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Efficacy of arthrocentesis with injection of hyaluronic acid in the treatment of inflammatory-degenerative disease of temporomandibular joint

A Project submitted to the Scientific Committee of the Department of Oral and Maxillofacial Surgery, College of Dentistry / University of Baghdad , in partial fulfilment of requirements for the BDS degree

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يرفع الله الذين آمنوا منكم والذين أوتوا العلم درجات

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Declaration

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Dedication

We dedicate this research to all our professors at Baghdad College of Dentistry in recognition of their great efforts.
Also we dedicate it to our families for their unlimited support throughout all these years and to all ourdear friends and colleagues ...
Finally, our appreciations and thanks to everyone taught us a letter from our childhood until today.

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List of Abbreviation

Abbreviation	Full text
DDwR	Disc derrangement with reduction
DDwoR	Disc derrangement without reduction
HA	Hyaluronic Acid
ID	Internal Derrangement
kDA	kilodalton
LLLT	Low Level Laser Therapy
MMO	Maximal mouth opening
OA	Osteoarthritis
SH	Sodium Hyaluronate
TENS	Transcutaneous electrical nerve stimulation
TMD	Temporomandibular Disease
TMJ	Temporomandibular Joint

Introduction

The temporomandibular joint (TMJ) is classified as a synovial joint, condylar, ellipsoid or bicondylar, and presents two main axes of movement, making it one of the most complex joints in the body **(Vasconcellos *et al.*, 2007)**. Temporomandibular joint disorders (TMDs) are one of the most misdiagnosed and mistreated maladies in the medical practice. TMDs are not life threatening but they may strongly affect the quality of life **(Malik, 2002)**. Internal derangement of the temporomandibular joint (TMJ ID) is one of the most frequent cause of TMD. TMJ ID is defined as a progressive disorder which usually starts as clicking associated with normal opening (anterior disc displacement with reduction), to a stage where clicking gradually ceases but restricted mouth opening ensues (closed lock) **(Nitzan, 1991)**. Different conservative and surgical treatments have been studied to restore stomatognathic function and improve clinical symptoms **(Kopp *et al.*,1985) .** Conservative treatments include behavioral therapy, administration of non-steroidal anti-inflammatory drugs and corticosteroids, bite splints, botulinum toxin injections, and physical therapy **(Morey-Mas *et al.*, 2010 ; Kopp *et al.*,1987)** .

Temporomandibular joint arthrocentesis is a minimally invasive treatment option for painful or degenerative TMJ internal derangements that enable the removal of synovial fluid and inflammatory mediators by means of irrigating the upper joint space and lysis of adhesions, resulting in diminished pain and improved jaw function **(Hegab, 2015; Liu, 2013).** HA is a glycosaminoglycan polysaccharide that is naturally found in cartilages and in the synovial fluid **(Hepguler *et al.*, 2002).** Hyaluronic acid (HA) is a fundamental component for normal joints, lubrication effect, so exogenous viscosupplementation was hypothesized to have a positive effect on temporomandibular joint (TMJ) disorders. Some early studies supported the efficacy of HA injections to treat TMJ internal derangements, but more recent evidence suggested that it may be effective in inflammatory-degenerative disorders as well, especially if combined with a thorough joint lavage **(Nitzan, 2001; Manfredini *et al.*, 2012).**

Chapter One
Review of Literatures

Review of Literatures

1.1 History

Arthrocentesis is traditionally defined as procedure in which the fluid in the joint cavity is aspirated in the needle and therapeutic substance is injected **(Abantagelo *et al*., 1995).** However, Arthrocentesis of the TMJ was first described by Nitzan et al. in 1991 involves irrigation of the upper joint space and manipulation of the joint, which releases the adhesions and so improves function. **(Nitzan *et al.,* 1991)**. The first study that can be referred to regarding HA dates from 1880: the French scientist Portes observed that mucin from vitreous body was different from other mucoids in cornea and cartilage and called it "hyalomucine" **(Boeriu, 2013)**. Nevertheless, only in 1934, Meyer and Palmer isolated from bovine vitreous humor a new polysaccharide containing an amino sugar and a uronic acid and named it HA, from "hyaloid" (vitreous) and "uronic acid" **(Meyer, 1934).**

During the 1930s and 1950s, HA was isolated also from human umbilical cord, rooster comb and streptococci **(Kandall, 1937)**. However , The first pharmaceutical-grade HA was produced in 1979 by Balazs, who developed an efficient method to extract and purify the polymer from rooster combs and human umbilical cords . Since the early 1980s, HA has been widely investigated as a raw material to develop intraocular lenses for implantation **(Balazs, 1979)**. HA intra-articular injection showed good effects in experimental models of osteoarthritis in animals **(Abatangelo, 1989; Shi, 2000)**. HA has been used for treating human osteoarthritis of knee and hip joints **(Peyron ,1974)**. Short term and long term effects of intra-articular injection of HA into the TMJ were first reported by Kopp in 1979 **(Kopp ,1979).** Since then several studies applying HA alone or in combination with other remedies for patients with TMD have been conducted and the results published **(Alpaslan, 2000; Hepguler, 2002; Kopp, 1985; Shi, 2002)**. During the 1990s and 2000s, particular attention was paid to identifying and characterizing the enzymes involved in HA metabolism, as well as developing bacterial fermentation techniques to produce HA with controlled size and polydispersity .

Nowadays, HA represents a key molecule in a variety of medical, pharmaceutical, nutritional and cosmetic applications. For this reason, HA is still widely studied to elucidate its biosynthetic pathways and molecular biology, to optimize its biotechnological production, to synthesize derivatives with improved properties and to optimize and implement its therapeutic and aesthetic uses **(Boeriu, 2013)** .

1.2 Temporomandibular Joint

The TMJ is one of the most complex joints in the body, presenting unique features that afford a great adaptive and reparative capacity **(Iturriaga *et al.*, 2017).** However, It is a synovial joint, condylar, ellipsoid or bicondylar, having a fibrous avascular disc **(Vasconcellos *et al.*, 2007)**.

First, it is not just a simple articulation between two bones, the mandibular condyle and the temporal bone; rather, there is an articular disc interposed between these two bones that divides the joint into two separate joint spaces allowing for complex movement. Second, the single bone of the mandible articulates bilaterally with the base of the skull, the two temporal bones, through both a right and a left TMJ. Lastly, the mandible also articulates with the maxilla through occlusion of the maxillary and mandibular teeth **(Auvenshine, 2018).**

1.2.1 Bones of Temporomandibular Joint

- **The Mandible** :

The mandible is a U-shaped bone that supports the lower teeth and makes up the lower facial skeleton. It has no bony attachments to the skull. It is suspended below the maxilla by muscles, ligaments, and other soft tissues, which therefore provide the mobility necessary to function with the maxilla. The body of the mandible extends posteroinferiorly to form the mandibular angle and posterosuperiorly to form the ascending ramus. The ascending ramus of the mandible is formed by a vertical plate of bone that extends upward as two processes; the anterior of these is the coronoid process, the posterior is the condyle **(Jeffrey, 2020).**

Condylar Process :

The condyle is the portion of the mandible that articulates with the cranium, around which movement occurs. From the anterior view, it has a medial and a lateral projection called poles .The actual articulating surface of the condyle extends both anteriorly and posteriorly to the most superior aspect of the condyle. The posterior articulating surface is greater than the anterior surface. The articulating surface of the condyle is quite convex anteroposteriorly and only slightly convex mediolaterally **(Jeffrey, 2020)**. The adult condyle is elliptical in shape the long axis being angled backwards at between 15° to 33° to the frontal plane. The long axis of each condyle is approximately at right angles to the body of mandible and, if projected medially would meet that of the opposite side at an angle somewhere near the anterior edge of foramen magnum Condyle has a lateral tubercle and a medial tubercle. The tubercles provide attachments to the lateral and medial collateral ligaments. A thick layer of fibroblastic tissue containing fibroblasts and a variable number of chondrocytes cover the articular surface of the condyle. The components of the condylar covering vary with age and with the region of the condyle. The fibrous layer covering the posterior aspect of the adult condyle is very thin and applied directly to the underlying bone. But over the convexity, it becomes thicker with an intervening layer of fibrocartilage. The condyle is vascular at birth and vessels anastomose over the articular surface, but these disappear by the age of 3 years **(Balaji, 2007)** .

- **The temporal bone** :

The articular surface of the temporal bone consists, posteriorly, of the concavity of the glenoid fossa and, anteriorly, of the convexity of the articular eminence; it extends from the anterior margin of the squamo-tympanic fissure to the margin of the articular eminence. The roof of this fossa is very thin, indicating that this part is not a load-bearing area. Anteriorly, however, the articular eminence is thicker and this area, together with the disc, may be the area that bears most of the load during function **(Gray and Al-Ani, 2021)**.

Temporal bone contents :

- Articular Eminence :

The articular eminence, which is present anterior to the glenoid fossa consists of a descending slope, a transverse ridge that is a medial extension of the zygomatic tubercle, and an ascending slope.

The eminence is covered by dense, compact, fibrous tissue that consists primarily of collagen with a few fine elastic fibres. The fibrous covering is thickest at the descending slope of the eminence, Underlying the fibrous tissue covering is chondroid bone and then compact bone. Unlike the glenoid fossa, the articular eminence is subjected to loading during function **(Balaji, 2007)** .

