in years) divided by 2; for women, the normal value is age (in years) plus 10 divided by 2 (Bray et al., 2016).

$$\text{ESR (mm/hr)} \geq \frac{\textbf{Age (in years)} + \textbf{10 (if female)}}{\textbf{2}}$$

b. Rheumatoid Factor (RF) is defined as an antibody against the Fc portion of IgG and different RFs can recognize different parts of the IgG-Fc (Falkenburg et al, 2015).

Normal Range of RF is ≤ 15 IU/ml. (Takeuchi et al., 2017)

c. Creatinine Reactive Protein (CRP) is an annular (ring-shaped), pentameric protein found in blood plasma, whose levels rise in response to inflammation (Thompson, Pepys and Wood, 1999). The normal concentrations of CRP varies between 0.8 mg/l to 3.0 mg/l. However, some healthy adults show elevated CRP at 10 mg/l. When there is a stimulus, the CRP level can rise from 50 μg/l to more than 500 mg/l (Bray , 2016).

d. Anti-Cyclic Citrullinated Peptide (anti-CCP) are autoantibodies that are directed against peptides and proteins that are Citrullinated. They are present in the majority of patients with rheumatoid arthritis. Anti-CCP of less than 20 U/ml consider as negative, 20-39U/ml moderate positive, more than 60U/ml strong positive (Puszczewicz and Iwaszkiewicz, 2011).

The result of the tests of each patient were recorded in a designed table with drugs taken from patient's Rheumatoid handbook.

2.4.4 CBCT examination

Cone beam computed tomography (CBCT) for TMJs for each patient taken by Sirona 3D machine (Galileos comfort ; model 2016) made in Germany.

2.4.4.1 Patient's preparation:

The following preparations need to be considered:

1. The patient asked to remove all removable metallic objects from head and neck region like jewelry, ear rings, eye glasses, hearing aids and hairpins.

2. The patient should wear a lead apron without thyroid collar.
3. The patient should be instructed not to move during this procedure.

2.4.4.2 Patient's positioning:

The positioning of the patient should include:

1. The patient standing still inside the machine with the back straight and the maxilla parallel to the floor.
2. The patient's chin rested on the chin rest of the machine.
3. The patient asked to bite on the notch of the bite-block with the teeth in edge –edge position.
4. The Frankfort plane (horizontal light beam) adjusted parallel with the floor.
5. The midsagittal plane (midline light bean) adjusted at middle of patient's face (Figure 2-3).

Figure (2-3): Cone Beam Computed Tomography (CBCT) machine

Examinations was performed through 360 degrees of rotation with the patient in an occlusal position (closed mouth) with selected fields of view for upper arch and pre-saved parameters (Table 2-1).

Table (2-1): CBCT machine parameters and specifications

Exposure factors	**98KV**
	25 mA
Exposure time	14s
Field of View	8.5cm*8.5cm
Voxel size	0.3*0.3*0.3
Exposure dose	738 mGy*cm^2
Reconstruction time	2.5 minutes
Raw data size	420 MB

After scanning, contiguous sectional images in three orientations, *i.e*. sagittal sections (vertical to the long axis of the condylar head), coronal sections (parallel to the long axis of the condylar head) and axial (horizontal) sections, were reconstructed (Multiplanar reconstruction MPR) from the data with a slice width (thickness) of 1 mm (Figure 2-4) using dedicated CBCT software (Sidex XG) .

Figure (2-4): TMJs CBCT (MPR windows) on computer monitor.

2.4.5 MRI examination

MRI examinations were taken in Shar hospital by (1.5 Tesla GE machine) under the supervision of an expert Radiologist.

A patient positioning and sequences planning were done according to a pre-saved protocol of the machine with modification according to TMJ protocol found in website (www.mastermri.com) and European society of musculoskeletal radiology (ESSSR) protocol.

2.4.5.1 Patient's preparation:

This includes the following:

1. A written consent was taken from the patient before entering the scanner room.

2. Patients was asked to remove all metallic objects like keys, wallets, cards with magnetic, jewelry, hearing aids and hairpins.
3. Patients was asked to undress and change to hospital gown.
4. Patients was instructed not to move during this long procedure (about 25 minutes).

2.4.5.2 Patient's positioning

This includes:

1. Positioning the head in supine position in head coil and immobilizing it with head cushions (Figure 2-5).
2. Giving cushions under the leg for extra comfort.
3. Centering the laser beam localizer over the glabella

Figure (2-5): a prepared patient on the MRI machine.

Scout images of brain (an axial, coronal and sagittal) were taken at the beginning to localize and plan the sequences. Localisers are normally less than 25 seconds in T1 weighted scans.

T1 and T2 coronal and sagittal sections and PD sagittal sections were taken for right and left TMJs.

T1 coronal sections were planned as below:

The coronal slices planned on axial plane, angle the position block parallel to the right or left condyle of the mandible.(Figure 2-6&2-7).

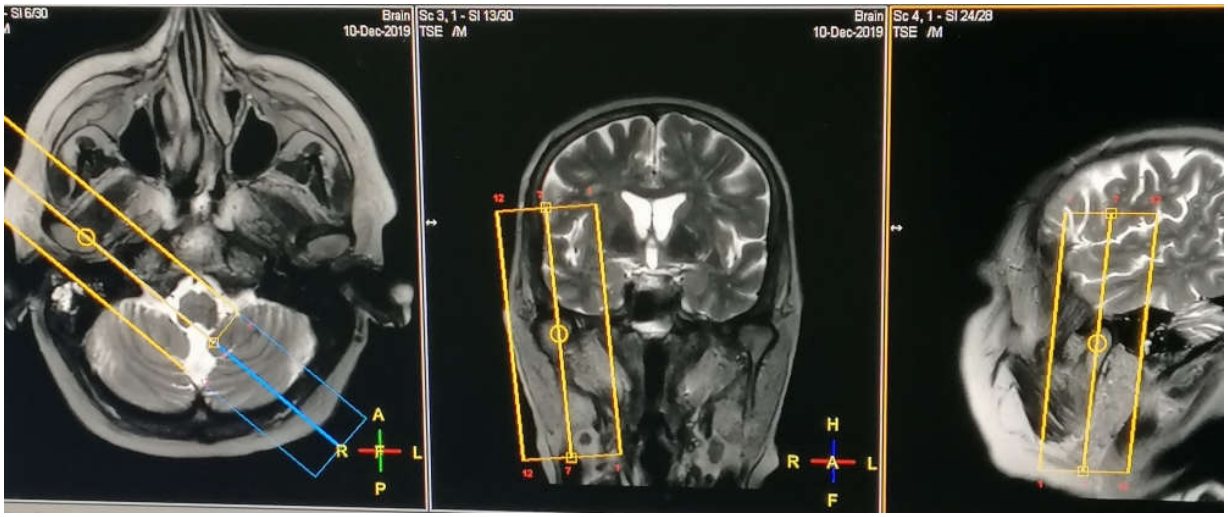


Figure (2-6): Localizer positioned for Right TMJ coronal view.

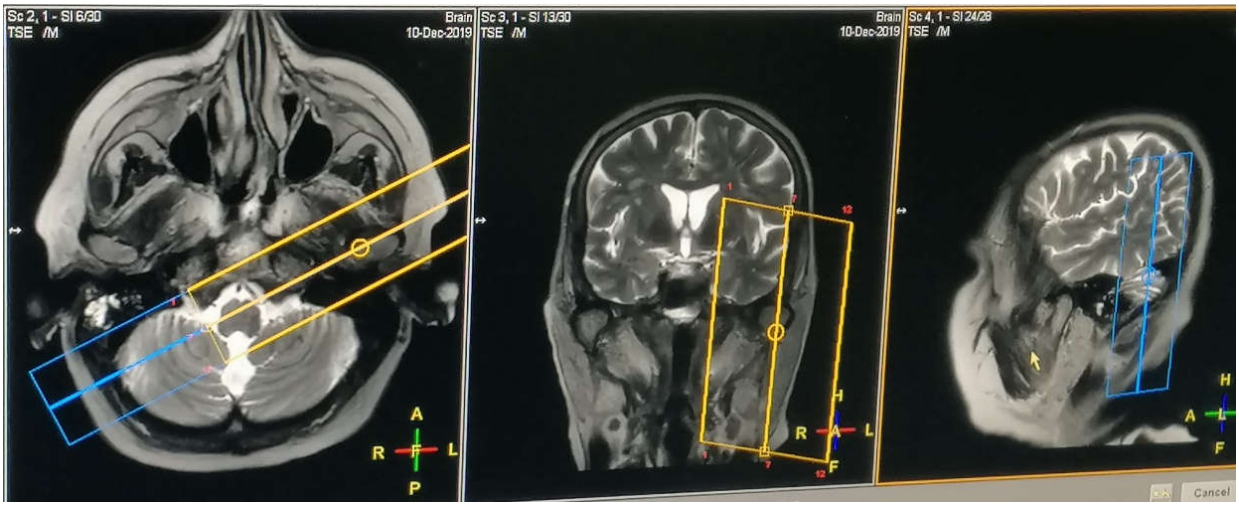


Figure (2-7): Localizer positioned for Left TMJ coronal view .

T2 coronal section was done with the same planning as T1 coronal but with different parameters.

T1 sagittal sections were planned as below:

The sagittal localizers planned on the axial plane; for right side localizer angle the position block perpendicular to the right condyle of the mandible and for the left side localizer angle the position block perpendicular to the left condyle of mandible. (Figure 2-8).

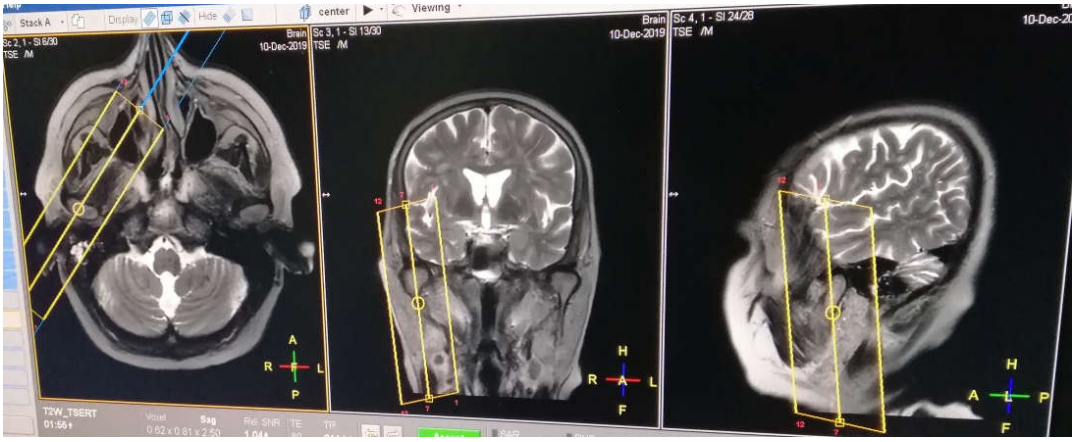


Figure (2-8): Localizer positioned for Right TMJ Sagittal view

T2 sagittal section was done with the same planning as T1 sagittal but with different parameters. (Figure2-9)

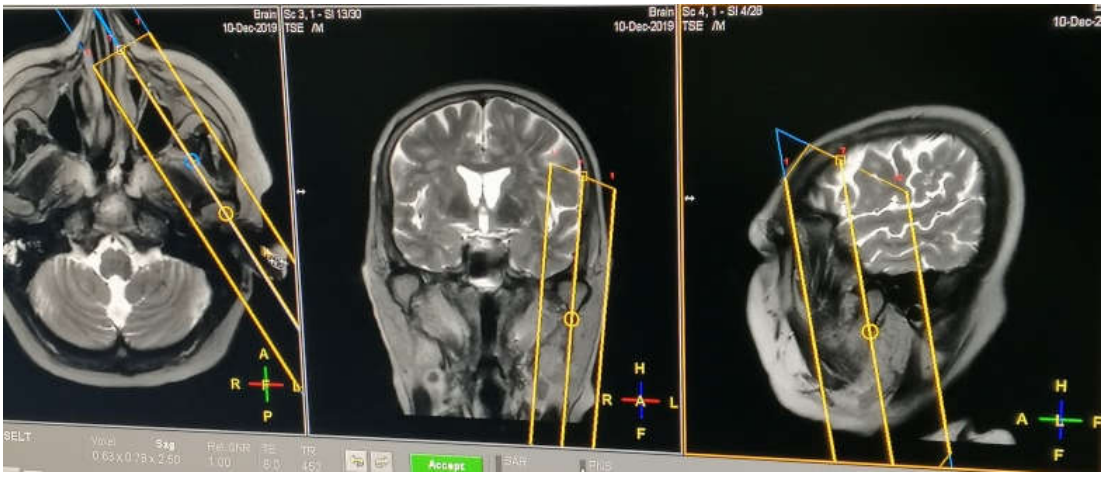


Figure (2-9): Localizer positioned for Left TMJ Sagittal view

PD sections were planned as below:

The position block placed parallel to the right or left condyle of the mandible. Slices must be sufficient to cover the TMJ from articular eminence up to the line of the internal auditory meatus.

The parameters of all sections described in (Table 2-2).