- Glenoid Fossa :

It has an anterior articular area formed by the inferior aspect of temporal squama. Its surface is smooth, oval and deeply hollowed out and the bone is very thin at the depth of the fossa. This roof of the glenoid fossa creates a partition between the middle cranial fossa and the joint. The fossa is lined by a dense avascular fibrocartilage. In cross section, the fossa and the eminence form a 'lazy S' posteroanteriorly. Squamotympanic fissure separates it from tympanic plate, which forms a posterior wall of the glenoid fossa **(Neelima, 2021).**

- **The joint capsule :**

The joint capsule envelops the articular disc and is attached superiorly to the rim of the glenoid fossa and articular eminence and inferiorly to the neck of the condyle. Posteriorly it is attached to the bilaminar zone and anteriorly becomes continuous with the pterygoid muscle attachment. Although it is thin both anteriorly and posteriorly, it is strengthened laterally by the lateral temporomandibular ligament which is not a discrete ligament but a thickened part of the capsule (**Gray and Al-Ani, 2021)** .

- **Articular Disc :**

The disc or the meniscus that fills the space between the condyle and the temporal bone is semilunar, avascular. non-innervated, and is a fibrocartilaginous structure. It is a shock absorber and acts as the protector of the bony components of the joint. Sagittal section of the disc reveals an anterior fibrous band (anterior disc ligament), thin intermediate zone, and posterior fibrous band (posterior disc ligament) **(Balaji, 2007)** as shown in Figure 1.

The joint is divided by the disc into an upper and lower compartments. The volume of upper compartment is about twice as large as that of the lower compartment. In the lateral and medial areas, the capsule and disc attachement fuse and become attached to the lateral and medial poles of the condyle. Puncture of the upper compartment involves only penetration of both the capsule and disc ligament **(Balaji, 2007).**

Puncture of the lower compartment always involves the slight risk of damaging the lateral disc attachment and consequently displacing the disc medially. The TMJ capsule is almost membrane thin in the anterior parts. This must be considered while distending the joint. Irrigation, if performed with too much performed with too much pressure, may cause rupture of the anterior and medial capsules.

Upper compartment:

The synovial lining is well developed in the posterior part of gleniod fossa. Between the temporal surface and the articular disc is ginglwoid, it permits hinge motion or rotation **(Balaji, 2007)**.

Lower Compartment:

In general, vascularity is less apparent in the lower compartment. Between the condyle and the articular disc is arthriodal, it permits sliding or translator motions **(Balaji, 2007).**

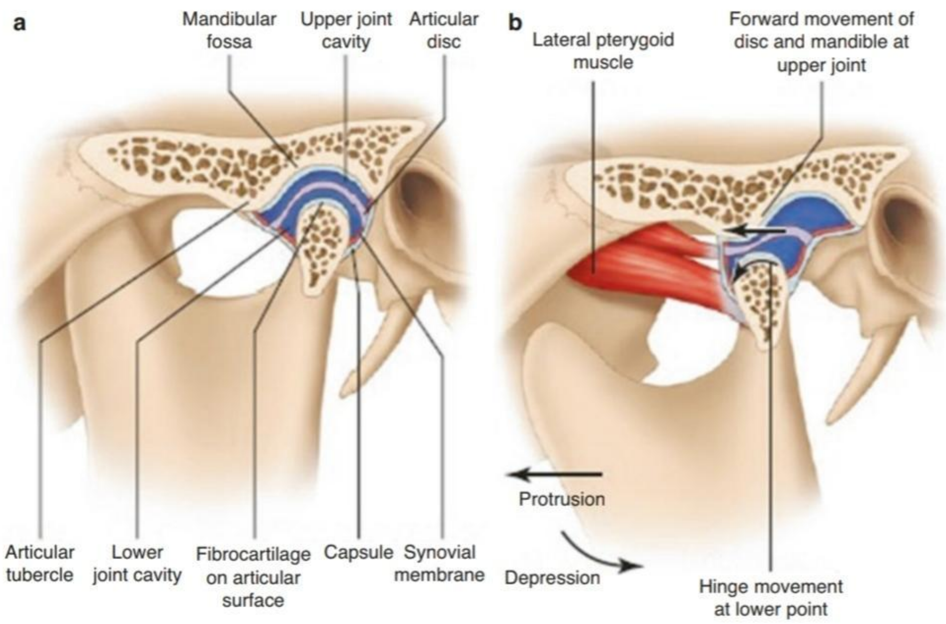

Figure 1 : Anatomy of the temporomandibular joint (a) Illustrated anatomy of the TMJ and (b) the rotational movement which occurs in the lower joint space and the gliding movement which occurs in the upper joint space **(Abdullakutty *et al.*, 2019)**

However, it is a biconcave structure, thick in the anterior and thin in the posterior region. It is attached by the collateral ligaments to the medial and lateral poles of the condyle. The condylar head and the disc move together on translation. The disc splits into two, both anteriorly and posteriorly each aiding in smooth joint function. Medially, it receives attachments from the lateral pterygoid muscle synchronizing the mandibular condyle movements with the disc on function **(Chandra *et al.*, 2010)**.

The most superficial layer of the articular surfaces is called the articular zone. It is found adjacent to the joint cavity and forms the outermost functional surface. Unlike most other synovial joints, this articular layer is made of dense fibrous connective tissue rather than hyaline cartilage. Most of the collagen fibers are arranged in bundles and oriented nearly parallel to the articular surface **(de Bont *et al.*, 1985; 1984)** It is generally less susceptible than hyaline cartilage to the effects of aging and, therefore, is less likely to break down over time. It also has a much better ability to repair than does hyaline cartilage **(Robinson, 2003)**.

The articular cartilage is composed of chondrocytes and intercellular matrix. The second zone is called the proliferative zone and is mainly cellular. It is in this area that undifferentiated mesenchymal tissue is found.

This tissue is responsible for the proliferation of articular cartilage in response to the functional demands placed on the articular surfaces during loading . The third zone is the fibrocartilaginous zone. Here the collagen fibrils are arranged in bundles in a crossing pattern, although some of the collagen is seen in a radial orientation. The fibrocartilage appears to be in a random orientation providing a three-dimensional network that offers resistance against compressive and lateral forces. The fourth and deepest zone is the calcified cartilage zone. This zone is made up of chondrocytes and chondroblasts distributed throughout the articular cartilage. The surface of the extracellular matrix scaffolding provides an active site for remodeling activity as endosteal bone growth proceeds as it does elsewhere in the body **(Ratcliffe *et al.*, 1992)** .

Synovial membrane :

It is a connective tissue membrane, which lines the joint cavities or spaces and secretes synovial fluid for lubrication of the joint **(Neelima, 2021)**. The glistening inner surface of the capsule comprises the synovial membrane.

At birth, this membrane covers all internal joint surfaces but is lost from articular surfaces as function commences. The flexibility of the inner surface of the capsule is increased by finger-like projections (villi) of the synovial membrane which disperse the synovial fluid.

The function of the synovial membrane is considered to be
• regulatory because it controls electrolyte balance and nutrients
• secretory via the interstitial cells
• phagocytic.

Synovial fluid is a clear, pale-yellow, viscous solution secreted by the synovial tissues and consists mainly of an ultrafiltrate of plasma enriched with a proteoglycan-containing hyaluronic acid synthesized by synovial cells. The high viscosity of this fluid is a result of the presence of sodium hyaluronate which provides lubrication. The synovial fluid also allows removal of degradation products from the joint space, lubrication of the joint surfaces, and nutrition of the vascular parts of the joint. However, it lubricates the articular surfaces by way of two mechanisms.

The first is called boundary lubrication, which occurs when the joint is moved and the synovial fluid is forced from one area of the cavity into another. The synovial fluid located in the border or recess areas is forced on the articular surface, thus providing lubrication.

Boundary lubrication prevents friction in the moving joint and is the primary mechanism of joint lubrication.A second lubricating mechanism is called weeping lubrication. This refers to the ability of the articular surfaces to absorb a small amount of synovial fluid **(Shengyi *et al*., 1991) .**

1.2.2 Ligaments of Temporomandibular Joint

- The temporomandibular ligament

The temporomandibular ligament is a strong band of fibrous tissue originating as a thickening of the lateral aspect of the joint capsule. It starts at the root of the zygoma and passes obliquely towards the posterior margin of the neck of the condyle, blending into the joint capsule. In the rest position, this ligament is relaxed, but it is thought that, during retrusive and protrusive movements of the condyle, it limits movement in an anteroposterior direction **(Gray and Al-Ani., 2021)**.

- The stylomandibular ligament :

This is considered as an accessory ligament. It is a specialized band of cervical fibrous tissue extending from the styloid process to the medial border of the mandible at its angle . The function of this ligament is not clear but it is thought to limit anteroposterior movements of the mandible **(Gray and Al-Ani, 2021).**

- The sphenomandibular ligament :

This ligament is also considered to be accessory. It comprises a flat band of fibrous tissue originating from the spine of the sphenoid bone and passes down to its insertion at the inferior margin of the mandibular foramen (lingula) .Again, its function is not certain, but it is thought to limit lateral condylar movements. **(Gray and Al-Ani, 2021).**

1.2.3 Nerve Supply

The mandibular nerve, the third division of the fifth cranial nerve innervates the jaw joint. Three branches from the mandibular nerve send terminals to the joint capsule.