Table (2-2): MRI parameters

Section	TR (mSec)	TE (mSec)	Slice thickness (mm)	FOV (mm)	Matrix	GAP
T1-coronal	380	9.3	3.0	18.0	256x 224	0.3
T2-coronal	1840	98.2	3.0	18.0	320x192	0.3
T1-sagittal	380	9.1	3.0	18.0	256x224	0.3
T2-sagittal	1620	96.8	3.0	18.0	320x192	0.3
T2–proton density	1720	29.0	3.0	18.0	256x224	0.3

2.4.6 Radiographic change finding

2.4.6.1 CBCT findings

The corrected sagittal and coronal sections of CBCT for each patients were examined (right TMJ and left TMJ examined separately) and the following radiographic changes were recorded:

1/Bone erosion which is defined as decreased density of cortical bone extending into the bone marrow (Figure2-10A)(Alexiou et al., 2009).

2/Subchondral cyst (a cavity below the articular surface that deviates from normal marrow pattern) (Figure 2-10B) (Ahmad et al., 2009).

3/Flattening (a flat bony contour deviating from the convex form) (Figure2-10C). (Alexiou et al., 2009).

4/Sclerosis (an area of increased density of cortical bone extending into the bone marrow) (Figure 2-10D) (Alexiou et al., 2009).

5/ Osteophytes (marginal bony outgrowths on the condyle) (Alexiou et al., 2009).

Severity of erosion was classified as grade 0 (absence of erosion), grade 1 (slight erosion, decreased density observed only in the cortical bone), grade 2 (moderate erosion, decreased density observed in the cortical bone and extending to the upper layers of the adjacent subcortical bone) or grade 3 (extensive erosion, decreased density observed in the cortical bone and extending below the upper layers of the adjacent subcortical bone).

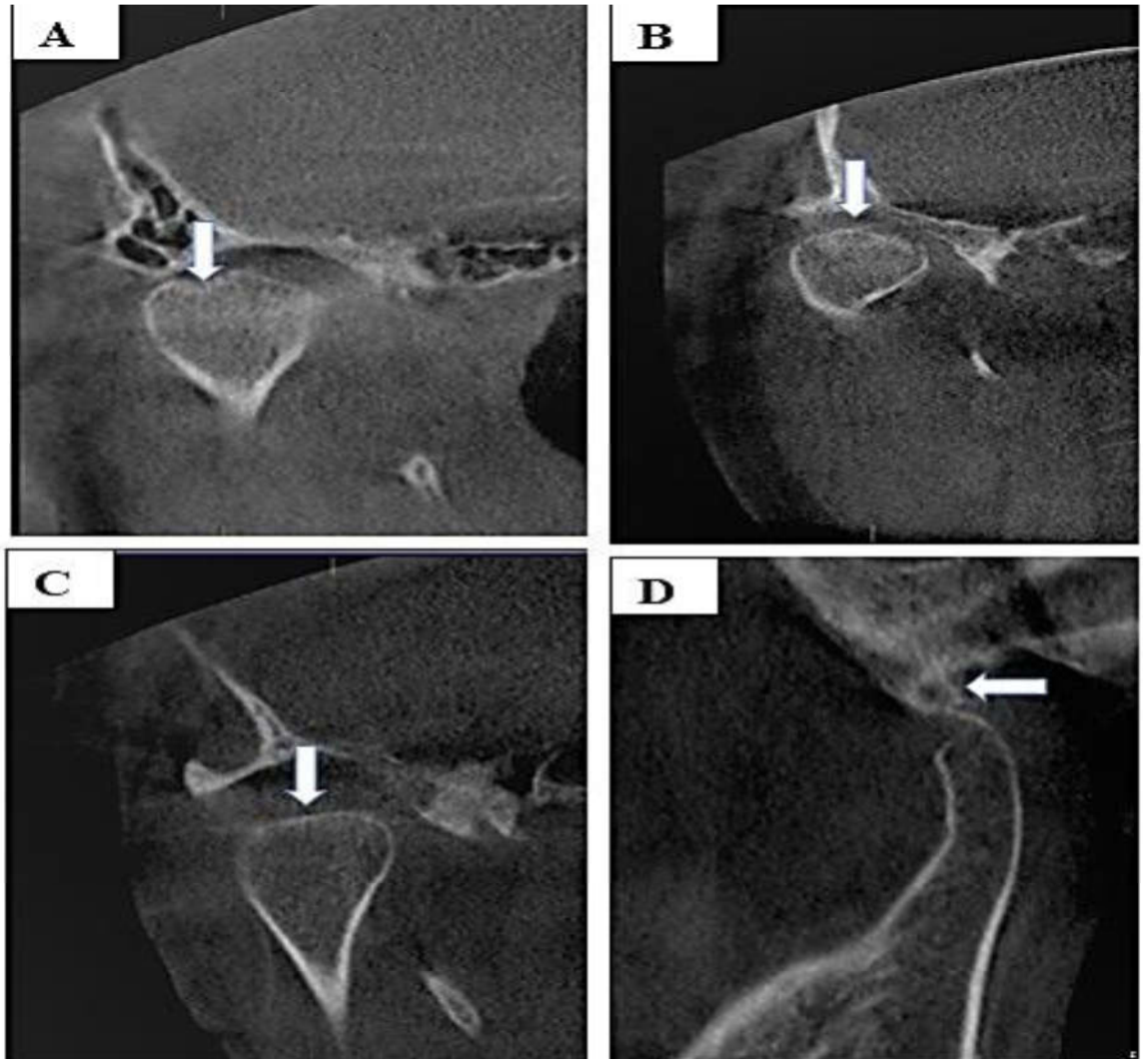


Figure (2-10): Radiographic changes of TMJ on CBCT. Condylar head erosion (A), subchondral cyst (B), flattening (C), and sclerosis (D).

2.4.6.2 MRI findings

The MRI of each patient exported to a CD then the data of the image of the CD are acquired in another computer and opened to be viewed by a program named RadiAnt DICOM viewer and the following radiographic changes were recorded:

1/ Osseous changes of the condyle were classified into:

- Type I, a condyle showing abnormal signal intensity of the bone marrow without erosion or absorption

- Type II, a condyle with erosion in the cortex
- Type III, a condyle with bone absorption extending within half of the condyle
- Type IV, A condyle with bone absorption extending over half of the condyle (Figures 2-11 and 2-12A).

2/ The osseous changes in the articular eminence/fossa, the presence or absence of erosion and deformation were assessed.

3/ Condylar head flattening (Figure 2-12B) (Kretapirom et al., 2013).

3/ Joint effusion which was established by identifying thin lines or an area of high signal intensity inside the articular space on T_2Weighted image; when such high signal was evident in at least two consecutive sections, it was considered positive for TMJ effusion (2-12C).

4/ Synovial thickening (Figure 2-12D).

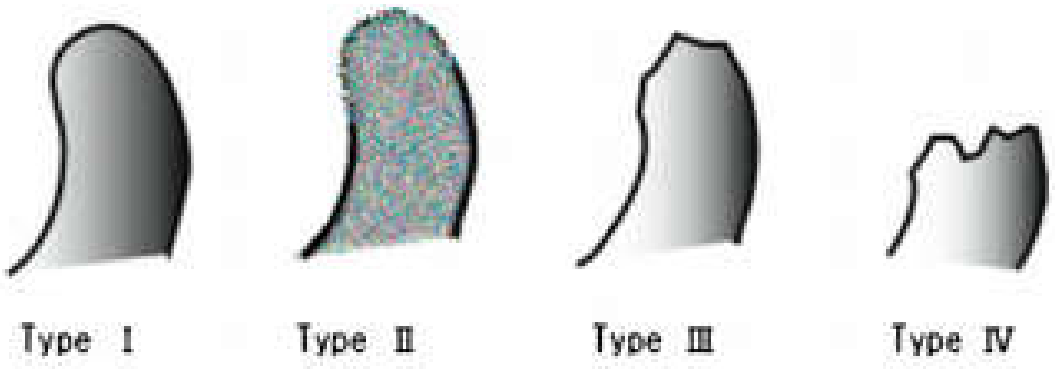


Figure (2-11): Schematic drawing showing the four types of osseous change in the condyle (Kretapirom et al., 2013).

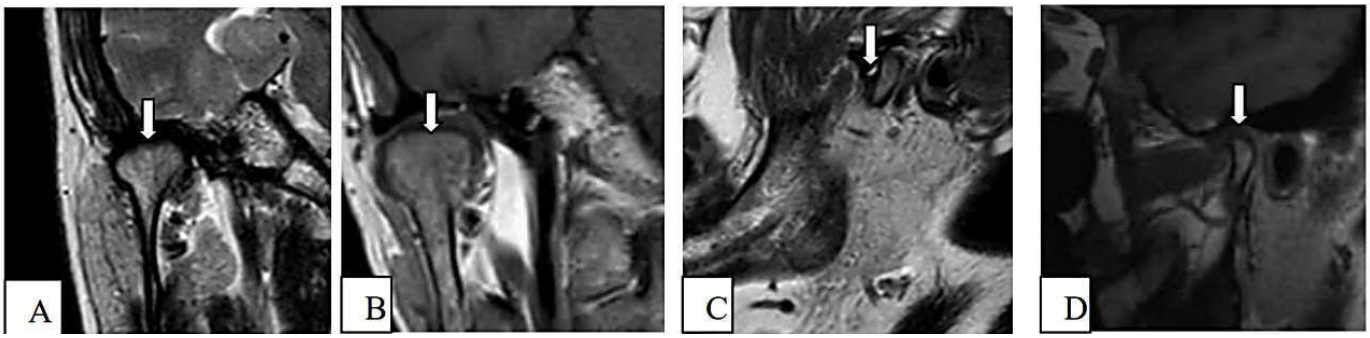


Figure (2-12): Radiographic changes of TMJ on MRI. (A) osseous change (erosion) of condylar head. (B) condylar head flattening. (C) effusion, (D) synovial thickening.

2.4.7 Measurements on CBCT

1/A condylar Length or AP dimension (Linear distance between posterior mandibular condyle and anterior mandibular condyle in sagittal plane) is measured on a selected sagittal section in which the condyle and glenoid fossa were clearly noticed. Anterior mandibular condyle point and posterior mandibular condyle point have been determined, both points have been located 4mm inferior to the superior mandible condyle. The linear distance between those two points represent the condylar length (Figure 2-13).

2/ A condylar width or ML dimension (Linear distance between medial mandibular condyle and lateral mandible condyle in coronal plane) is measured on a coronal section, a most medial point of condyle and most lateral point of condyle determined, both points located 4mm inferior to superior surface of condylar head and a linear distance between those two points represent the condylar width (Figure 2-14).

3/ A Condylar height (Perpendicular linear distance from superior mandible condyle to tangent constructed between most inferior point of coronoid sigmoid notch perpendicular to tangent of posterior surface of ramus in sagittal plane) was measured on a sagittal section. a superior mandible condyle is determined and a line constructed between the most inferior point of the sigmoid notch

perpendicular to the tangent of the posterior surface of the ramus then a vertical line drawn from perpendicular to the tangent line that represents the condylar height (Figure 2-15).

The measurements methodology used in this study has been described by (Hilgers et al., 2005 and Al-koshab et al., 2015).

The measurements of each patient were recorded in a table for statistical analysis.

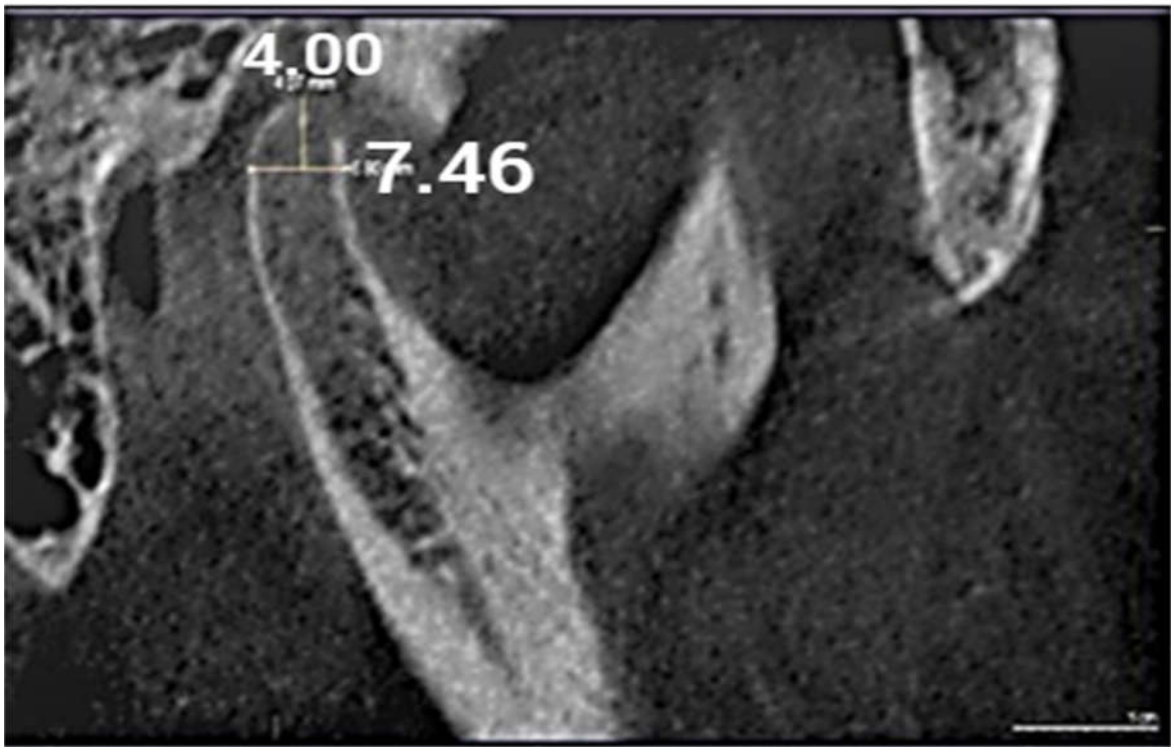


Figure (2-13): measured condylar length on sagittal section

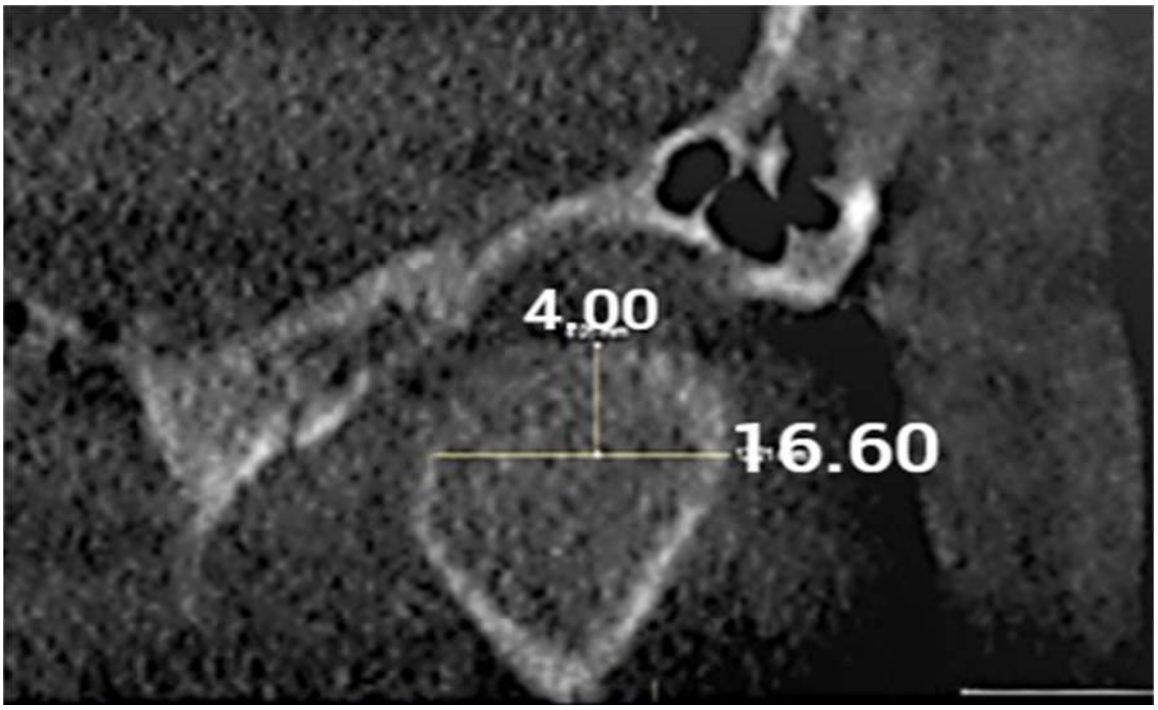


Figure (2-14): measured condylar width on coronal section

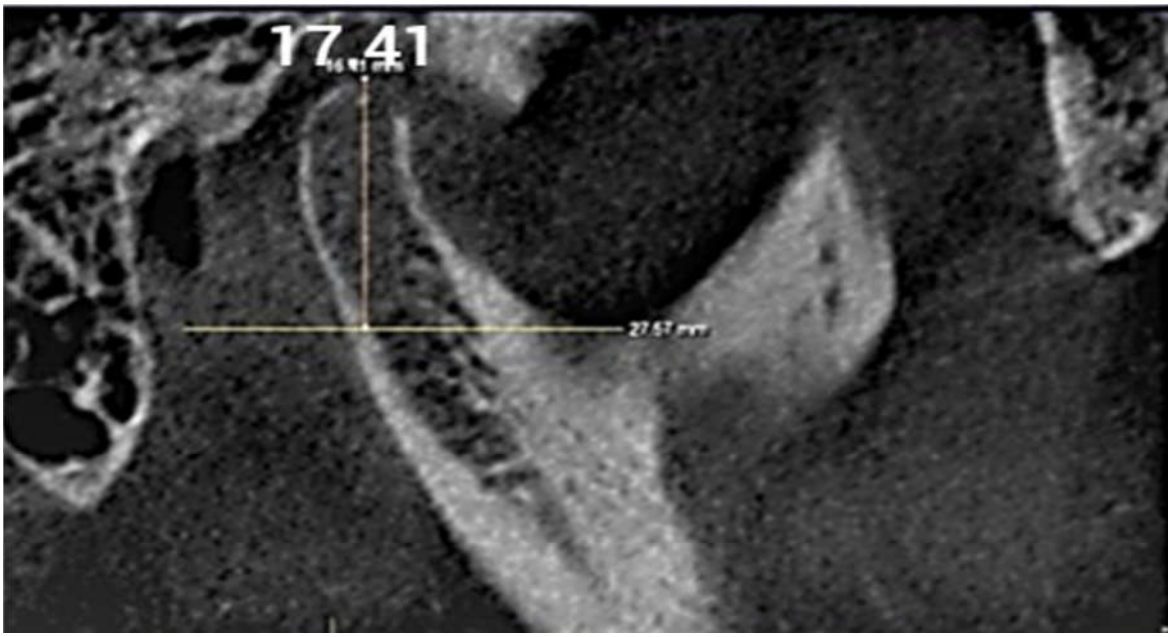


Figure (2-15): measured condylar height on sagittal section

2.5 Statistical analysis

The collected data were analyzed using IBM SPSS statistics (Statistical Package for Social Sciences), version 26.0 (Chicago, USA).

Qualitative data were presented as numbers and percentages. Quantitative data were presented as a mean and a standard deviation. Numerical data were tested for normality of their distributions using Shapiro-Wilk test.

Age, condylar length and condylar height measurements have shown normal (parametric) distribution while condylar width, assisted and unassisted jaw opening with lateral Jaw excursions and mandibular protrusion showed Skewed (non-parametric) distribution.

Student t-test used for parametric data; Independent t-test used for comparison between groups, and Paired t-test used for comparison between right and left sides TMJs.

Pearson correlation coefficient were used to determine correlations between variables.

The Significant level was set at $P \leq 0.05$ and values of less than 0.05 were considered statistically significant.

Chapter Three

Results

Chapter 3: Results

3.1 Demographic description of participants

First group (A) include of 20 RA patients with mean age of (49.1 ± 9.481) years and second group (B) include 20 RA patients with mean age of (52.15 ± 11.375) years, third group (C) include 10 healthy persons (controls) with mean age of (37.5 ± 6.18) years (Table 3-1).

Table (3-1): Age and gender distribution of study participants

Group	Gender		Total	Age			
	Male	Female	N(%)	Minimum	Maximum	Mean	SD
	N(%)	N(%)					
A	2 (10)	18 (90)	20 (100)	31	66	49.1	9.48
B	0(0)	20n(100)	20 (100)	30	74	52.15	11.37
C	0	10 (100)	10 (100)	30	47	37.5	6.18

3.2 Clinical findings of TMJ

3.2.1 Frequency of involvement

Figure (3-1) showed that the frequency of TMJ involvement clinically (with at least one symptom) in RA patients was 15% in Group A and 40% in Group B.

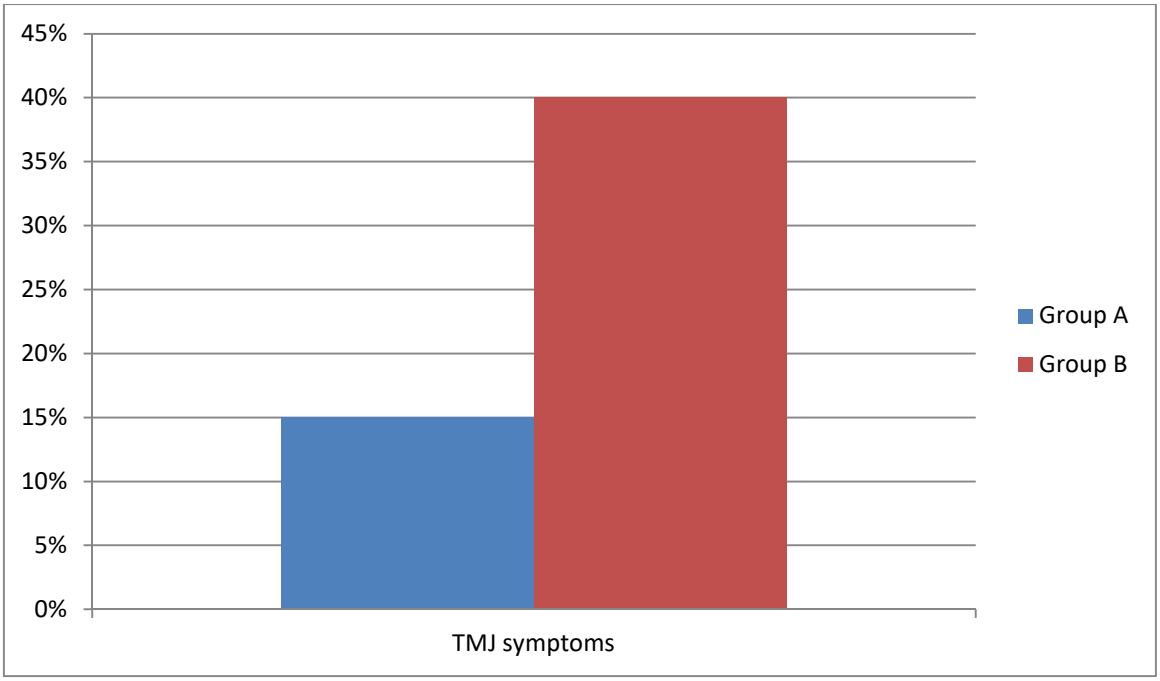


Figure (3-1): Frequency of TMJ involvement clinically in RA patients.

3.2.2 Symptoms

In RA patients, the jaw lock was absent in group A while 2 cases (10%) of group B had jaw lock. Three cases (15%) of group A and 7 cases (35%) of group B complained for facial pains. Moreover, 3 patients (15%) in group A felt jaw pain on the right side and 2 patients (10%) on the left side. While 5 cases (25%) in group B felt jaw pains on the right side and 6 cases (30%) on the left side. However, in group B, only 1 case (5%) had clicking during mouth opening, and 1 case (5%) had pains during right lateral jaw excursion (Table 3-2).

Table (3-2): Frequency of symptoms of TMJs of RA and control cases

Group	Jaw Lock	Pain Face	Jaw Pain		Muscle Pain	Joint Pain	Joint Click Open	Joint Click Close	Right Lateral Excursion		Left Lateral Excursion		Protrusion	
	No. (%)	No. (%)	RT	LT	No. (%)	No. (%)	No. (%)	No. (%)	Muscle Pain	Joint Pain	Muscle Pain	Joint Pain	Muscle Pain	Joint Pain
			No. (%)	No. (%)					No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
A	0	3 (15)	3 (15)	2 (10)	0	0	0	0	0	0	0	0	0	0
B	2 (10)	7 (35)	5 (25)	6 (30)	0	0	1 (5)	0	1 (5)	1 (5)	0	0	0	0
Total	2 (5)	10 (25)	8 (20)	8 (20)	0	0	1 (2.5)	0	1 (2.5)	1 (2.5)	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0

3.2.3 Range of jaw movements

Regarding the mean of maximum unassisted mouth opening in RA and control groups, there was a significant difference between both groups (P-vale=0.008) as it was 39 mm in the RA group and was 44.5 mm in the control group. Similarly, a significant difference (P-vale=0.012) in the mean of maximum assisted mouth opening was observed between both RA and control groups (39.5 mm in group A and 39.8 mm in group B, with 44.8 mm in the control group) (Table 3-3).

Table (3-3): Mean and standard deviation of mouth opening of the participants

Group	Unassisted Opening			Maximum Unassisted Opening			Maximum Assisted Opening		
	Mean	**SD**	**P-value**	**Mean**	**SD**	**P-value**	**Mean**	**SD**	**P-value**
A	39	8.97	0.289	39	8.97	0.289	39.5	10.11	0.179
B	39	6.03		39	6.03		39.8	6.22	
C	44.5	1.9	**0.008**	44.5	1.9	**0.008**	44.8	1.99	**0.012**

Additionally, the mean of right lateral jaw excursion was 5.85 mm in group A, 5.4 mm in group B, and 9.5 mm in group C with a significant difference (P-value= 0.002) between RA patients and control cases. Moreover, the mean left lateral jaw excursion was 5.5 mm in group A, 5.75 mm in group B, and 7.2 mm in group C with no significant difference (P-value= 0.952) between RA patients and control cases. On the other hand, the mean of mandibular protrusion was 2.05 mm in group A, 3.2 mm in group B, and 5.1 mm in group C with no significant difference (P-value= 0.444) between RA patients and control cases (Table 3-4).

Table (3-4): Mean and standard deviation of lateral excursion and protrusion of mandible of participants

Group	Right Lateral Excursion			Left Lateral Excursion			Protrusion		
	Mean	**SD**	**P-value**	**Mean**	**SD**	**P-value**	**Mean**	**SD**	**P-value**
A	5.85	2.96	0.719	5.5	3.51	0.783	2.05	1.7	0.663
B	5.40	3.56		5.75	3.66		3.2	1.47	
C	9.5	0.7	**0.002**	7.2	3.61	0.952	5.1	1.59	0.444

3.3 Laboratory Investigations

The ESR was positive in 15 (75%) and 17 (85%) cases of group A and B, respectively, with no significant difference (P-value=0.695). The RF was positive in 16 cases (80%) of group A and 10 cases (50%) of group B with no significant difference (P-value= 0.096). Similarly, the CRP was positive in 17 cases (85%) of group A and 18 cases (90%) of group B with no significant difference (P-value=1.000). The Anti-CCP was positive in 15 cases (75%) and 13 cases (65%) of groups A and B, respectively, with no significant difference (P-value=0.731) (Table 3-5).