1. The largest is the auriculotemporal nerve, which supplies the posterior, medial and lateral parts of the joint.
2. Masseteric nerve
3. A branch from the posterior deep temporal nerve, supplies the anterior parts of the joint **(Neelima, 2021).**

1.2.4 Muscles of Temporomandibular Joint

Masticatory Muscles Controlling the Mandibular Movement :

- Temporalis muscle arises from the temporal fossa on the lateral aspect of the skull bounded above by the temporal lines and below by the zygomatic arch. It embraces parts of the frontal, parietal and squamous temporal bone and greater wing of the sphenoid bone **(Bhargava *et al.,* 2021).**
- Masseter: Masseter is a quadrilateral muscle located superficial to the ramus of the mandible. It originates from the zygomatic arch. On the basis of origin, the fibers of this muscle are divided into superficial and deep fibers. The most superficial fibers originate from anterior two thirds of the lower border of the zygomatic arch, whereas the deep fibers arise from the posterior one third of its lower border. The anterior fibers of this muscle originate from the zygomatic process of the maxilla. The muscle is inserted into the lateral aspect of the ramus and angle of the mandible **(Bhargava *et al.,* 2021).**

- Lateral Pterygoid muscle is divided into two heads, the upper and lower head. The upper head originates from the infratemporal crest of the greater wing of the sphenoid, runs backward and laterally to get inserted at the pterygoid fovea on anterior surface of mandibular neck.The lower head originates from the lateral surface of the lateral pterygoid plate. A portion of these fibers are also inserted into the intra articular disc and capsule of the TMJ **(Bhargava *et al.,* 2021).**

- Medial Pterygoid: Superficial head arises from the tuberosity of maxilla and adjoining bone, whilst the deep head originates from the medial surface of the lateral pterygoid plate and adjoining process of the palatine bone as shown in Figure 2. The muscle fibres run downward, backward and laterally to get inserted into the roughened surface of the medial aspect of the mandibular angle and adjoining ramus, inferior and posterior to the mandibular foramen and mylohyoid muscle **(Bhargava *et al*., 2021)**

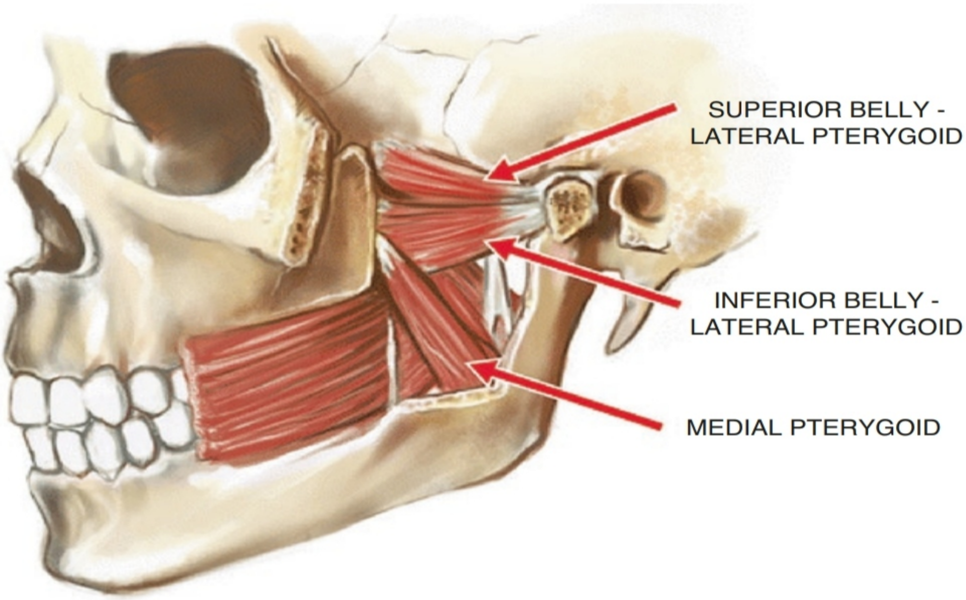

Figure 2 : Lateral and medial pterygoid muscles
(Stockstill *et al.,* 2015)

The movements performed by these muscles are :-
• Elevation: temporalis, masseter, and medial pterygoid.
• Protrusion: lateral and medial pterygoids.
• Depression: lateral pterygoid, infra- and suprahyoid muscles.
• Lateral excursion: contralateral pterygoids and ipsilateral temporalis. **(Bhargava *et al*., 2021).**

The TMJ is a ginglymoarthrodial joint **(Bodnar and Zdilla, 2018)** that allows for rotation and translation in the sagittal plane .
It has four articular surfaces:
• Mandible condyle
• Temporal fossa
• Inferior and superior surfaces of the articular disc, (The superior surface faces the temporal fossa،The inferior surface is in contact with the mandible condyle the articular capsule **(Reboredo, 2021).**

1.3 Maintenance of Jaw Position

The maintenance of jaw position depends on mandible reflexes and the action of gravity. It is also affected by an individual's position / posture and specific variations which allow functional jaw movements to occur **(Reboredo, 2021)**.

When the mandible is at rest, the mouth is slightly open, so that the teeth are not in contact **(Shewman, 2013)**.This resting position is called physiological non-occlusion **(Reboredo, 2021; Miles, 2007).**

• In this position, the lips close the oral cavity without pressure - the teeth remain separated by a distance of around 2 mm - this distance is measured between the superior and inferior incisors **(Reboredo, 2021)**.

• This resting position is maintained by various reflexes as well as active and passive mechanisms **(Ogino, 2021).**

- Passive mechanisms:

Passive tension of the elevators of the mandible and connective tissue.

- Active mechanisms:

1.Peripheral afferents including:
• Muscle and articular proprioceptors
• Periodontal mechanoreceptors and mechanoreceptors of the mucosa (i.e. gums, lips, tongue, palatal area).
2.Central control from the:
• Cortico-visual system
• Limbic system
• Fusimotor-extrapyramidal system **(Reboredo, 2021).**

1.4 Classification of TMJ disorders

Temporomandibular joint disorders which affects approximately 12% of the population. In a recent study, the incidence of TMD symptoms was found to be greater in females and decreased in older age groups, although patients between 18 and 44 years of age were reported to have TMD **(Von Korff *et al.*, 1993).** Some prospective cohort studies have reported that this condition may be explained by differences in behavioral, psychosocial,hormonal, and constitutional aspects **(Aggarwal *et al.*, 2010; Slade *et al.*, 2013)**

<u>Developmental</u>

• Aplasia/hypoplasia of the joint/condyle may be part of hemifacial microsomia.
• Condylar hyperplasia.

<u>Acquired</u>

• Traumatic:
1. soft tissue : internal derangement, capsular tearing, retrodiscal tissue shearing, subluxation, effusion, haemarthrosis;
2. hard tissue : fracture, condylar dislocation, heterotopic ossification.

• Osteoarthritis.
• Inflammatory:
1. seronegative spondyloarthropathies : psoriatic arthritis, ankylosing spondylitis, reactive arthritis
2. other autoimmune disorders : rheumatoid arthritis, juvenile idiopathic arthritis

• Infectious:
1. haematogenous spread : most common cause of septic TMJ arthritis
2. local spread : mandibular osteomyelitis, otitis media, parotitis

• direct inoculation : open joint trauma.
• Metabolic: gout, pseudogout.
• Neoplastic/metaplastic:
1. benign : osteochondroma, chondroblastoma, synovial chondromatosis, pigmented villonodular synovitis
2. malignant : primary, secondary, both extremely rare

• Idiopathic: Idiopathic condylar resorption, and coronoid (0.2%)

Most oral and maxillofacial surgeons who treat TMJ disorders utilize the Wilkes classification system which largely focuses on TMJ internal derangement and osteoarthritis. It is a simple classification that describes five stages of escalating TMJ disease which is why it has gained such widespread acceptance for over 30 years since it was first published. Unfortunately, the Wilkes classification does not include other TMJ disorders such as tumors, trauma, and ankylosis which are, in turn, covered by other sub-classifications **(Wilkes, 1989).**

1.5 Osteoarthritis

Osteoarthritis (OA), classified as a degenerative joint disease, is a low inflammatory arthritic condition, characterised by deterioration and abrasion of articular tissue that becomes soft or frayed or thinned and resulting in eburnation of subcondylar bone or outgrowths of marginal osteophytes due to overload of the remodelling mechanism. OA affecting the TMJ is not uncommon and is seen more in females, above 40 years of age. The common presenting complaints include unilateral joint pain that is aggravated by mandibular movement, and worsening in the late afternoon or evening hours.

When the precise cause of the osteoarthritis can be identified such as trauma, hypermobility, or internal derangement and is seen in older population, the condition is referred to as secondary osteoarthritis. When the cause of the arthritic condition is idiopathic or associated with wear and tear and is seen in younger population, it is referred to as primary osteoarthritis **(Einstein *et al.*, 2021).**

1.6 Internal derangement

1.6.1 Definition:

Internal derangement of the temporomandibular joint (TMJ) is one of the most common forms of temporomandibular disorders **(Nitzan *et al.*, 1991)** It may be defined as a disruption within the internal aspects of the TMJ, in which there is a displacement of the disk from its normal functional relationship with the mandibular condyle and the articular portion of the temporal bone which exists between the disc and the condyle, fossa and articular eminence **(Lee *et al.*, 2009)** .In the initial stages of internal derangement, the shape of the disc would be normal. In the late stages of internal derangement, the articular disc may tear or show perforation **(Bhargava *et al.*, 2015)**. This disorder results in abnormal positioning of the articular disc, resulting in mechanical interference and restriction of the normal range of mandibular activity **(Sato *et al.*, 1997)** .

ID is a common form of TMJ disorder (TMD), The incidence of TMJ ID is very high in women between the second and fifth decade of life (18-45 years). Women in this age group also have a high incidence of TMJ clicking and tenderness. The female to male ratio in the population is between 3:1 to 10:1, with a high predisposition for women of reproductive age **(Byun *et al.*, 2005).**

1.6.2 Pathogenesis of internal derangement of temporomandibular joint

The displaced disc can degenerate, become misshaped, perforated, or even torn. If the patient cannot achieve proper treatment, ID gets progressively worse with time, inflammation accompanied, and osteoarthritic changes (abrasion of articular cartilage and underlying bone, flattening of articular surfaces, less pronounced articular eminence, osteophyte formation, subchondral cyst, and resorption of the condyle) occur **(Schiffman *et. al,* 2014)**. Several inflammatory mediators (such as tumor necrosis factor-α, interleukin 1-β, prostaglandin E2, etc.) play crucial roles in the pathogenesis of ID **(Ernberg ,2017)**.

Another relevant issue in TMDs is the high prevalence in females, with a peak incidence in young adults. The low prevalence of TMD in childhood and in the postmenopausal period suggests the participation of sex hormones, such as estrogen, in the pathophysiology of this disorder (**Ribeiro *et al.*, 2017)**.

The challenge for clinicians is to diagnose the accurate condition that causes the ID. Once identified, the basis for the treatment is to relieve the patient's symptoms and to improve healing while simultaneously removing the causal factors. The following causal factors or diseases may lead to ID and should be addressed carefully: the excessive loading of the joint, and systemic and localized arthropathies may cause ID of TMJ **(Israel, 2016)**.

1-Excessive loading

Joint overload is the most common cause of ID. The joint overload (often caused by stress-mediated parafunction, acute or chronic trauma, unstable occlusion, and increased joint friction) deteriorates cartilage metabolism. This pathologic process causes the fibrillation of cartilage and ultimately leads to biomechanical failure impairing the sliding of the articular surfaces. Clinically, joint noise (clicking) is detected in this stage.

The individuals who have persistent parafunction continue to overload articular structures beyond their adaptive capacity leading to pain, synovitis, intra-articular adhesions, osteoarthritis, and disc perforation , Thus, the key principles in the management of ID caused by joint overloading are the reduction of joint loading and inflammation, maximizing joint mobility, and relieving pain. If the patients with ID have the signs of joint overload and if all other causal factors are ruled out, these patients should be managed by an intense 2–3 week regimen of conservative therapies. If the symptoms begin to resolve, then conservative treatment should be continued. However, if the symptoms persist, minimally invasive surgical interventions should be considered. The advanced stages of ID leading to fibrosis, disc deformation or perforation, and TMJ ankylosis require arthrotomy **(Israel, 2016)**.

. 2-Systemic arthropathy

A number of systemic and rheumatoid disorders play a role of causal factor and can contribute to inflammatory/degenerative arthropathy and ID. Since systemic disorders affect the structure and function of articular tissues, TMJ of the patients with systemic arthropathy may fail under normal joint loads. Thus, clinicians should be aware of this issue when considering patient management. The examples of systemic disorders, which can cause ID, include rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, pseudogout, ankylosing spondylitis, polymyalgia rheumatica, chondrocalcinosis, Ehler-Danlos syndrome, Lyme disease, lupus erythematosus, and other connective tissue disorders For these patients, management of systemic disorders is essential for the treatment of TMJ ID and requires coordination between a maxillofacial surgeon and a rheumatologist. Conservative therapies and arthrocentesis or arthroscopy can relieve symptoms. Moreover, arthroscopic biopsy led to the diagnosis **(Kalaykova *et al.*, 2017)**.

3- Localized arthropathy

This term describes an articular disorder that is atypical and not caused by joint overloading or systemic disease. A localized atypical arthropathy usually affects one joint only. The clinical signs and symptoms are nonspecific and include joint pain, noise, limited function, and changes in the occlusion. The imaging techniques and arthroscopic biopsy show unusual findings (multiple loose calcifications or synovial effusions) and confirm the diagnosis. The localized arthropathy of TMJ can be summarized as follows: osteochondroma, synovial chondromatosis, crystal deposition disease, and synovial cyst.

The localized arthropathies may cause or mimic TMJ ID. The secondary inflammatory component from neighboring regions (otitis, tonsillitis, and maxillary sinusitis) can affect TMJ and cause ID The correct diagnosis is crucial in these kinds of disorders and treatment usually includes arthroscopy or arthrotomy **(Araz *et al*.,2017)**

Two major components responsible for free joint movement are:

1. Surface active phospholipid: is a major boundary lubricant protecting the articular surfaces.
2. Hyaluronic acid: is a high molecular weight mucopolysaccharide which forms a film that keeps the articular surfaces separated and prevents friction.

not be performed in all the patients diagnosed with TMDs and has definitive indications for a favourable outcome. Disc derangement is associated with an increased intra-articular friction which prevents smooth gliding of the joint resulting in progressive dilapidation of the joint tissues **(Milaro *et al*., 2004)** The pathophysiology of such a dilapidation process is summarized in Figure 3.

In a prolonged period of overload, the tinny film of the synovial fluid that prevents a direct contact between the joint surfaces does not work, leaving only the boundary lubrication mechanism to protect the joint components. However, overload also acts on the composition of synovial fluid through oxidative stress. According to this mechanism, the increased production of reactive oxygen species, both through hypoxia-reperfusion mechanisms and the presence of inflammatory cytokines, lead to oxidative stress due to a disturbance in the balance between the production of reactive oxygen species and the antioxidant defense **(Valachova *et al.,* 2021)**. The oxidative stress can act in different ways on joint tissues, such as damaging different molecules of the articular cartilage, modulating pro-inflammatory cytokines, and degrading synovial fluid HA **(Kuroda *et al.,* 2009; Tanaka *et al*., 2010)**. In addition to promoting the degradation of high-molecular-weight HA in the synovial fluid, oxidative stress also inhibits HA synthesis by synoviocytes, affecting the viscoelastic property of the synovial fluid. Figure 3 illustrates this whole process.

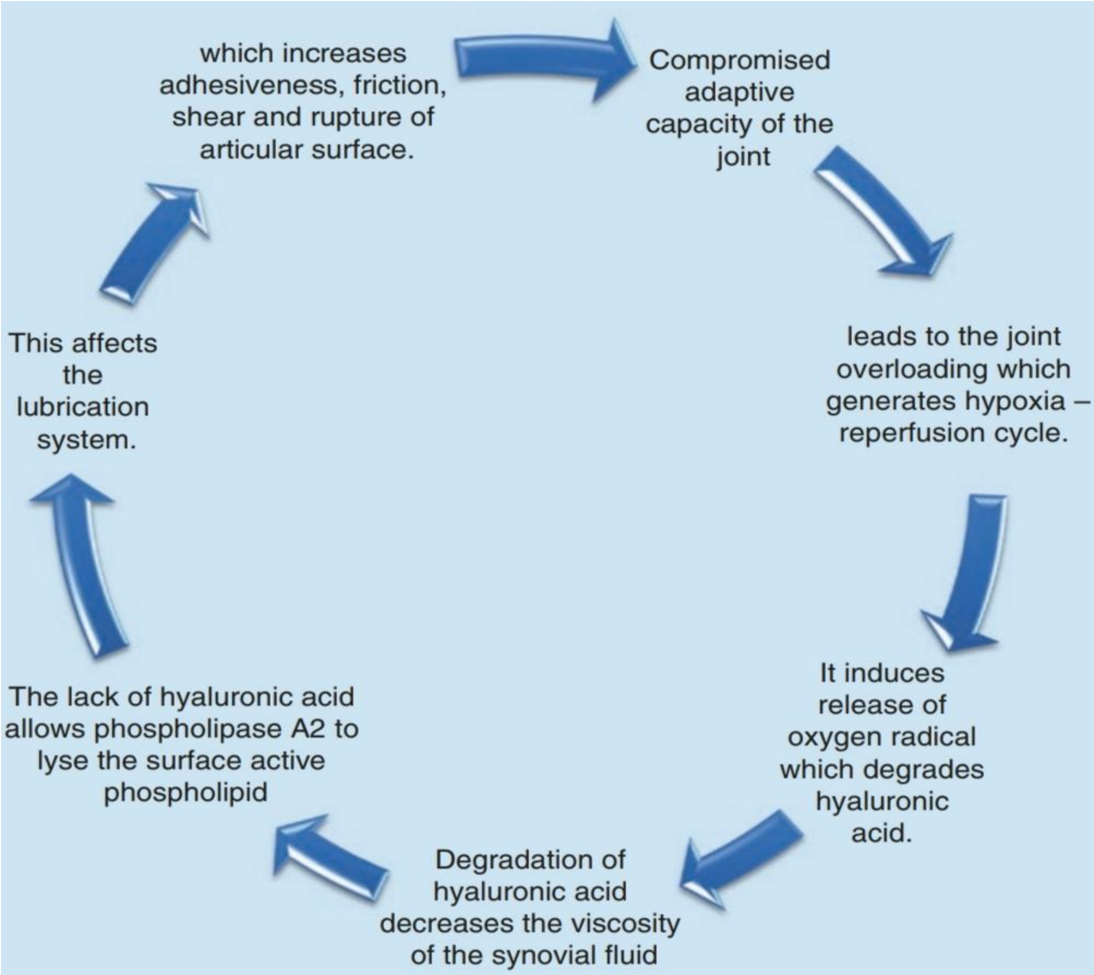

Figure 3 : Pathophysiology of degenerative progression in a TMJ disorder (**Gonzále., 2015**)

1.6.3 Classification of Internal derangement

ID is classified according the Wilkes system **(Wilkes, 1989)** :
Stage I Early reducing disc displacement
Stage II Late reducing disc displacement
Stage III Nonreducing disc displacement-acute/subacute
Stage IV Nonreducing disc displacement-chronic
Stage V Nonreducing disc displacement-chronic with osteoarthrosis

Surgery for ID stages I-IV (and mild stage V), except for those cases requiring major joint reconstruction, in which a perforated or partially degenerated disk has enough diskal and retrodiscal tissues remaining to perform the bilaminar flap repair or temporalis muscle fascia flap .

1. Disc displacement with reduction

Patients with stage I internal derangement generally have no symptoms except minor joint noise. Joint noise (i.e., clicking) is commonly heard with opening, when the condyle moves from the area posterior to the disk into the thin concave area in the middle of the disk. In some cases, clicking can be heard or palpated during the closing cycle as mentioned in the Figure 4.

2. Disc displacement with reduction with intermittent locking

This condition is identical to disc displacement with reduction, with the additional feature of intermittent limited mandibular opening on the occasions that the disc does not reduce .