Table (3-5): Number and frequency of patients with positive laboratory test results

Test	**Group A**		**Group B**		**P-value**	**Total**	
	No.	**%**	**No.**	**%**		**No.**	**%**
ESR	15	75	17	85	0.695	32	80
RF	16	80	10	50	0.096	26	65
CRP	17	85	18	90	1.000	35	87.5
Anti-CCP	15	75	13	65	0.731	28	70

Table (3-6) showed that 50% of group (A) patients had positive results of all four serological tests and 35% of group B have all positive results, 65% of group A and 50% of group B had three positive tests , 70% of group (A) and 75% of group (B) patients have two positive tests, 85% of group (A) and 90% of group (B) patients have only one positive test .

Table (3-6): Numbers and frequencies of positive laboratory tests

Group	**All tests**		**Three tests**		**Two tests**		**One test**	
	positive		positive		positive		positive	
	No.	%	No.	%	No.	%	No.	%
A	10	50	13	65	14	70	17	85
B	7	35	10	50	15	75	18	90

3.4 Radiographic assessment of TMJs

The frequency of TMJ involvement in RA patients using CBCT was (75% in group A and 90% in group B) and using MRI was (80% in group A and 95% in group B) and in the control group were 10% and 30%, respectively (Figure 3-2).

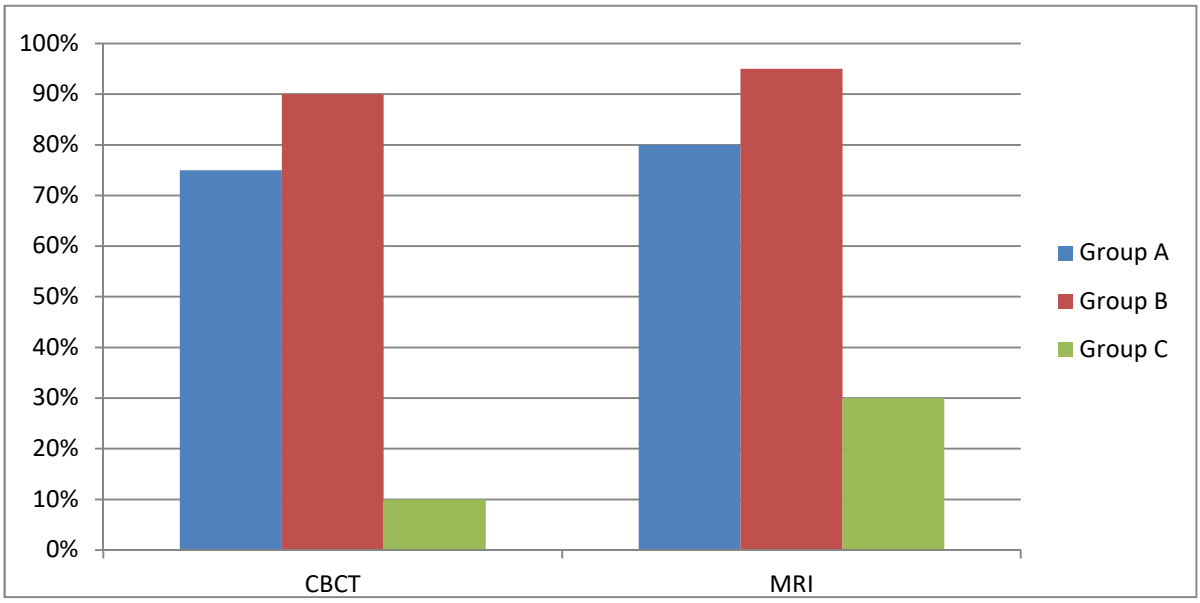


Figure (3-2): the frequency of TMJ involvement radiographically

3.4.1 Radiographic findings on CBCT

In RA patients, the frequency of condylar head erosion was 70% in group A and 65% in group B, with no significant difference (P-value=0.516). The frequency of articular eminence erosion was 5% in group A and 10% in the group B, with a significant difference (P-value=0.032). The frequency of condylar head flattening was 55% in group A and 75% in group B, with no significant difference (P-value=0.834). The frequency of condylar sclerosis was 15% in both groups A and B, with no significant difference (P-value=0.245). The frequency of subchondral cyst was 30% and 5% in groups A and B, respectively, with a significant difference (P-value=0.000), and there was no osteophyte in both groups. On the other hand, the only observed radiographic change in group C was the flattening of condylar head (10%) with significant difference with RA patients (P-value=0.003) (Table 3-7).

Table (3-7): Frequencies of radiographic changes by CBCT

Group	Condylar Erosion			Articular Eminence Erosion			Osteophyte		Sclerosis			Subchondral Cyst			Flattening		
	No.	**%**	**P-value**	**No.**	**%**	**P-value**	**No.**	**%**	**No.**	**%**	**P-value**	**No.**	**%**	**P-value**	**No.**	**%**	**P-value**
A	14	70	0.516	1	5	0.032	0	0	3	15	0.245	6	30	≤0.01	11	55	0.834
B	13	65		2	10		0	0	3	15		1	5		15	75	
Total	27	67.5		3	7.5		0	0	6	15		7	17.5		26	65	
C	0	0	**≤0.01**	0	0	**≤0.01**	0	0	0	0	**≤0.01**	0	0	**≤0.01**	1	10	**0.003**

In group (A) patients; the frequency of G1erosion of the condyle was (15% in Rt and 40% in Lt) with no significant difference (P-value=0.096), frequency of G2 erosion was (25% in Rt and 20% in Lt) with no significant difference (P-value=0.716) and frequency of G3 erosion was (5% in Rt and 0% in Lt) with no significant difference (P-value=0.330) (Table 3-8).

The frequency of condylar head flattening was (45% in Rt and 55% in Lt) with no significant difference (P-value=0.042) and frequency of sclerosis was (10% in each side) with no significant difference (P-value=1.000) and frequency of articular eminence erosion was (5% in Rt and 0% in Lt) with no significant difference (P-value=0.330) and frequency of subchondral cyst was (30% in Rt and 0% in Lt) with significant difference (P-value=0.001) and Osteophyte was absent in both sides (0%) (tables 3-9 and 3-10).

In group (B) patients; the frequency of G1erosion of the condyle was (20% in Rt and 10% in Lt) with no significant difference (P-value=0.330), frequency of G2 erosion was (15% in Rt and 20% in Lt) with no significant difference (P-value=0.186) and frequency of G3 erosion was (15% in Rt and 5% in Lt) with no

significant difference (P-value=0.163) (Table 3-8). the frequency of condylar head flattening was (60% in Rt and 65% in Lt) with no significant difference (P-value=0.577) and frequency of sclerosis was (15% in each side) with no significant difference (P-value=1.000) and frequency of articular eminence erosion was (10% in each side) with no significant difference (P-value=0.068) and frequency of subchondral cyst was (0% in Rt and 5% in Lt) with no significant difference (P-value=0.330) Osteophyte was absent in both sides (0%) (Tables 3-9 and 3-10).

In group (C); the only change seen was condylar head flattening (10% in each side) with no significant difference (P-value= 0.119) (Table 3-9) , the other changes was absent on both sides of TMJs (0%) (Tables 3-8 and 3-10).

Table (3-8): The Frequencies of Condylar head erosion in response to different grades in both TMJ sides by CBCT

Group*	**G1 erosion**					**G2 erosion**					**G3 erosion**				
	RT		LT		P-value	RT		LT		P-value	RT		LT		P-value
	No	%	No	%		No	%	No	%		No	%	No	%	
A	3	15	8	40	0.096	5	25	4	20	0.716	1	5	0	0	0.330
B	4	20	2	10	0.330	3	15	6	20	0.186	3	15	1	5	0.163
C	0	0	0	0	**≤0.01**	0	0	0	0	**≤0.01**	0	0	0	0	**≤0.01**

*Some patients presented with bilateral TMJ condylar head erosion

Table (3-9): Numbers and Frequencies of flattening, sclerosis and articular eminence erosion in both sides of TMJ by CBCT

Group *	Condylar flattening					Sclerosis					Articular eminence erosion				
	RT		LT		P-value	RT		LT		P-value	RT		LT		P-value
	No	%	No	%		No	%	No	%		No	%	No	%	
A	9	45	11	55	0.042	2	10	2	10	1.000	1	5	0	0	0.330
B	12	60	13	65	0.577	3	15	3	15	1.000	2	10	2	10	0.068
C	1	10	1	10	0.119	0	0	0	0	**≤0.01**	0	0	0	0	**≤0.01**

*Some patients presented with bilateral TMJ condylar head erosion

Table (3-10): Numbers and frequencies of subchondral cyst and osteophyte detection by CBCT

Group	**Subchondral cyst**					**Osteophyte**				
	RT		LT		P-value	RT		LT		P-value
	No	%	No	%		No	%	No	%	
A	6	30	0	0	0.001	0	0	0	0	≤0.01
B	0	0	1	5	0.333	0	0	0	0	≤0.01
C	0	0	0	0	**≤0.01**	0	0	0	0	**≤0.01**

3.4.2 Radiographic findings on MRI

In RA patients, the frequency of condylar head erosion was 75% in group A and 85% in group B. The frequency of articular eminence erosion was 20% in group A and 30% in group B with no significant differences (P-value=0.122 and 0.174, respectively). The condylar head flattening was 30% and 20% in groups A and B, respectively, with no significant difference (P-value=0.367). Moreover, there

is no significant differences (P-value=0.423) in the frequency of synovial thickening in groups A and B (20%). In comparison, the frequency of effusion was 15% in group A and 5% in group B, with a significant difference (P-value=0.017). In group C, the most frequent radiographic change was the osseous condylar head (30%) followed by condylar head flattening (10%) with a significant difference with patients (P-value=0.000 and 0.001, respectively) (Table 3-11).

Table (3-11): Frequencies of radiographic changes by MRI in participants

Group	Condylar erosion			Articular Eminence erosion			Synovial thickening			Effusion			Condylar Flattening		
	No.	**%**	**P-value**	**No.**	**%**	**P-value**	**No.**	**%**	**P-value**	**No.**	**%**	**P-value**	**No.**	**%**	**P-value**
A	15	75	0.122	4	20	0.174	4	20	0.423	3	15	0.017	6	30	0.367
B	17	85		6	30		4	20		1	5		4	20	
Total	32	80	0.234	10	25	**≤0.01**	8	20	**≤0.01**	4	10	**≤0.01**	10	25	**0.001**
C	3	30		0	0		0	0		0	0		1	10	

In group (A) patients, the frequency of OS1 of condyle was (15% in Rt and 5% in Lt) with no significant differences (P-value=0.330), the frequency of OS2 of condyle was (40% in Rt and 55% in Lt) with no significant differences (P-value=0.267) and the frequency of OS3 of condyle was (5% in Rt and 0% in Lt) with no significant differences (P-value=0.330) and the frequency of OS4 of condyle was (0% in each side) (Table 3-12). The frequency of condylar head flattening was (25% in Rt and 30% in Lt) with no significant differences (P-value=0.330) and the frequency of effusion was (10% in each side) with no

significant differences (P-value=1.000) and the frequency of articular eminence erosion was (10% in Rt and 15% in Lt) with no significant difference (P-value=0.577) and the frequency of synovial proliferation was (10% in Rt and 15% in Lt) with no significant difference (P-value=0.577) (Table 3-13).

In group (B) patients; the frequency of OS1 of condyle was (15% in Rt and 20% in Lt) with no significant differences (P-value=0.666), the frequency of OS2 of condyle was (30% in Rt and 40% in Lt) with no significant differences (P-value=0.541) and the frequency of OS3 of condyle was (30% in Rt and 5% in Lt) with no significant differences (P-value=0.056) and the frequency of OS4 of condyle was (0% in each side) (Table 3-12). The frequency of condylar head flattening was (20% in Rt and 20% in Lt) with no significant differences (P-value=1.000) and the frequency of effusion was (5% in Rt and 0% in Lt) with no significant differences (P-value=0.330) and the frequency of articular eminence erosion was (25% in Rt and 15% in Lt) with no significant differences (P-value=0.330) and the frequency of synovial proliferation was (10% in each side) with no significant differences (P-value=1.000) (Table 3-13).

In group (C); two cases were detected with OS1 of Rt TMJ (20%) with no significant difference (P-value= 0.168) , one case with OS2 of Rt and Lt TMJs (10%) with no significant difference (P-value= 1.000), and one case of Lt condylar head flattening (10%) with significant difference (P-value= 0.001), the other changes was absent on both sides of TMJs (0%) (Tables 3-12 and 3-13).

Table (3-12): Numbers and frequencies of Osseous changes of condyle detected by MRI

Group	OS1					OS2					OS3					OS4				
	RT		LT		P-value	RT		LT		P-value	RT		LT		P-value	RT		LT		P-value
	No	%	No	%		No	%	No	%		No	%	No	%		No	%	No	%	
A	3	15	1	5	0.330	8	40	11	55	0.267	1	5	0	0	0.330	0	0	0	0	≤0.01
B	3	15	4	20	0.666	6	30	8	40	0.541	6	30	1	5	0.056	0	0	0	0	≤0.01
C	2	20	0	0	0.168	1	10	1	10	1.000	0	0	0	0	**≤0.01**	0	0	0	0	**≤0.01**

Table (3-13): Numbers and Frequencies of effusion, flattening, Osseous change of articular eminence and synovial thickening detection by MRI

Group	effusion					flattening					OS articular eminence					Synovial thickening				
	RT		LT		P-value	RT		LT		P-value	RT		LT		P-value	RT		LT		P-value
	No	%	No	%		No	%	No	%		No	%	No	%		No	%	No	%	
A	2	10	2	10	1.000	5	25	6	30	0.330	2	10	3	15	0.577	2	10	3	15	0.577
B	1	5	0	0	0.330	4	20	4	20	1.000	5	25	3	15	0.330	2	10	2	10	1.000
C	0	0	0	0	**≤0.01**	0	0	1	10	**0.001**	0	0	0	0	**≤0.01**	0	0	0	0	**≤0.01**

3.4.3 Condylar measurements on CBCT

The mean of condylar length in group A was 6.84 ± 0.91, and in group B was 6.93 ± 1.27 with no significant differences between them (p-value=0.202). The mean of condylar width in group A was 17.23 ± 1.74, and in group B was 16.31 ± 2.21 with no significant differences between them (p-value=0.633). The mean of condylar height was 18.25 ± 2.01 and 17.79 ± 1.94 in groups A and B, respectively, with no significant differences between them (p-value=0.915). In control cases; the mean of condylar length was 7.61 ± 0.71, the mean of condylar width was 16.53 ± 1.71, and the mean of condylar height was 21.14 ± 1.51 with

no significant differences between control cases and patients (P-values=0.215, 0.844, and 0.219, respectively) (Table 3-14).

Table (3-14): Mean and standard deviation of condylar measurements on CBCT

Group	Condylar Length/mm			Condylar Width/mm			Condylar Height/mm		
	Mean	**SD**	**P-value**	**Mean**	**SD**	**P-value**	**Mean**	**SD**	**P-value**
A	6.84	0.91	0.202	17.23	1.74	0.633	18.25	2.01	0.915
B	6.93	1.27		16.31	2.21		17.79	1.94	
C	7.61	0.71	0.215	16.53	1.71	0.844	21.14	1.51	0.219

In group (A) patients; the mean of condylar length is (6.86 ± 1.37 in Rt) and (6.82 ± 0.82 in Lt) with no significant differences (P-value= 0.885), the mean of condylar width is (17.43 ± 1.68 in Rt) and (17.02 ± 2.01 in Lt) with no significant difference (P-value=0.154), the mean of t condylar height is (18.69 ±2.33 in Rt) and (17.81 ±1.98 in Lt) with significant difference (P-value= 0.025) (Table 3-15).

In group (B) patients; the mean of condylar length is (6.84 ±1.36 in Rt) and (7.01 ±1.32 in Lt) with no significant difference (P-value= 0.407), the mean of condylar width is (16.03 ±2.41 in Rt) and (16.58 ±2.21 in Lt) with no significant difference (P-value=0.085, the mean of condylar height is (18.31 ±2.08 in Rt) and is (17.27 ±2.03 in Lt) with significant difference (P-value= 0.004) (table 3-15).

In control cases (group C); the mean of condylar length is (7.54 ±0.83 in Rt) and (7.68 ±0.67 in Lt) with no significant difference (P-value= 0.425), the mean of condylar width is (16.56 ±1.74 in Rt) and (16.49 ±1.78 in Lt) with no significant difference (P-value=0.804) , the mean of condylar height is (21.06 ±1.50 in Rt)

and (21.22 ±1.57 in Lt) with no significant difference (P-value= 0.425) (Table 3-15).

Table (3-15): Mean and standard deviation of measurements of right and left condyles on CBCT

Group	Condylar length					Condylar width					Condylar height				
	Rt		Lt		P-value	Rt		Lt		P-value	Rt		Lt		P-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
A	6.86	1.37	6.82	0.82	0.885	17.43	1.68	17.02	2.01	0.154	18.69	2.33	17.81	1.98	0.025
B	6.84	1.36	7.01	1.32	0.407	16.03	2.41	16.58	2.21	0.085	18.31	2.08	17.27	2.03	0.004
C	7.54	0.83	7.68	0.67	0.425	16.56	1.74	16.49	1.78	0.804	21.06	1.50	21.22	1.57	0.425

3.5 Correlation of laboratory results with clinical and radiographic findings

Table (3-16) has shown that there is a positive correlations between ESR and clinical symptoms while RF have positive correlations with joint clicking only and negative correlations with the remaining symptoms. CRP showed a positive correlations with all symptoms except joint clicking, and Anti-CCP showed a positive correlations with all symptoms except face pains and jaw pains only

Table (3- 16): Correlations of laboratory test results with clinical symptoms of TMJs

Test	Jaw lock		Face pain		Jaw pain		Joint clicking		Pain during lateral excursion	
	*r	**p-value	r	P-value	r	P-value	r	p-value	r	P-value
ESR	0.115	0.481	0.094	0.565	0.120	0.462	0.080	0.623	0.080	0.623
RF	-0.072	0.658	-0.157	0.333	-0.107	0.512	0.118	0.470	-0.218	0.176
CRP	0.087	0.595	0.189	0.243	0.204	0.208	-0.424	0.006	0.061	0.711
Anti-CCP	0.150	0.355	-0.082	0.616	-0.039	0.810	0.105	0.520	0.105	0.520

***Pearson correlation coefficient, ** Significance level set at 0.05.**

Table (3-17) has shown that the ESR have a negative correlations with an unassisted and assisted openings and left lateral excursion but RF have negative correlations with left lateral excursion and protrusion only. CRP have positive correlations with all movements but Anti-CCP have negative correlations with all movements.

Table (3-17) : Correlations of laboratory test results with Jaw movements

Test	Unassisted opening		Maximum unassisted opening		Maximum assisted opening		Rt lateral excursion		Lt lateral excursion		Protrusion	
	r	p-value	r	P-value	r	P-value	r	p-value	r	P-value	r	P-value
ESR	-0.065	0.688	-0.065	0.688	-0.098	0.549	0.100	0.546	-0.196	0.225	0.000	1.000
RF	0.073	0.655	0.073	0.655	0.026	0.872	0.132	0.422	-0.243	0.131	-0.166	0.305
CRP	0.052	0.750	0.052	0.750	0.030	0.854	0.285	0.078	0.0412	0.008	0.326	0.04
Anti-CCP	-0.122	0.453	-0.122	0.453	-0.161	0.320	-0.214	0.191	-0.304	0.057	-0.214	0.184

The ESR have negative correlations with condylar dimensions but positive correlations with radiographic changes. RF have negative correlations with condylar width and height but positive correlations with condylar length and radiographic changes. CRP have positive correlations with condylar dimensions but negative correlations with radiographic changes. Anti-CCP have negative correlations with condylar dimensions but positive correlations with radiographic changes (Table 3-18).

Table (3-18): Correlations of laboratory test results with condylar dimensions and radiographic changes

Test	Condylar length		Condylar width		Condylar height		Radiographic changes	
	r	p-value	r	P-value	r	P-value	r	p-value
ESR	-0.165	0.307	-0.134	0.410	-0.344	0.030	0.042	0.799
RF	0.033	0.842	-0.045	0.781	-0.347	0.028	0.105	0.520
CRP	0.063	0.700	0.059	0.717	0.296	0.063	-0.126	0.439
Anti-CCP	-0.223	0.167	-0.004	0.979	-0.227	0.159	0.145	0.370

3.6 Correlations of condylar dimensions with jaw movements in RA patients

Table (3-19) has shown that the condylar length has positive correlations with all movements except right lateral excursion and mandibular protrusion, and the condylar width and height have positive correlations with all movements except protrusion.

Table (3-19): Correlations of condylar dimensions with Jaw movements

Condylar dimensions	Unassisted opening		Maximum unassisted opening		Maximum assisted opening		Right lateral excursion		Left lateral excursion		Protrusion	
	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value
Length	0.014	0.933	0.014	0.933	0.049	0.766	-0.077	0.638	0.093	0.570	-0.170	0.294
Width	0.196	0.226	0.196	0.226	0.225	0.163	0.105	0.519	0.061	0.707	- 0.161	0.322
Height	0.038	0.815	0.038	0.815	0.084	0.604	0.151	0.353	0.339	**0.032**	- 0.016	0.920

3.7 Comparisons between CBCT and MRI outcomes

Sensitivity and specificity tests were done to compare the diagnostic ability of CBCT and MRI in detecting osseous abnormalities of TMJs. The results have shown that the MRI had a sensitivity of 75% and specificity of 84% than CBCT test (using CBCT as a gold standard) (Figure 3-3).

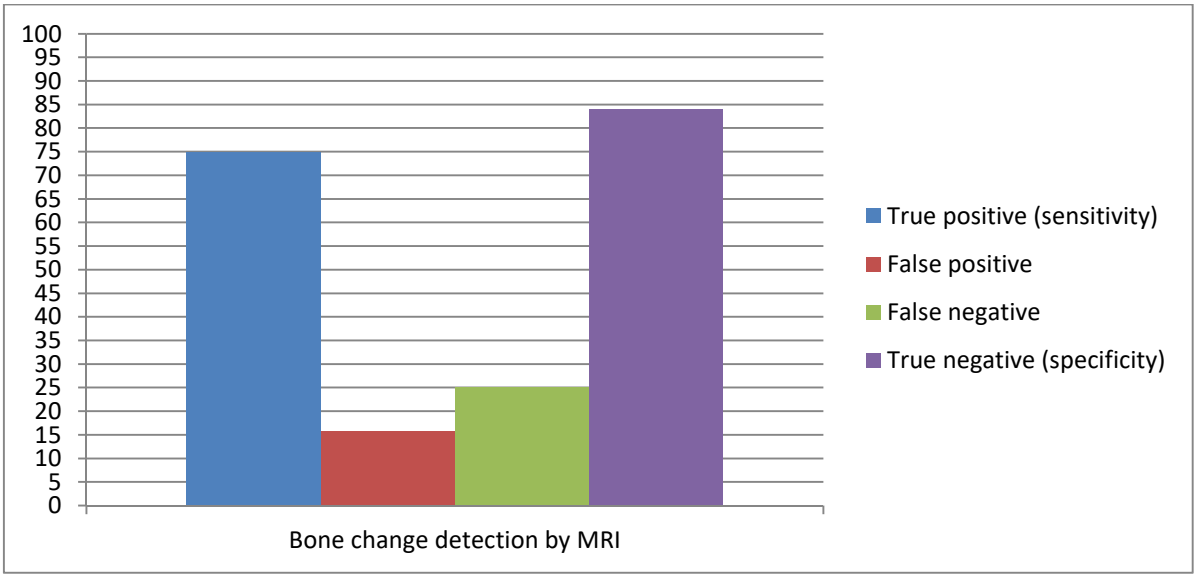


Figure (3-3): Sensitivity and Specificity of MRI in detecting osseous changes.

Chapter Four

Discussion

Chapter 4: Discussion

This study was done to evaluate TMJ changes in RA patients and their relations to disease chronicity and to compare the diagnostic effectiveness of CBCT and MRI in detecting radiographic changes of TMJs. There is no international radiographic classification or scoring measurements to evaluate TMJ changes in RA patients (Youssef et al., 2020).

4.1 TMJ involvement clinically in RA

In the present study, the prevalence of TMJ involvement clinically was 15% in Group A and 40% in Group B which was lower than the results reported by (Sodhi et al., 2015, Savtekin & Şehirli 2018, and Akhlaghi et al. 2019).

Such differences could be due to the different types of examination, patient selection criteria, sample size, the use of diagnostic techniques and the inclusion criteria. According to previous studies, TMJ involvement follows the same destructive path as in other joints and is directly correlated with the severity and duration of RA; therefore, the duration of RA is regarded as an aggravating factor for the involvement of TMJ (Cunha et al., 2012). This finding was confirmed in the present study and the TMJ involvement was higher in patients with a longer duration of the disease (Group B).

4.1.1 Clinical findings

In RA patients, 25% had facial pains followed by jaw pains (20%), then clicking during mouth opening (2.5%), and muscle pains and joint pains during a right lateral excursion of the mandible (2.5%). TMJ pain was found in 65%, muscle pains in 42%, and joint sounds in 51% of RA patients in a study done in Iran (Akhlaghi et al., 2019). Such differences might be related to the examination

methods of TMJs, variation in the number of included cases, types and frequencies of drug intake in RA patients and inclusion of cases with TMD.

In this thesis, the mean of an unassisted opening and a maximum unassisted opening of mouth were close to each other in RA (39.03 mm) and control (44.5 mm) groups. In contrast, the mean of maximum assisted mouth opening in RA patients was 39.65 mm and 44.8 mm in the control group, which was higher than the results found by (Ardic et al., 2006) who reported an unassisted opening to be 37.5 mm in RA and 39.1 mm in control groups, however, they reported higher range of assisted opening (44.3 mm in RA and 45.2 mm in control groups), such difference in an unassisted opening might be related to the included RA patients with possibly longer duration of disease that cause more degenerative changes and reducing mouth opening range.

Additionally, the mean of right lateral jaw excursion was 5.63 mm in RA and 9.5 mm in control groups, while the mean of left lateral jaw excursion was 5.63 mm and 7.2 mm in RA and control groups. These findings were lower than the results of a study that reported right excursion of 6.7 mm and 8.7 mm in RA and control groups, respectively and left excursion of 6.9 mm and 7.9 mm in RA control groups, respectively (Ardic et al., 2006). Most studies have shown a decreased range of motion in RA patients which might be caused by reduced joint space, sclerosis, or changed condylar positioned as an adaptive procedure.