3. Disc displacement without reduction with limited opening

This diagnosis is given when the articular disc consistently does not reduce, resulting in limiting opening. Limited opening is defined as <40 mm between maxillary and mandibular incisor incisal edges with opening assisted by the dentist. This maximum assisted opening range must have factored in the vertical incisal overlap at maximum intercuspal position. The percentage of displaced discs that reduce on opening is roughly similar to the percentage that does not reduce.

4. Disc displacement without reduction without limited opening

This condition is identical to the previous condition as in the figure below with the exception that mandibular movement is not limited. However, such limitation must have occurred in the past to the extent that eating was hindered. This condition typically follows the previous condition as mentioned in Figure 5. **(Santos *et al.,* 2013).**

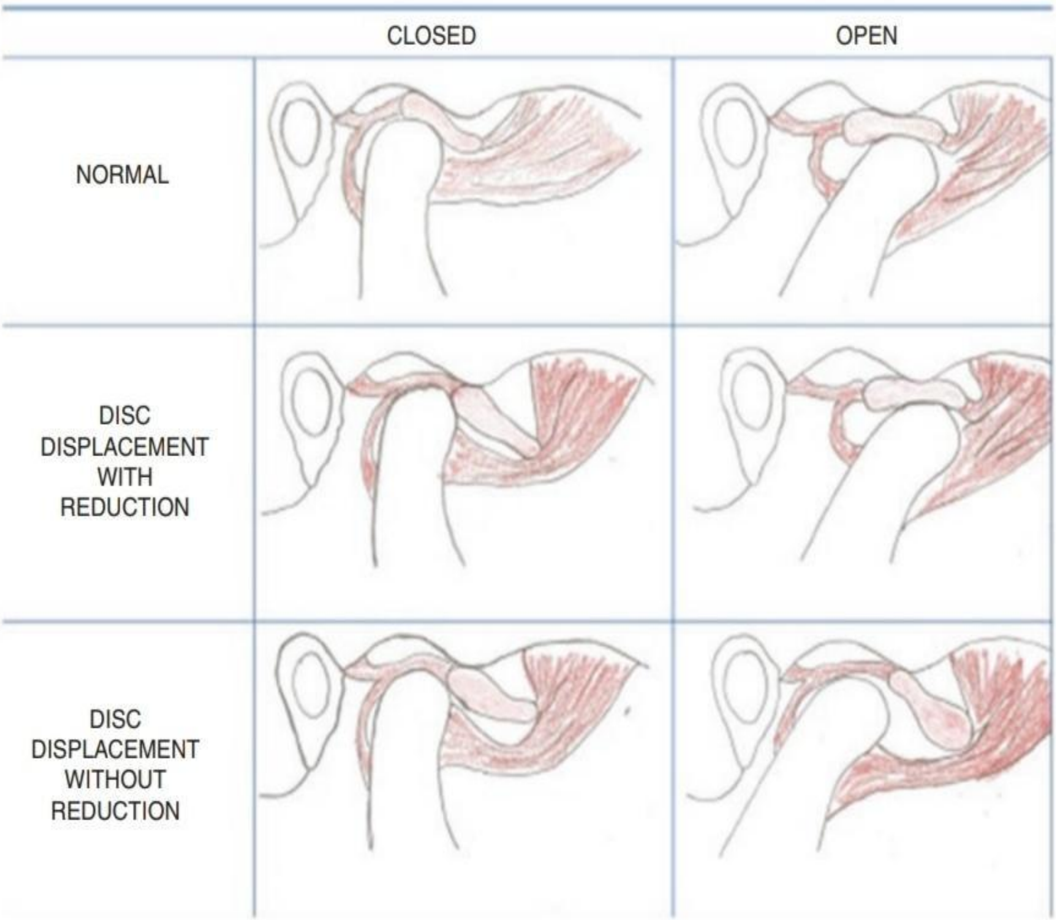

Figure 4: Dynamics during normal joint function and in a deranged joint **(Bhargava *et al.*, 2015)**

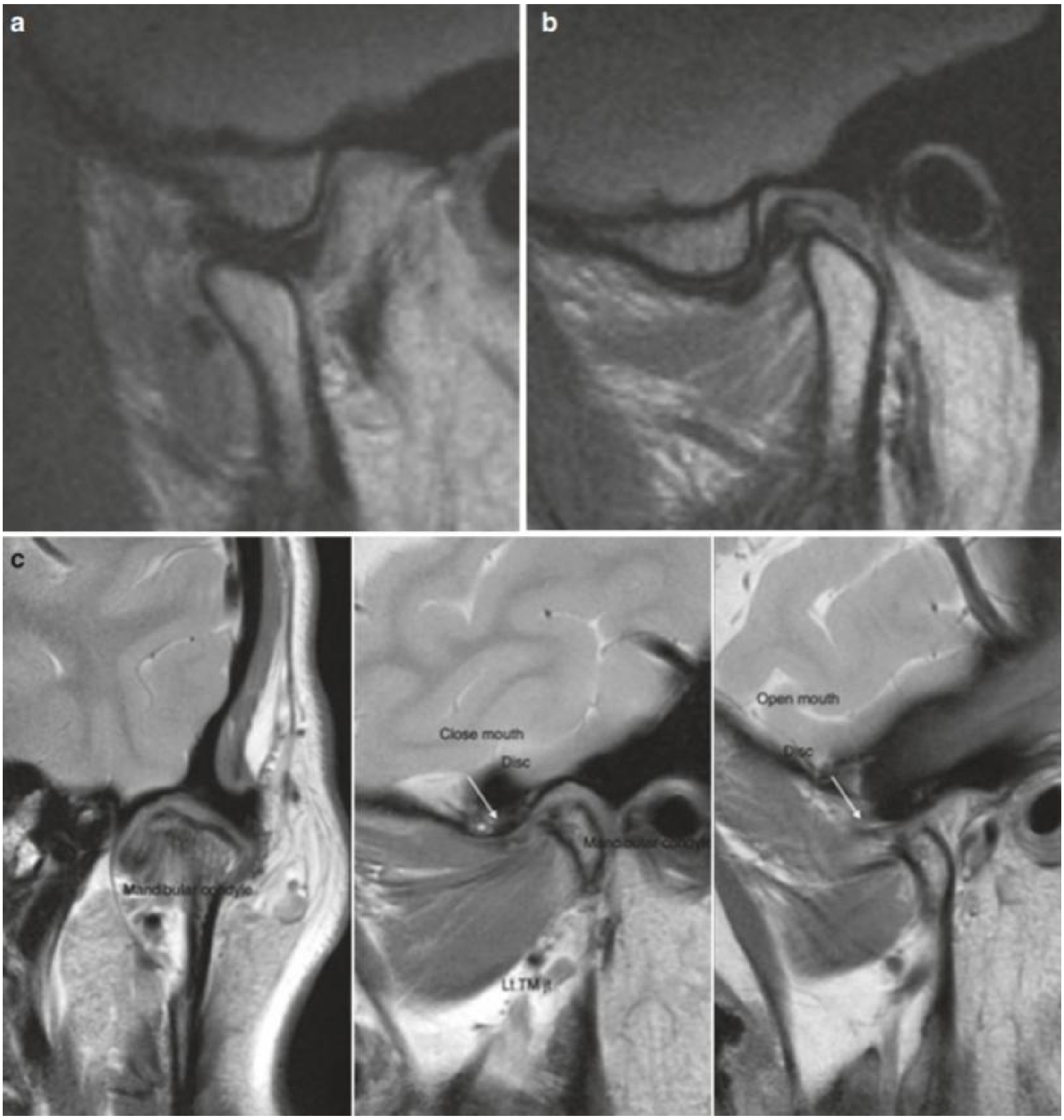

Figure 5: (a, b) MRI of joint with internal derangement. Axially-corrected sagittal T1-weighted MRI of the TMJ in the closed (a) and open (b) mouth position, respectively, exhibits anterior disc displaced with reduction (c) Antero-medial disc location of the left TMJ disc along with osteoarthritic changes.

5. Posterior disc displacement

Because this condition occurs so rarely (0.7–2.2% of patients with internal derangement **(Santos *et al.*, 2013)** little has been written on it. Westesson et al. described three different presentations: (1) A thin disc spans from the superior portion of the condylar head to posterior to the condylar head (2) a centrally-perforated disc is present, with a small portion anterior to the condylar head, and a larger portion posterior to the condylar head, and (3) the entire disc is posterior to the condylar head **(Westesson *et al.*, 1998).**

Of 4000 patients with suspected internal derangement, 84% had the first type, 16% had the second, and none had the third **(Okochi *et al.*, 2008)**

1.6.4 Symptoms and Signs of Internal TMJ Derangement

The term temporomandibular joint internal derangement has characteristic clinical findings such as restricted mouth opening, pain, irregular deviated jaw function, clicking sounds, chronic headache, masticatory muscle tenderness and impaired joint movements.