4.2 Laboratory investigations

In this study, four laboratory tests of RA (ESR, RF, CRP and Anti-CCP) have been investigated to find any correlations between them and radiographic changes of TMJs. ESR is a diagnostic test commonly used to detect inflammation resulting from autoimmune diseases. Although it is a non-specific test which is usually used to monitor the disease course (Assasi et al.,

2015) . The ESR level was elevated in 80% of RA patients which was close to the results of (Kurup, Gharote and Jose, 2019) 87%, however, lower frequencies were detected by (Voog et al.,2003 and Yilmaz et al., 2012) who found that the ESR were elevated in 53% and 28.57% of the cases, respectively.

The RF is a non-specific antibody that may be produced in some autoimmune diseases and might be present in approximately 70% of RA patients (Rindfleisch and Muller, 2005). In this study, RF was positive in 65% from total RA patients. This agrees with the results of (Gheita et al.2012, Yilmaz et al. 2012, Rehan et al., 2018, Kurup, Gharote and Jose, 2019) who found RF positivity in 64.3% , 75%, 67%, and 60.71% of the cases, respectively.

In this study, the CRP was positive in 87.5% of RA patients which was higher than the result found by (Mortazavi et al., 2018) which was 46.15%.

In this study, the Anti-CCP was positive in 70% of patients which was lower than the result found by (Mortazavi et al., 2018) 94.23%. Such difference between our results and other studies might be related to the sensitivity of the test machines, tests carried out at different disease activity stage (might be at remission stag) and type and frequency of the drugs used for treatment of RA.

4.3 TMJ involvement radiographically in RA

In this study, the frequency of TMJ involvement in RA patients using CBCT was (75% in group A and 90% in group B) and using MRI were (80% in group A and 95% in group B) while it was reported to vary from 2% to 86% in other studies (Lin et al., 2007, Witulski et al., 2014, Sadura-Sieklucka et al., 2021). The differences in results might be related to the difference in patient selection criteria, the use of difference machine and different imaging techniques and the inclusion criteria.

4.3.1 CBCT findings

In RA patients, the most frequent osseous change was condylar head erosion (67.5%) which was higher than the results of other studies (Bayar et al., 2002, Voog et al., 2003) who reported 13.3% and 50%, respectively, close to the result found by (Gheita et al., 2012) (62.5%) but lower than those found by other studies (Hajati et al., 2009, Deoghare and Degwekar, 2010) who reported 72% and 85%, respectively. Flattening in both RA and control groups (65% and 50%, respectively) has been detected which was close to the results of a study conducted in Egypt (Rehan et al., 2018) who found 89.3% and 50%, respectively and higher than the results of (Voog et al., 2003) who found 30% flattening in RA patients.

Moreover, subchondral cyst only in the RA group (17.5%) has been found which was higher than the outcomes reported by (Deoghare and Degwekar, 2010) (10%), but was lower than some other studies (Bayar et al., 2002, Voog et al. 2004, Gheita et al. 2012, and Rehan et al. 2018) who reported 20.83%, 23.3%, 32.1%, 30%, and respectively. Furthermore, sclerosis in the RA patients (15%) was found which was much lower than the results reported by other studies (Voog et al., 2004, Gheita et al., 2012, Rehan et al., 2018) who reported 41.67%, 64.3% and 75% respectively. Such differences between the selected studies might be related to the number of cases, the difference in CBCT machines' quality, and selected TMJ assessment sections or different reading by radiologists.

4.3.2. MRI findings

In RA patients, the frequency of osseous change of condyle (erosion) was 80% which was in agreement with the results found by other studies (El-Melegy et al.,

2017, Hirahara et al., 2017) who reported 80% and 83.3%, respectively, but higher than (Abdel Aziz and Esha, 2017) (52.5%), and lower than the results of a study conducted in Japan (Kretapirom et al., 2013) who found erosion in 96% of RA cases. On the other hand, the frequency of articular eminence erosion was 25% which was higher than the results reported by other studies (Kretapirom et al., 2013, Hirahara et al., 2017) who found 8.2% and 9.5% respectively, but lower than the reported results (Abdel Aziz and Esha, 2017) (50%). While the condylar head flattening was seen in 25%, higher than the results found by (Abdel Aziz and Esha, 2017, Hirahara et al., 2017) (15% and 16.6%, respectively).

In the current study, synovial proliferation was found in 20%, of RA patients which is different from the results of other studies (Kretapirom et al., 2013, Hirahara et al., 2017) who reported 100% and 85.7%, respectively. The frequency of effusion was 10% which was much lower than the results reported by other studies (Kretapirom et al., 2013, El-Melegy et al., 2017, Hirahara et al., 2017) who reported 67.5%, 30.9%, and 33%, respectively. Differences in the results of these studies might be related to differences in MRI techniques, the use of contrast media and differences in parameters and selected slices.

A study done by Uchiyama, Murakami and Furukawa (2013) have shown that erosion in 38.5% of group A and 42.9% in group B which was lower than our results but they found flattening in 34.6% of group A and 21.4% of group B which was close to our results.

In this thesis, the condylar erosion was the most common radiographic manifestation for the assessment of rheumatoid arthritis severity. The results of this study is compatible with Uchiyama, Murakami and Furukawa (2013) work

in that the erosion of the mandibular condyle was observed within 1 to 10 years of rheumatoid arthritis involvement.

4.3.3 CBCT measurements

The mean condylar length was 6.88 mm in RA patients and 7.61 mm in control cases, which was lower than the results of (Youssef et al., 2020), who found 8.66 mm in RA and 8.27 mm in control groups. Our results for control cases were close to the results of a study done in Malaysia (Al-koshab et al., 2015) (7.50 mm in Malays and 7.20 mm in Chinese). The mean of condylar width was 16.77 mm in RA patients and 16.53 mm in control cases which were slightly lower than the results reported by other researchers (Al-koshab et al., 2015, Youssef et al., 2020) who found 17.89 mm in RA/17.99 mm in controls and 17.18 mm in Malays and 17.80 mm in Chinese, respectively but was higher than the results reported by (Manja and Rajaduray, 2019) who found 11.67 mm in patients with clicking and 11.18 mm in patients without clicking.

Consequently, in this study, the mean of condylar height was 18.02 mm in RA patients and 21.14 mm in control cases which were close to the results found by (Manja and Rajaduray, 2019), who found 18.9 mm in patients with clicking and 22.81 mm in patients without clicking) and (Al-koshab et al., 2015) (17.0 mm in Malays and 18.37 mm in Chinese). Our results were much higher than (Youssef et al., 2020) (4.3 mm in RA and 4.87 mm in control cases). These drastic differences might be related to the height measurement method that is almost done from the most superior point of the condylar head down to the line of measuring the ML dimension of the condyle. The only decreased measurement was in the condylar height of RA patients concerning control cases that indicate bone changes in the upper condylar surface with less or no destruction in the other directions.

Regarding the difference in dimensions between right and left TMJs, there was no significant differences between them except that the right condylar height was more than left in group B of RA patients. Our results differ from results found by (Al-koshab et al., 2015) who argued that the condylar length and width were significantly larger on the right side while condylar height was larger on the left side. This could be explained by the presence of different types of malocclusions in their sample.

A study was carried out by Calle et al. (2021) on juvenile idiopathic arthritis (JIA) and control cases with MRI to measure condylar excursion angle (CEA). The height of articular eminence (HAE) and inclination of the articular eminence (IAE) revealed lower measurements in JIA, as there was a positive correlations between HAE and IAE mandibular range of motion and pain on assisted mandibular opening in the patient's group. This supports our study in that the measurements of the dimension of TMJ structure can be used as a helpful tool in confirming TMJ changes in RA patients.

4.4 Correlation of laboratory results with clinical and radiographic findings

There were a positive correlations between ESR and all clinical symptoms of TMJ while RF had positive correlations with joint clicking only. CRP showed positive correlations with all symptoms except joint clicking, and Anti-CCP showed positive correlations with all symptoms except face pains and jaw pains only. Regarding Anti-CCP and RF, our outcomes agreed with the results of (Mortazavi et al., 2018) who found correlations between RF and Anti-CCP with TMDs in RA patients.

The ESR and Anti-CCP had negative correlations with all condylar dimensions (length, width and height) and RF had negative correlations with condylar width and height. CRP show positive correlations with all condylar dimensions. Regarding Anti-CCP, the study findings greed with Youssef et al. (2020) who found negative correlations between Anti-CCP and condylar height and length but disagreed with their results in that there were no correlations between RF and condylar dimensions.

There were a positive correlations between ESR, RF, Anti-CCP with radiographic changes detected on TMJs. Regarding the ESR and RF outcomes in this study, they were agreed with a study done in Iran (Akhlaghi et al., 2019). However, our results for the relation between RF and Anti-CCP with radiographic changes were controversial to a study done in Egypt (Youssef et al., 2020).

4.5 Correlations of condylar dimensions with jaw movements in RA patients

There was a positive correlations between condylar dimensions (length, width and height) and vertical and horizontal jaw movements (mouth opening and lateral jaw excursion) which mean that the decrease in condylar dimensions will lead to the reduction in range of mouth opening and lateral jaw excursion.

4.6 Comparison of CBCT and MRI

Many researchers reported the excellent ability and superiority of CBCT in evaluating osseous abnormalities of the TMJ than other imaging modalities (Larheim et al., 2015). Due to the high reliability of CBCT demonstrated by previous studies, we considered CBCT a gold standard in evaluating osseous changes compared to MRI.

However, other studies evaluated the diagnostic ability of MRI to detect osseous abnormalities of the TMJ using cadaver specimens. The result have shown that the MRI had 75% sensitivity and 84% specificity in detecting osseous abnormalities. In this regard, evaluation of 106 TMJs was done by CBCT, and MRI and low sensitivity (30 - 82%) with high specificity (84-90%) of MRI for detecting osseous abnormalities were also seen (Alkhader et al., 2010), as well as a study on 20 TMJs was done and sensitivity of 25% - 90.9% with a specificity of 70.8% -97.2% were found (Abdel Aziz and Esha, 2017). Generally, the low sensitivity of MRI in detecting osseous abnormalities might be due to the limited spatial resolution of MRI, and the slice thickness of MRI, as mainly ≥ 3 mm is used, which might be too thick to detect subtle osseous changes (Stomp et al., 2014). Other problems include the presence of fibrous tissues inside the TMJ and the attachment of the lateral pterygoid muscle near the articular surface of the condyle, which can be interpreted as either an osseous abnormality or as a disc. They may result in false-positive or false-negative results (Nieuwenhuis et al., 2017). In addition, when detecting osseous abnormalities in the articular fossa and eminence, difficulties sometimes arise due to magnetic susceptibility artefacts (Sudoł-Szopińska et al., 2015, Nieuwenhuis et al., 2016).

Limitation of this study were total number of samples was small due to presence of pandemic corona virus and lock down at time of case collection and unavailability of many MRI machines (especially 3 Tesla) and unavailability of well-trained radiographer for taking MRI of TMJs.

Chapter Five

Conclusions and Recommendations

Chapter 5: Conclusions and Recommendations

5.1 Conclusions

The following conclusions are drawn:

1- Osseous changes such as erosion are associated with TMJs affection in RA patients that might occur with no/mild clinical signs. Thus, TMJ imaging must be done for RA patients to avoid severe complications even if there are no clinical signs.

2- Elevated levels of ESR, RF, and Anti-CCP might expect RA and TMJ changes, further more an elevated level of Anti-CCP and RF predict clinical symptoms of TMJs and reduced dimensions of the mandibular condyles.

3- The chronicity of RA affects the frequency of TMJ involvement clinically, patients with longer disease duration have more clinical symptoms of TMJs.

4- Rheumatoid arthritis patients had decreased height and width of the mandibular condyle which indicate a presence of bony changes in the top of condylar head..

5- RA patients have limitation of jaw movements which might be a consequence of bony changes and reduction in condylar dimension

6- MRI can be used as an excellent diagnostic imaging modality compared to CBCT due to its high sensitivity and specificity in detecting osseous changes of the TMJs.

5.2 Recommendations

The following recommendations need to be considered:

1- Studies on patients with longer duration of RA (more than 10 years of disease) needed to assess if further changes are happen in TMJs.

2- Other studies needed to be carried out using MRI machine with higher magnetic field (3 Tesla) for getting images with higher resolutions for better diagnosis and assessment of Articulating disc of the TMJ.