Disc derangement with reduction (Figure 6) often causes a painless clicking or popping sound when the mouth is opened. Pain may be present, particularly when chewing hard foods. Patients are often embarrassed because they think others can hear noise when they chew. Indeed, although the sound seems louder to the patient, others can sometimes hear it **(Gary, 2009)**

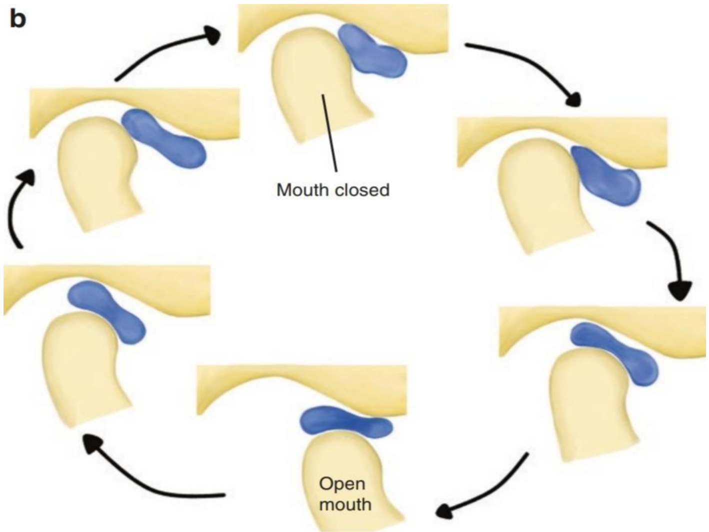

Figure 6: Anterior disc displacement with reduction **(Moturi, 2021)**

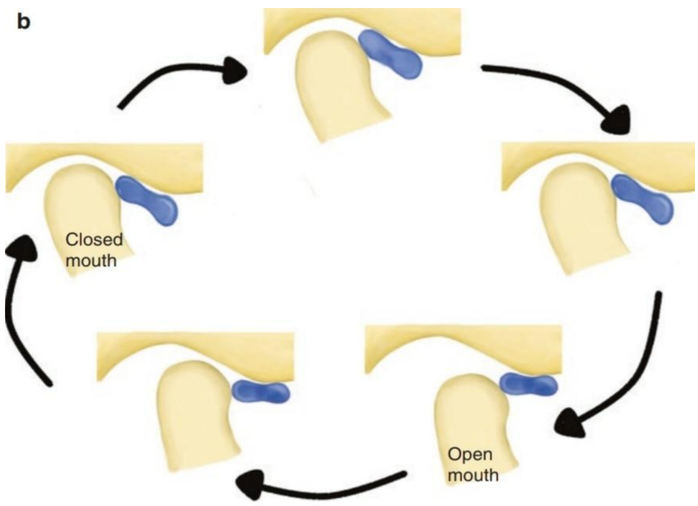

Figure 7: Anterior disc displacement without reduction **(Moturi, 2021)**

Disc derangement without reduction (Figure 7) usually causes no sound, but maximum opening between the upper and lower incisors is reduced. Pain and a change in the patients' perception of their bite generally result. It usually manifests acutely in a patient with a chronically clicking joint; about 8 to 9% of the time, the patient awakens unable to open the jaw fully. In a small percentage of patients, the symptoms of disk derangement without reduction spontaneously resolve after 6 to 12 month **(Gary, 2009) .**

1.6.5 Management of Internal derangement

Management of TMJ internal derangements has always been a therapeutic challenge for maxillofacial surgeons. Approximately 38% of the entire population suffers from TMJ internal derangements **(Guarda *et al.,* 2007).**

The main aim of the treatment involves removal of the causative factors, reduction of symptoms and promote healing of the articular structures. Early stages of ID can be managed by conservative or minimally invasive methods. Advanced stages would require surgical interventions including the open joint surgery. Management of ID of TMJ may be divided into two broad categories:

• Non-surgical
• Surgical

1. **Conservative or Non-surgical Management**

The main objective of the conservative therapy is reduction of joint loading and pain. It is usually the first line of therapeutic management. The conservative management includes a number of different treatment modalities **(Moturi, 2021).**

- **Patient Education**

The essential aspect of a treatment starts with informing the patient regarding the cause, pathogenesis of the disease. Diet modification, awareness of parafunctional habits and the stress reduction protocols should be established by educating the patient **(Moturi, 2021).**

- **Pharmacological Management**

It includes various drugs ranging from analgesics to immune suppressing agents such as corticosteroids , non steroidal anti inflammatory drugs , Muscle relaxants and Anti-anxiety and antidepressants. Ordinarily, management of TMDs require a combination of various group of drugs **(Moturi, 2021)**

- **Thermotherapy**

Thermal stimuli in the form of heat or cold application can be done in ID cases. Heat is frequently used in the form of hot compresses. Application of moist hot fomentation on the symptomatic area for 10–15 min not more than 30 min is beneficial. The primary goal is to increase blood supply through vasodilatation, leading to decreased pain and joint stiffness **(Moturi, 2021).**

- **Physiotherapy**

Physiotherapy is a common therapeutic method indicated in discopathy and hypermobility of TMJ. It helps in improving the strength of articular capsule, along with the improvement in the desired crusade of the masticatory/cervical muscles **(Moturi, 2021).**

- **Intraoral Appliance**

Use of an intraoral orthodontic appliance fnds application in management of many TMJ disorders. Specific malocclusions include the absence of posterior support, loss of vertical dimension of occlusion resulting in mandibular over closure and severe class II division II malocclusions benefit from an appliance therapy. Using an intraoral appliance such as night guard in patients with known clenching/bruxism protects the dentition from wear,decreases the muscle hyperactivity to some degree and alters the joint loading, thereby improving the symptoms **(Moturi, 2021).**

- **Occlusal Splints**

It is a removable appliance with a thickness of 1.5–3 mm commonly made from acrylic resin. The splints can be fabricated for maxilla/mandible and can be partial/complete. It aids in reduction of the intra-articular pressure reducing overload and pain, balancing and deprograming occlusion, thus reducing the muscle spasm **(Moturi, 2021).**

- **Ultrasound Therapy**

It has the same concept of thermotherapy, but is found to be more effective as it acts on deeper tissues and not just the surface. Ultrasound not only increases the blood flow in deep tissues but also seems to separate collagen fibers, which improve the flexibility and extensibility of connective tissues **(Rai *et al.*, 2016).**

- **Trans-cutaneous Electrical Nerve Stimulation (TENS)**

Electric stimulation devices for treatment of TMD are claimed to have two primary purposes of relieving pain and muscle hyperactivity or spasm **(Shanavas *et al.*, 2014)**

- **LASER (Light Amplification by Stimulated Emission of Radiation)**

Low-level laser therapy (LLLT) may help in repair of tissues by its action as an analgesic and an anti-inflammatory. It claims to stimulate blood flow to tissues, increases lymphatic drainage and reduces muscle contraction. **(Shukla *et al.*, 2016).**

2. **Surgical Treatment**

Surgery to the TMJ plays an essential role in the management of patients who have late or advanced stage ID. Patients categorized to the initial stages of Wilkes classification can be managed effectively with conservative to minimally invasive modalities. Advanced and non-salvageable stages may require open joint surgeries.

Many surgical techniques have been suggested for the treatment of ID **(Fonseca, 2016).** These include:

1. Arthrocentesis and lavage
2. Arthroscopy
3. Arthrotomy with disc repair
4. Arthrotomy with discectomy
5. Arthrotomy with discectomy and autologous graft disk replacement
6. Arthrotomy with discectomy and alloplastic disk replacement
8. Condylotomy

Probably more than other oral and maxillofacial surgeons, TMJ surgeons tend to centrate on one or two procedures to treat. the same diagnosis rather than using the full range of operations. However, surgery should be considered only when the facial pain or dysfunction is not corrected to a level of patient satisfaction by nonsurgical modalities. The surgical modalities include arthroscopy, condylectomy, discectomy, disc repair and repositioning **(Dimitroulis *et al.*, 1995)**. Currently, the minimally invasive treatments such as arthrocentesis as well as arthroscopic lysis and lavage are often used as a first-line surgical treatment or in conjunction with nonsurgical modalities with low morbidity and high efficacy **(Lee *et al.*, 2009)**.

Arthrocentesis is recommended for the treatment of acute or subacute closed lock of the TMJ for disc displacement without reduction of less than 3 months evolution, whereas arthroscopy is definitively preferred for the treatment of chronic closed lock of the TMJ (>3 months evolution). Arthroscopy is indicated for ID of the TMJ, mainly Wilkes stages II, III, and IV, degenerative joint disease, synovitis, painful hypermobility, or recidivist luxation of discal cause, and hypomobility caused by intra-articular adherences **(González, 2015).**

1.7 Arthrocentesis

Arthrocentesis is considered as the first line procedure and one of the least invasive intervention for internal derangements of the TMJ. It involves lysis and lavage of the joint space and is traditionally accomplished in a closed fashion, without viewing the joint. It involves active irrigation of the joint space together with joint manipulation. It aids in releasing adhesions, improves function, clears inflammatory mediators from the joint, and is also utilized for intra-articular administration of pharmacological agents. Like any other surgical procedure, arthrocentesis can not be performed in all the patients diagnosed with TMDs and has definitive indications for a favorable outcome **(González-García, 2015)**. It is recommended that corticosteroids or sodium hyaluronate can be injected to reduce intra-capsular inflammation while improving function. They are also useful for reducing pain, and dysfunction associated with inflammatory process within the joints and reduce functional friction. Injecting the joint with sodium hyaluronate has shown a quicker and long-lasting analgesic effect as it is viscous, high molecular weight polysaccharide which lubricates and allows subsequent protection of the joint cartilage **(Alpaslan *et al.,* 2001).**

1.7.1 Indications for Arthrocentesis

- Dislocation of the articular disk with or without reduction
- Limitation of the oral opening
- Joint pain and internal derangement of the TMJ. All patients who had proved refractory to conservative treatment (medication, bite appliance, physiotherapy and manipulation of the joint) **(Neelima, 2021).**

The simple lavage of the upper joint compartment under local anesthesia enables the disc to slide and reestablishes a normal range of mouth opening in patients with closed lock as presented in Figure (8,9).

Intra-articular corticosteroid injection after arthrocentesis provides long-term palliative effects on subjective symptoms and clinical signs of TMJ pain. Unfortunately, intra-articular corticosteroid injection has an unpredictable prognosis and also can cause local side effects on joint tissues. Recently, sodium hyaluronate (SH) has been proposed as an alternative therapeutic agent with similar therapeutic effects. A combined technique providing the injection of hyaluronic acid at the end of the procedure to improve joint lubrication has shown promising results **(Alpaslan *et al.,* 2001; Shakya *et al.,* 2010)**

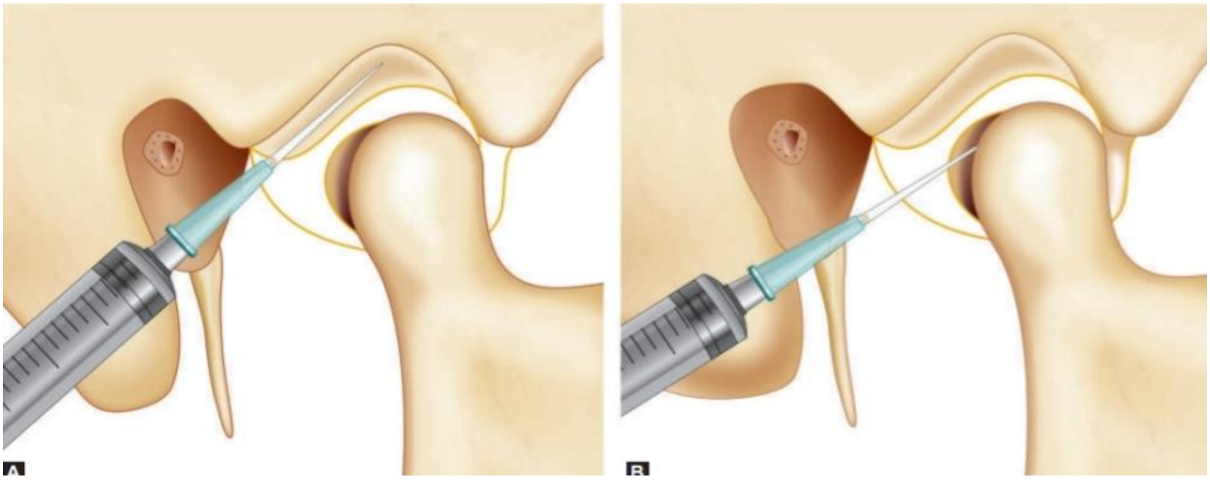

Figure 8 : Intra-articular injection technique for temporomandibular joint **(Neelima, 2021)**

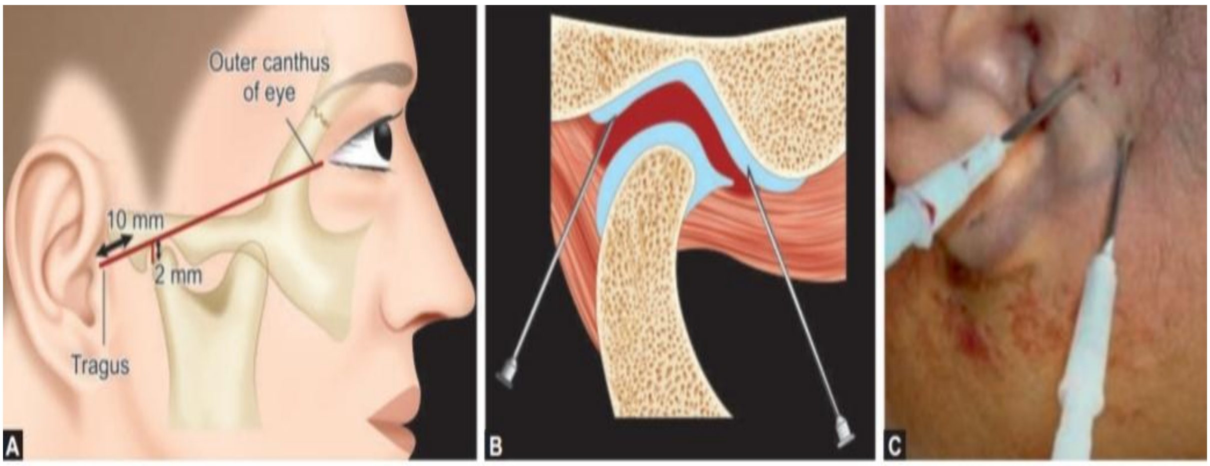

Figure 9: Anatomic landmarks for the needles entries into the joint space for arthrocentesis **(Neelima, 2021)**

1.8 Arthroscopy

Arthroscopy is another treatment modality employed in the management of ID of TMJ. It involves the use of endoscope introduced into the joint cavity which allows the intra-articular examination or treatment. Usually a diameter of 1.9–2.7 mm endoscope is used to perform TMJ arthroscopy. It is as effective and sometimes superior to arthrocentesis to remove articular adhesions, improve function and reduces pain in ID. It can be diagnostic or therapeutic The success of arthroscopic TMJ lavage was followed by the introduction of arthrocentesis. This technique is also shown to be effective in the treatment of ID, particularly in cases of symptomatic closed lock **(Kisnisci *et al.*, 2001)**

The indications for diagnostic arthroscopy are as follows:

- ➢ Internal derangement
- ➢ Osteoarthritis
- ➢ Arthritis
- ➢ Pseudotumors
- ➢ Post-traumatic complaints

1.9 Hyaluronic acid

Hyaluronic acid is an anionic (Figure 10), nonsulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. It is unique among glycosaminoglycans as it is non-sulfated, forms in the plasma membrane instead of the Golgi apparatus, and can be very large: human synovial HA averages about 7 million Da per molecule, or about 20,000 disaccharide monomer **(Fraser *et al.*,1997)**, while other sources mention 3–4 million Da **(Saari *et al.*, 1993)**.

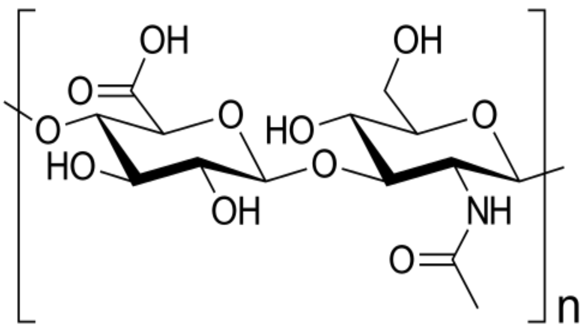

Figure 10: Skeletal formula of hyaluronan — a polymer consisting of D-glucuronic acid and N-acetyl-D-glucosamine linked via alternating β-(1→4) and β-(1→3) glycosidic bonds **(Saari *et al.*, 1993)**

As one of the chief components of the extracellular matrix, it contributes significantly to cell proliferation and migration, and is involved in the progression of many malignant tumors. The average 70 kg (150 lb) person has roughly 15 grams of hyaluronan in the body, one-third of which is turned over (i.e., degraded and synthesized) per day **(Stern, 2004;2009)** .

Hyaluronic acid is also a component of the group A streptococcal extracellular capsule, and is believed to play a role in virulence **(Schrager *et al.*, 1996)**.

HA is involved in many key processes, including cell signaling, wound reparation, tissue regeneration, morphogenesis, matrix organization and pathobiology, and has unique physico-chemical properties, such as biocompatibility, biodegradability, mucoadhesivity, hygroscopicity and viscoelasticity. For these reasons, exogenous HA has been investigated as a drug delivery system and treatment in cancer, ophthalmology, arthrology, pneumology, rhinology, urology, aesthetic medicine and cosmetics. To improve and customize its properties and applications, HA can be subjected to chemical modifications: conjugation and crosslinking **(Fallacara *et al.*,2018).**

1.10.1 Types of Hyaluronic acid

Hyaluronic acid is naturally present in our body and has a molecular weight of 4000 to 8,000,000 daltons. In cosmetics, there are different types of hyaluronic acid that can be used in cosmetic formulations. And they vary based on their molecular size and their effects can vary based on the molecular size that is indicated by its daltons, type in relation to the molecular size which has different effects on the skin. Once it sinks into skin, hyaluronic acid can hold up to 1,000 times its weight in water — and in doing so gives skin a soft, plumper texture and more even skin tone. It can improve fine lines and wrinkles as well. On top of that, hyaluronic acid is gentle on the skin barrier, making it a good choice whether you have dry or dehydrated skin **(Cyphert et al., 2015)**.

But not all hyaluronic acid molecules are created equal. In fact, there are six different sizes. Different molecular weights penetrate to different levels of the skin. Molecules with lower molecular weight are smaller, and can therefore reach the deeper layers of skin. There, they sustain skin's moisture content.

Those with high molecular weights, on the other hand, remain closer to the surface, where they can deliver the most visible results with a shorter life-span. As the results will be washed away with the next cleansing ritual.

Roughly, we distinguish between 2 molecular sizes: high molecular weight hyaluronic acid and low molecular weight hyaluronic acid. However, there are more specific ones that you can see below outlined in the table **(Fallacara *et al.*, 2018)**

Type of HA	Molecular weight (in Dalton)	kDA	Use
High molecular weight	>1.800.000	<1.800	- works only for a short time
			- forms a moisturizing film on the skin surface
			- has anti-inflammatory effects
Middle molecular weight	1.000.000 to 1.800.000	1000 – 1800	- is stored in the connective tissue of the skin
			- works long term
Low molecular weight	400.000 to 1.000.000	400 – 1000	- works long term
			- is stored in the connective tissue of the skin
			- has a lasting anti-wrinkle effect
S	100.000 to 400.000	100-400	- Works in deeper levels of the skin
XS	<100.000	>100	- Regenerating

Table (1) table to outline the different molecular sizes Sodium Hyaluronate can represent and its effect **(Fallacara *et al.*, 2018)**

1.10.1.1 HIGH MOLECULAR WEIGHT

High molecular weight hyaluronic acid is the much larger variant as per outlined in the table above. It consists of molecules of 1,500 kD and larger and cannot penetrate the skin barrier. However, it forms a film with the keratin of the skin on evaporation, which moisturizes the skin and improves its elasticity. Unfortunately, this film is washed off relatively quickly, so that no real long-term effect occurs. Finally, this type has anti-inflammatory properties.