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❖ **A**

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Appendix I

Case Sheet

Case No. : **Date:** **Gender:**

Patient's name: **Age:**

Occupation: **Address:**

Phone No.:

Social history :

1. Smoking: **2. Alcohol:**

Family history of Rheumatoid Arthritis:

Duration of RA :

Lab. Findings:

1. ESR level: **2. RF level:**

3. CRP level: **4. Anti-CCP level:**

Types of treatment: **Dose:**

Appendix II

Research Diagnostic Criteria

TMD CLINICAL EXAMINATION FORM

Have you ever had your jaw lock or	No	0
catch so that it won't open all the way? .	Yes	1
[If no problem opening all the way, SKIP to question 2]		
If Yes,		
Was this limitation in jaw opening severe	No	0
enough to interfere with your ability to eat?	Yes	1

Do you have pain on the right side				
of your face, the left side or both sides?	None	0		
	Right	1		
	Left'	2		
	Both	3		
Could you point to the areas where you	Right		Left	
feel pain?	None	0	None	0
	Jaw Joint	1	Jaw Joint	1
	Muscles	2	Muscles	2
	Both	3	Both	3

{Examiner feels area subject points to, if

it is unclear whether it is joint or muscle pain]

Opening Pattern	Straight	0
	Right Lateral Deviation (uncorrected)	1
	Right Corrected ("S") Deviation	2
	Left Lateral Deviation (uncorrected)	3
	Left Corrected ("S") Deviation	4
	Other	5
	Type:.....	
	(specify)	

Comments:_____

_____

_____

_____

_____

_____

5. Vertical Range of Motion — Maxillary incisor used

a. Unassisted opening without pain ___ ___mm

b. Maximum unassisted opening ___ ___mm

c. Maximum assisted opening ___ ___mm

	MUSCLE PAIN				JOINT PAIN			
	None	Right	Left	Both	None	Right	Left	Both
	0	1	2	3	0	1	2	3

d. Vertical incisal overlap _____ mm

6. Joint Sounds (palpation)

			LEFT	RIGHT
a.	Opening	None	0	0
		Click	1	1
		Coarse Crepitus	2	2
		Fine Crepitus	3	3
	Measurement of Opening Click_ _____ mm		____ mm	
b.	Closing	None	0	0
		Click	1	1
		Coarse Crepitus	2	2
		Fine Crepitus	3	3
	Measurement of Closing Click mm		____mm	____
c.	Reciprocal click eliminated on protrusive opening	No	0	0
		Yes	1	1
		NA	9	9

7. Excursions

		MUSCLE PAIN				JOINT PAIN			
		None	Right	Left	Both	None	Right	Left	Both
a. Right Lateral Excursion	___ ___mm	0	1	2	3	0	1	2	3
b. Left Lateral Excursion	___ ___mm	0	1	2	3	0	1	2	3
c.Protrusion	___ ___mm	0	1	2	3	0	1	2	3

		RIGHT	LEFT
	NA		
d. Midline Deviation	___ ___mm	1	2 9

8. Joint Sounds on Excursions

Right Sounds:			Coarse	Fine
	None	Click	Crepitus	Crepitus
Excursion Right	0	1	2	3
Excursion Left	0	1	2	3
Protrusion	0	1	2	3

Left Sounds:			Coarse	Fine
	None	Click	Crepitus	Crepitus
Excursion Right	0	1	2	3
Excursion Left	0	1	2	3
Protrusion	0	1	2	3

DIRECTIONS, ITEMS 9-11

The examiner will be palpating (touching) different areas of your face, head and neck. We would like you to indicate if you do not feel pain or just feel pressure (0), or pain (1-3). Please rate how much pain you feel for each of the palpations according to the scale below. Circle the number that corresponds to the amount of pain you feel. We would like you to make a separate rating for both the right and left palpations.

0 = No Pain/Pressure Only

1 = Mild Pain

2 = Moderate Pain

3 = Severe Pain

9. Extra oral muscle pain with palpation:

	RIGHT				LEFT			
a.Temporalis (posterior) "Back of temple"	0	1	2	3	0	1	2	3
b.Temporalis (middle) "Middle of temple"	0	1	2	3	0	1	2	3
c.Temporalis (anterior) "Front of temple"	0	1	2	3	0	1	2	3
d.Masseter (origin [superior]) "Cheek/under cheek bone"	0	1	2	3	0	1	2	3
e. Masseter (body [middle]) "Cheek/side of face"	0	1	2	3	0	1	2	3
f. Masseter (insertion (inferior)) "Cheek/jawline"	0	1	2	3	0	1	2	3
g. Posterior mandibular region (Stylohyoid/posterior digastric region) "Jaw/throat region"	0	1	2	3	0	1	2	3
h. Submandibular region (Medial pterygoid/Suprahyoid/anterior digastric region) "Under chin"	0	1	2	3	0	1	2	3

10. Joint pain with palpation:

	RIGHT				LEFT			
LEFT .								
a... Lateral pole"outside"	0	1	2	3	0	1	2	3
b. Posterior attachment "inside ear"	0	1	2	3	0	1	2	3

11. Intraoral muscle pain with palpation:

	RIGHT				LEFT			
a. Lateral pterygoid area "Behind upper molars" .	0	1	2	3	0	1	2	3
b. Tendon of temporalis "Tendon"	0	1	2	3	0	1	2	3

Appendix III

زانکۆی سلێمانی/کۆلێجی پزیشکی ددان

فۆرمی زانیاری بەشداریکردن لەتوێژینەوەی زانستی

داوا لە بەڕێزت دەکەین بە بەشداریکردن لەم توێژینەوەی دکتۆرایەی کە ئە نجامی ئەدەین بە ناونیشانی (بەراوردی﴿وێنەی لەرەی موگناتیسی﴾ و﴿تیشکیسێ دِوری کۆمپیوتەری﴾جومگەکانی شەویلگەیخوارەوە بۆ کەسانی تووشبوو بە نەخۆشی ڕۆماتیزم) .

پێش بڕیاردان لەسەر بەشداریکردن تکایە ئەم خاڵانەی خوارەوە بە ووردی بخوێنەرەوە دواتر ئازادانە بڕیاربدە لەسەر بەشداریکردن یان بەشداری نەکردن لەم توێژینەوەیەدا.

- **بۆچی ئەم توێژینەوەیە ئە نجام ئەدەین؟**

-دەمانەوێت بزانین نەخۆشی ڕۆماتیزم هەیە لەسەر جومگەکانی شەویلگەی خوارەوە وەك جومگەکانی تر لەش وە ئەو گۆڕانکاریانە دەستنیشان بکەین کە ڕِوودەدات لەو جومگانەدا هەروەها بزانین ماوەی تووشبون بە نەخۆشیەکە پەیوەندی چیە بەو گۆڕِانکارییانەوەی کە ڕِوودەدات لەو جومگانەدا.

- دەمانەوێت بزانین وێنەی لەرەیی موگناتیسی ووردترە یان تیشکی سێ ڕسوویی کۆمپیوتەری لە دۆزینەوەی ئەو گۆڕِانکاریانەی کە ڕِوودەدات لە جومگەکانی شەویلگەی خوارەوە .

- **ئەو زانیاریانەی کە لە بەشداربوو وەردەگیرِیت (وەك ناو ژمارە تەلەفۆن) لەگەڵ زانیاری کۆنی نەخۆشیەکە (وەك ئە نجامی پشکنینی خوێن و دەرمانی بەکارهاتو) تۆمار دەکرێت لە فۆرمی تایبەت بە کەسە بەشداربووەکە لەگەڵ ئە نجامیی پشکنینە تیشکیەکان هەمووی بە نهێنی دەمێنێتەوە لای توێژەر وە هیچ کەسێکی تر نایبینیت وە هیچ توێژەرێکی تر مافی بەکارهێنانی ئەو زانیاریانەی نیە بۆ توێژینەوەی تر .**

- **دوو جۆر وێنەی تیشکی دەگیرێت بۆ بەشداربوو کە بریتین لە (لەرەیی موگناتیشی MRI و تیشکی سێ ڕِوویی کۆمپیوتەری CBCT) وە پاشان بەشداربوو ئاگادارەدەکرێتەوە لە ئە نجامەکان .**

- **تێچووی دارایی گرتنی وێنە تیشکییەکان لەلایەن تۆێژەرەوە دەدرێت واتە هیچ بڕە پارەیەك لە بەشداربوو وەرناگیرێت وهیچ ئەرکێکی دارایی ناکەوێتە ئەستۆی بەشداربوو .**
- **هەر بەشداربوویەك ئارەزووی کرد وازبێنێت دوای بەشداریکردنی دەتوانێت پاشگەز بێتەوە بە بێ ئەوەی هیچ بەرپرسیاریەتیەك بکەوێتە ئەستۆی .**

Appendix IV

فۆرمی ڕەزامەندی بەشداریکردن لە تـوێژینەوەدا

پاش خوێندنەوەی فۆرمی زانیاری بەشداریکردن لە تـویژینەوەدا کە هاوپێچە بەم فۆرمەوە بڕیارم دا بە :

بەشداری کردن ☐

بەشداریـنەکردن ☐

نـاوی بەشداربوو : **نـاوی تـوێژەر:**

ئیمزا **ئیمزا**

بەروار

Appendix V

Published Article I

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ORIGINAL ARTICLE

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Correlation of clinical findings of temporomandibular joint with serological results in rheumatoid arthritis patients

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Abstract

Objectives: This study aimed to determine the frequency of temporomandibular joint (TMJ) involvement in patients with rheumatoid arthritis (RA) and to find out the correlation of serological tests with clinical symptoms of TMJs in RA patients.

Patients and Methods: This cross-sectional study was performed on 40 patients with RA classified into two groups according to their duration of the disease. Clinical examination as well as laboratory tests were done for participants.

Results: The frequency of TMJ involvement clinically was 15% in Group A and 40% in Group B. The most frequently observed clinical symptom was facial pain (25%), and the slightest symptom was clicking (2.5%) during mouth opening. There was a positive correlation between ESR, RF, CRP and anti-CCP and clinical sign and symptoms of TMJs in RA patients. An elevated ESR, RF CRP and anti-CCP may indicate the presence of TMJ complains in RA patients. The chronicity of RA affects the frequency of TMJ involvement clinically, patients with longer disease duration have more clinical symptoms of TMJs. An elevated level of ESR, RF, CRP and anti-CCP predict clinical symptoms of TMJs.

KEYWORDS
correlation, rheumatoid arthritis, serological test, temporomandibular joint

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease characterized by chronic inflammation, joint swelling, joint tenderness, and destruction of synovial joints (Jameson, 2018). It usually affects multiple joints of the body, often starting in the peripheral joints (Jameson, 2018; Silman & Pearson, 2002).

The temporomandibular joint (TMJ) is a vital organ which closely associated with masticatory and swallowing functions, and its defect or damage severely reduces the quality of life. Generally, the TMJ pain complaints in patients with RA were recorded to be higher than 50%, the most frequent being bilateral involvement. However, it is rarely the first joint to be affected, thus, posing diagnostic challenges for the dentist (Cordeiro et al., 2016).

RA consider a systemic etiological factor with major influences on the development of temporomandibular disorders. The clinical manifestations of TMJ are often silent, so TMJ involvement in patients with RA has been ignored (Cordeiro et al., 2016).

The frequency of clinical TMJ involvement ranges from 5% to 86%, with bilateral involvement reported as the most frequent (Aliko et al., 2011; Sodhi et al., 2015).

Common clinical signs and symptoms of TMJ involvement are bilateral pain, swelling, stiffness during mouth opening, weakness of the masticatory muscles with decreased bite force, joint noises, and

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A comparison of magnetic resonance imaging and cone beam computerized tomography in the evaluation of temporomandibular joint changes in rheumatoid arthritis patients

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Keywords:
Rheumatoid Arthritis, case-control study, CBCT, MRI, degenerative changes.

ABSTRACT

This study aimed to determine the features of temporomandibular joint (TMJ) involvement in rheumatoid arthritis (RA) patients and comparing the diagnostic efficacy of cone-beam computerized tomography (CBCT) to magnetic resonance imaging (MRI) in identifying changes of TMJs. This case-control study was performed on 40 RA patients with ten healthy adults (control cases). CBCT and MRI examination were done for participants. Independent and paired t-tests and correlation coefficient tests were used for data analysis by SPSS program. The frequency of TMJ involvement using CBCT and MRI techniques were 82.5% and 87.5% in RA patients and were 50% and 30% in control cases. The commonest change in CBCT of RA patients was condylar head erosion (67.5%), and the less common change was articular eminence erosion (7.5%). The commonest changes in MRI of RA patients were an osseous change of condylar head (80%), and the minor change was effusion (10%), while in controls were an osseous change of condylar head (30%) and condylar head flattening (10%). Osseous changes occur in TMJs of RA patients with mild to moderate symptoms, MRI can be used as an efficient imaging modality for detecting changes in TMJ.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systematic, autoimmune, irreversible, inflammatory disorder of the joints throughout the body characterized by swelling, tenderness, pain and destruction of the joint. The synovium is the key target of the disease process in rheumatoid arthritis (RA). It can be anticipated that examination of synovial tissue samples may provide insight into the pathogenesis of the disease and the mechanism of action of treatment [1].

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Assessment of dimensions of mandibular condyles and their correlation with jaw movements in rheumatoid arthritis patients

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Abstract

Objectives: the aim of this study is to assess the condylar dimensions in Rheumatoid Arthritis (RA) patients and compare them to condylar dimensions of healthy persons and try to find out correlations between condylar dimensional changes and jaw movements in RA patients. **Methods:** This case-control study was performed on 40 RA patients with ten healthy adults (control cases). Clinical examination with Cone Beam Computerized Tomography (CBCT) was done for participants. Independent and paired t-tests with correlation coefficient tests were used for data analysis by the SPSS program. **Results:** There was a significant difference between RA and controls regarding the means of their unassisted and assisted maximum mouth opening and the mean of right lateral jaw excursion also. The mean condylar length in RA patients was 6.88 mm while in control cases was 7.61 and the mean condylar width in RA was 16.77 and in controls was 16.53 mm and the mean condylar height was 18.02 mm in RA and 21.14 mm in controls without significance difference between both groups. There was a positive correlation between the condylar dimensions and the jaw movements. **Conclusions:** Condylar height and width were decreased in RA patients incomparison to control group, indicating bony changes in the upper condylar surface. In addition, RA patients have decreased range of jaw movements like mouth opening, which might result from bony changes and reduction in condylar dimensions.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease of unknown etiology, that affects several body joints usually symmetrically and bilaterally, it affects women 2 to 3 times more than men at any age but usually between the fourth and sixth decades of life (Myasoedova et al., 2010). ***[1, 2]***. This disease is characterized by inflammation of the synovial tissue, which lead to the destruction of the cartilage and resorption of bone of the involved joint. destruction of bone of the joint may occur 2 to 3 years after the onset of RA and may progress rapidly after this period and may lead to loss of function. Patients with RA usually have persistent synovitis, joint swelling, and joint tenderness. Clinical manifestations may have episodes of exacerbations and remissions, which lead to loss of function and pain ***[1,3,4,5]***.

The temporomandibular joint (TMJ) is considered one of the most important human body joints, which is responsible for movement of mandible during chewing, swallowing, and speech. TMJ involvement in RA

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We are very pleased to inform you that your paper entitled: **Assessment of dimensions of mandibular condyles and their correlation with jaw movements in rheumatoid arthritis patients** is accepted by Chief Editor of our journal: *Journal of Zankoy Sulaimani-Part A (JZS-A)*, and it will be published in **Vol. 25 (No. 1): 2023**.

Nawroz

Prof. Dr. Nawroz Abdul-razzak Tahir

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حكومة إقليم كردستان العراق

وزارة التعليم العالي والبحث العلمي

جامعة السليمانية

كلية طب الأسنان

مقارنة بين صورة الرنين المغناطيسي (MRI) و التصوير الحاسوبي ذو الحزمة المخروطية (CBCT) لتقييم تغيرات المفصل الفكي عند مرضى ألتهاب المفاصل الرثوي

أطروحة مقدمة الى مجلس كلية طب الاسنان جامعة السليمانية

كجزء من متطلبات نيل شهادة الدكتورا

في أشعة الفم والوجه والفكين

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٢٠٢٣ م **٢٧٢٢ ك** **١٤٤٤ هـ**

الخلاصة

الاهداف: تهدف هذه الأطروحة إلى تحديد نوعية التغيرات الحاصلة للمفصل الفك عند مرضى إلتهاب المفاصل الرثوي و فحص العلاقة بين التغييرات الشعاعية ومدة المرض و المقارنة بين الكفاءة التشخيصية بين صورة الرنين المغناطيسي و التصوير الحاسوبي ذو الحزمة المخروطية لتحديد التغييرات الحاصلة لمفصل الفك، وإيجاد العلاقة بين الفحوصات الدموية والأعراض السريرية للمفصل الفكي، وإيجاد العلاقة بين التغييرات في أبعاد المفصل الفكي وحركة المفصل لدى مرضى الروماتيزمي.

المرضى والطرائق: هذه الأطروحة للحالة-مراقبة تم أجراوءها على (٤٠) مريض من حالات ألتهاب المفاصل الرثوى مقسمة الى مجموعتين حسب مدة المرض، في نفس الوقت تم أدخال (١٠) أشخاص صحيين لغرض المقارنة. تم أجراء الفحص السريري و أخذ الصورالشعاعية (CBCT) و (MRI) مع فحص المختبري للمشتركيين في هذه الأطروحة.

النتائج: تكرار الأعراض السريرية للمفصل الفكي لدى مرضى ألتهاب المفاصل الرثوي كانت (١٥% عند المجموعة آ) و(٤٠% عند المجموعة ب)، و تكرر التغييرات المفصل الفك باستخدام (CBCT) كانت (٧٥%عند المجموعة آ و٩٠% عند المجموعة ب) و باستخدام (MRI) كانت ٨٠% عند المجموعة آ و٩٥% عند المجموعة ب) لمرضى ألتهاب المفاصل الرثوي (RA) و ١٠٪ و٣٠٪ على التوالي للحالات الصحية الطبيعية. أكثر الاعراض السريرية الملاحظة كانت ألام الوجه بسنبة ٢٥٪ و أقل الأمراض السريرية كانت النقر المفصلي عند فتح الفم بنسبة ٢,٥٪.

لم يوجد فرق ملحوض في (طول، سمك وعرض) لقمة (عظمة) الكوندايل بين مرضى الروماتيزمي والحالات الصحية.

أكثر التغييرات الحاصلة لمرضى ألتهاب المفاصل الرثوي المشخصة بأشعة (CBCT) كانت تآكل رأس عضمة الكوندايل بنسبة ٦٧,٥٪ وكانت أقل التغييرات الحاصلة هي تآكل عضمة أرتفاعي المفصل بنسبة ٧,٥٪، لكن في مجموعة الحالات الصحية كانت عبارة عن تسطيح رأس عضمة الكوندايل بنسبة ٥٠٪.

أكثر التغييرات الحاصلة لمرضى ألتهاب المفاصل الرثوي المشخصة بأشعة (MRI) كانت عبارة عن تغيير في رأس عضمة الكوندايل بنسبة ٨٠٪ و أقل التغييرات الحاصلة كانت تدفق المفصلي بتسبة ١٠٪، لكن في الحالات الصحية كانت تغيير في رأس عضمة الكوندايل بنسبة ٣٠٪ وتسطيح رأس عضمة الكوندايل بنسبة ١٠٪.

ويبين النتائج بأن هناك علاقة ايجابية بين نتائج الفحوصات (Anti-CCP, RF, ESR) وتغييرات عضمة المفصل الفكي، وكانت هناك علاقة ايجابية بين نتائج الفحوصات الدموية ومعظم الأعراض السريرية للمفصل الفكي لدى مرضى ألتهاب المفاصل الرثوي ، وأيضآ هناك علاقة ايجابية بين أبعاد المفصل الفكي (طول، سمك وعرض) وحركة المفصل العمودي والافقي.

ألاستنتاجات: التغيير في عضمة مفصل الفك لمرضى ألتهاب المفاصل الرثوي يحدث مع عدم/قليل من الشكوى. يمكن اعتماد صورة (MRI) كطريقة جيدة لتشخيص تغييرات المفصل الفكي، المدة الزمنية لمرض الروماتيزم له تآثيرعلى زيادة عدد الأعراض السريرية لمفصل الفك ، الارتفاع نسبة (Anti-CCP, RF, ESR) قد يدل على وجود أعراض سريرية و حدوث تغييرات في عظمة المفصل الفكي لدى مرضى ألتهاب المفاصل الرثوي و النتيجة الايجابية لفحص (Anti-CCP) يدل على تقليص أبعاد عضمة المفصل الفكي، مرضى ألتهاب المفاصل الرثوي عندهم تقليص في مدى حركة الفك.

حکومەتی هەرێمی کوردستان

وەزارەتی خوێندنی باڵا و توێژینەوەی زانستی

زانکۆی سلێمانی

کۆلێجی پزیشکی ددان

بەراووردکاری لە نێوان وێنەی لەرینەوەی موگناتیسی (MRI) و تیشکەوێنەی تۆموگرافی کومپیوتەری (CBCT)لەمەڕ هەڵسەنگاندنی گۆڕانکاری جومگەی شەویلگە لەنێوان نەخۆشانی جومگەسۆی ڕۆماتۆیدی

تیزێکە پێشکەشە بە ئەنجوومەنی کۆلێژی پزیشکی ددان- زانکۆی سلێمانی

وەک بەشێک لە جێبەجێکردنی پێویستیەکانی وەرگرتنی

پرۆگرامەی دکتۆرا

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٢٠٢٣ زایینی **٢٧٢٢ کوردی** **١٤٤٤ کۆچی**

پوختە

مەبەستەکان: ئەم لێکۆڵینەوەیە بەمەبەستی بڕیاردان لەسەر ڕوودان و شێوەی گۆڕانکاری جومگەی شەویلگەی نەخۆشانی جومگەسۆی ڕۆماتۆیدی (RA)هەروەها بەمەبەستی پشکنینی گۆڕانکاریی تیشکەوێنەی ئەو نەخۆشانە و بەراوردکردنیان لەگەڵ بڕی توانای دەستنیشانکردنیان بەهۆی تیشکەوێنەی تۆموگرافی کۆمپیوتەری (CBCT) و تەکنیکی وێنەی لەرینەوەی موگناتیسی (MRI) بەمەبەستی دۆزینەوەی گۆڕانکارییەکانی جومگەی شەویلگە،وەدۆزینەوە ی پەیوەندی نێوان پشکنینی خوێن و سکاڵا کلینیکیەکانی جومگەی شەویلگە، وەدۆزینەوە ی پەیوەندی لە نێوان قەبارە و جوڵە لە جومگەی شەویلگەدا لە نەخۆشەکانی جومگەسۆی ڕۆماتۆیدی.

نەخۆشەکان و ڕێگەکان: ئەم حاڵەت-کۆنترۆلە لێکۆڵینەوەیە ئەنجامدراوە لەسەر (٤٠) نەخۆشی جومگەسۆی ڕۆماتۆیدی (RA)، دابەشکراون بەسەر دوو گروپدا بەپێی ماوەی نەخۆشیەکە. لەهەمان کاتدا (١٠) لاوی پێگەیشتووی تەندروست وەك حاڵەتی کۆنترۆل بەکارهێنراوون. پشکنینی کلینیکی و تیشکی (CBCT)و (MRI)و هەروەها پشکنینی تاقیگەیی ئەنجامدراوە بۆ بەشداربووان لە لێکۆڵینەوەکەدا.

ئەنجامەکان دەریانخست کە دووبارەبوونەوەی تێوەگلانی جومگەی شەویلگە لە نەخۆشانی (RA)بەپێی سکاڵا کلینیکیەکان بریتی بووە (١٥٪ لە گروپی ا و ٤٠٪ لە گروپی ب)، ئەنجامی دووبارەبوونەوەی تێوەگلانی جومگەی شەویلگە بەکارهێنانی تەکنیکی (CBCT) بریتی بووە (٧٥٪ لە گروپی ا و ٩٠٪ لە گروپی ب) وە بەکارهێنانی تەکنیکی (MRI)بریتی بووە (٨٠٪ لە گروپی ا و ٩٥٪ لە گروپی ب) لە نەخۆشانی ڕۆماتۆید (RA)، هەروەها ١٠٪ و ٣٠٪ یەك بەدوای یەکدا ، لەحاڵەتی کۆنترۆڵەکاندا. زۆرێك لە سکاڵا کلینیکیەکان کە بینراون بریتیبوون لە ئازاری ڕوو (دەموچاو) بوو بەڕێژەی (٢٥٪) هەروەها سکاڵایەکی کەم کە بریتیی بوو لە قرتوقرتی جومگە (٢,٥٪) لەکاتی دەمکردنەوەدا.

هیچ جیاوازییەکی بەرچاو بەدینەکراوە لە: درێژی، ئەستووریی وبەرزیی کۆندایڵدا لە هەردوو نەخۆشانی (RA)و کۆنترۆڵدا.

گۆڕانکاری بڵاو لە نەخۆشانی (RA)بە (CBCT) بریتیی بوو لە داخورانی سەری کۆندایڵ (٦٧,٥٪) هەروەها گۆڕانکاریی کەمتر بەدیکراوە لە داخورانی بەرزایی ئێسکی جومگەکە (٧,٥٪) ، بەڵام لەگروپی کۆنترۆڵدا بریتیی بوو لە پانبوونەوەی سەری کۆندایڵ (٥٠٪) . زۆرترین گۆڕانکاریی نەخۆشانی (RA) لە وێنەی (MRI)دا بریتیی بوو لە گۆڕانکاریی لە ئێسکی سەری کۆندایڵ (٨٠٪) هەروەها گۆڕانکارییەکی کەم جووڵەی کۆندایڵدا بە بڕی (١٠٪)،بەڵام ڕێژەی گۆڕانکاریی لە ئێسکی سەری کۆندایڵ لە کۆنترۆڵدا بریتیی بوو لە (٣٠٪) و پانبوونەوەی سەری کۆندایڵ بە ڕێژەی (١٠٪) .

بەراووردکارییەکی یان پەیوەندیدارییەکی بەراوردکاریی ئەرێنی بەدیکرا لەنێوان (Anti-CCP, RF, ESR) و گۆڕانکاریی لە ئێسکی جومگەی شەویلگەدا، هەروەها پەیوەندیدارییەکی ئەرێنی بەدیکرا لەنێوان پشکنینی خوێن و سکانّا کلینیکییەکانی جومگەی شەویلگە، پەیوەندیدارییەکی بەراووردکاری نەرێنی نیشاندراوە لەنێوان پێوانەکانی کۆندایڵ وجووڵەکانی شەویلگەدا.

دەرئەنجام: گۆڕانکاری لەئێسکی شەویلگە (TMJ)ڕوودەدات لەنەخۆشانی جومگەسۆی ڕۆماتۆیدی (RA) بە بڕی هیچ/کەمێك لە سکانّا. وێنەی (MRI) ئەتوانرێت پشتی پێ ببەسترێت وەك ئامرازێك بۆ دەستنیشانکردنی گۆڕانکاریی لە جومگەی شەویلگەدا. درێژخایەنی جومگەسۆی ڕۆماتۆیدی کاریگەر ی هەیە لەسەر تێوەگلانی کلینیکی جومگەی شەویلگە، هەروەها بەرزی ڕێژەی (Anti-CCP, RF, ESR) لەوانەیە ئاماژەبێت بە بوونی سکانّا کلینیکییەکان وگۆڕانکاریی لەئێسکی شەویلگەدا لەنەخۆشانی جومگەسۆی ڕۆماتۆیدی (RA)، هەروەها پشکنینی ئەرێنی لە (Anti-CCP) وەك بۆچوونێك لەکەمبوونەوەی پێوانەکانی (قەبارە و بەرزی و درێژی) کۆندایڵدا، وە کەمبوونەوەی جووڵەی شەویلگە لەنەخۆشانی جومگەسۆی ڕۆماتۆیدی.