So it is quite nurturing and soothing **(Bothner, 1987).** Several preparations of HA such as high molecular weight hyaluronan used in the treatment of degenerative TMJ disease.

This treatment, called viscosupplementation is administered as a course of injections into the joint and is believed to supplement the viscosity of the synovial fluid, thereby lubricating and cushioning the joint **(Basterzi *et al.*, 2009).**

1.10.1.2 LOW MOLECULAR WEIGHT

Low molecular weight hyaluronic acid makes it possible to enter the skin. It consists of molecules of 50 kD and smaller and ensures that water is stored in the connective tissue of the skin. The additional moisture not only makes the skin more firm and firmer, but also visibly reduces wrinkles. When using low molecular weight hyaluronic acid, the moisture is stored in the skin sustainably. Therefore, it has more advantages and above all a more lasting effect **(Bothner, 1987).**

In relation to the physicochemical effects of HA in relation to TMJ disorders, it is suggested that the higher the molecular weight the more positive the effect; however, some authors hypothesize that excessive molecular size (between 1-6 x 10^6 Da) would prevent the HA from moving from the intra-articular environment to the intercellular environment in such a way that it would not be able to act on synoviocytes and chondrocytes, which is why products with a molecular weight between 0.5-1 x 10^6 would be the most effective **(Iturriaga *et al.*, 2017).**

1.11 Mechanism of action of Hyaluronic Acid

HA performs its biological actions according to two basic mechanisms: it can act as a passive structural molecule and as a signaling molecule. Both of these mechanisms of action have been shown to be size-dependent **(Volpi *et al*, 2009).**

HA binding proteins can be distinguished into HA-binding proteoglycans (extracellular or matrix hyaloadherins) and HA cell surface receptors (cellular hyaloadherins). HA has shown two different molecular mechanisms of interaction with its hyaloadherins. First, HA can interact in an autocrine fashion with its receptors on the same cell . Second, it can behave as a paracrine substance, which binds its receptors on neighboring cells and thus activates different intracellular signal cascades.

If HA has an HMW, a single chain can interact simultaneously with several cell surface receptors and can bind multiple proteoglycans. These structures, in turn, can aggregate with additional ECM proteins to form complexes, which can be linked to the cell surface through HA receptors .

Hence, HA acts as a scaffold that stabilizes the ECM structure not only through its passive structural action, but also through its active interaction with several extracellular hyaloadherins, such as aggrecan (prominent in the cartilage), neurocan and brevican (prominent in the central nervous system) and versican (present in different soft tissues) . For these reasons, pericellular HA is involved in the preservation of the structure and functionality of connective tissues, as well as in their protection from environmental factors **(Girish *et al.;* 2000; Toole, 2004).**

1.12 Uses of Hyaluronic acid

HA possesses many important functionalities, such as cell signaling , wound healing/tissue regeneration **(Fallacara *et al.*, 2018)** , assistant device in ophthalmic surgeries **(Campoccia *et al.*, 1998)**, treatment of joint disease as a lubricant and/or shock-absorbing fluid **(Brown *et al.*, 2005)** , treatment of bone and skin inflammatory diseases **(Chen *et al.*, 2018)** .

As a result of its unique viscoelasticity, biocompatibility, biodegradability, non-immunogenicity **(Sandri *et al.*, 2004)** HA has been extensively applied on skin for its biomedical benefits, such as skin anti-aging **(Papakonstantinou *et al.*, 2012)** anti-wrinkle **(Tokudome *et al.*, 2018)** , anti-nasolabial folds **(Goldman *et al.*, 2007)** , tissue regeneration **(Collins *et al.*, 2018)** , and skin hydration properties **(Jegasothy *et al.*, 2018).**

Conclusively, HA can be applied ophthalmically, nasally, parenterally, topically **(Brown *et al.*, 2005)** , orally and intravenously **(Adams *et al.* 2000).** In medical, pharmaceutical, nutritional and cosmetic industries.

Low molecular weight HA is suitable for developing transdermal delivery systems, while high molecular weight HA provides high viscosities in the formulation and facilitates the localization and sustained release of drugs/nutraceuticals, therefore it can be used to develop topical delivery systems. **(Zhu *et al.*, 2020).**

1.13 Uses in TMJ

HA was a more suitable treatment since it is a physiological component of synovial fluid and therefore the risk of the progression of joint degeneration, which may be caused by corticosteroids, is reduced **(Kopp *et al.*, 1987)** Regarding the use of HA, the majority of studies also report an absence of complications related to the application of HA, with a rate of less than 1% **(Long *et al.*, 2009)**. Hyaluronan should also be injected strictly intra-articularly, because an extra-articular injection causes severe pain **(Fonseca, 2016)**. Intra-articular hyaluronic acid (HA) injection alone or after arthrocentesis provides long-term palliative effects on subjective symptoms and clinical signs of TMJ pain **(Neeli *et al.*, 2010).** Arthrocentesis plus HA injection and single HA injection effectively alleviated the signs and symptoms of patients with painful TMJ DDwR or DDwoR except for TMJ sounds **(Yilmaz *et al.*, 2019)**. Viscosupplementation of the TMJ with hyaluronic acid (HA) is a simple, minimally invasive and low-risk therapeutic alternative **(Souza *et al.*, 2012).**

Bonet et al. demonstrated that the intradermal administration of low molecular weight HA induces a mechanical hyperalgesia of similar magnitude in male and female rats. However, the duration of hyperalgesia is longer in females. The difference in the duration of the hyperalgesia between male/female rats was eliminated by bilateral ovariectomy, indicating this effect highly depends on the estrogen levels **(Bonet *et al.*, 2021).**

Because of their frequency among the TMDs, we highlight the internal derangement of the temporomandibular joint (TMJ), which account for 80% to 90% of the cases and are defined as an abnormal relationship between the mandibular disc and condyle, often associated with degenerative changes or condyle osteoarthrosis **(Jung *et al.*, 2015).**

HA injection and stabilization splinting are acceptably successful treatment modalities to alleviate the clinical signs and symptoms of TMJ Disc Displacement with Reduction **(Korkmaz *et al.*, 2016).**

In cases of internal derangement of the TMJ, including TMJ disc displacement, the concentration and molecular weight of the HA present in the synovial fluid are reduced due to dilution as well as fragmentation as we discussed earlier.

Internal TMJ derangement has been associated with the production of lower-molecular-weight HA by the synoviocytes **(Guarda *et al.*, 2015; Sharma *et al.*, 2013)**. The effectiveness of arthrocentesis with injection of hyaluronic acid in treatment of internal derangement of the TMJ in this study was based on 3 clinical parameters: increase in MMO, reduction in pain and clicking sound during function. A range of 9% to 30% improvement in MMO has been reported in TMJ-ID patients receiving HA injection in combination with arthrocentesis **(Guarda *et al.*, 2015; Manfredini D *et al.*, 2012).**

Bjornalnd et. al suggested that direct administration of exogenous HA to the TMJ could have both anti-inflammatory and analgesic effects **(Bjornland *et al.*, 2007) .**

In addition, HA administration could activate a cascade of biochemical events that would ultimately lead to tissue repair in the articular cartilage/fibrocartilage, which in turn would normalize the synthesis of endogenous HA by the synovial cells and reduce the coefficient of joint friction **(Altman *et al.,* 2015)**. Acting together, these effects could potentially reduce the risk of damage to the articular surfaces **(Machado E *et al.*, 2013; Ozdamar SM *et al.*, 2017)** .

1.14 Preprocedural considerations

TMJ arthrocentesis is a minimally invasive procedure and can be comfortably performed under local anaesthesia or intravenous conscious sedation or general anaesthesia, depending on patient comfort and surgeon preference. Before performing the procedure, the following points should be kept in mind **(Grossmann, 2012)**.

-The surgical field is properly draped and cleaned with povidone iodine or similar substance, particularly in the preauricular region and ear.
-External auditory canal is protected from accumulation of blood and fluid using a cotton pledget.
-The auriculotemporal nerve block is given, and the areas of joint penetration should be infiltrated.

1.15 Techniques used in Arthrocentesis

1. The two-needle technique

The classical technique to perform TMJ arthrocentesis utilizes double access to the joint cavity. This technique uses two needles, one for injecting and the other for aspirating the solution **(Tozoglu *et al.*, 2011)**.

• For two-needle technique, access is performed by taking as indicator the Holmlund–Hellsing line (canthotragal line) as depicted in (Figure 13). A straight line is drawn on the skin joining the medial portion of the tragus of the ear to the outer canthus of the ipsilateral eye. **(Guarda *et al.*, 2008)**

Figure 11: Holmlund–Hellsing line or canthotragal line **(Guarda, 2008)**

•Two points are marked on this line for needle insertion. The first, more posterior point will be marked at a distance of 10 mm from the tragus and 2 mm inferior to canthotragal line. This point corresponds to the posterior extent of the glenoid fossa. The second point will be marked at 20 mm anterior to tragus and 10 mm inferior to canthotragal line, which corresponds to the height of articular eminence **(Reddy *et al.*, 2013)**.

•The glenoid fossa is thin, with a range of 0.5–1.5 mm **(Warnke *et al.*, 1996)** The dura and temporal lobe are located beneath the glenoid fossa. Joints may also be eroded by degenerative arthritis or previous infections. Hence, it is possible that during the procedure, this structure may get perforated. Therefore, the surgeon must be cautious not to insert the needle much into the joint space. About 25 mm depth is enough to reach to upper joint space **(Nitzan, 2006)**.

•To increase the joint space during arthrocentesis, the patient is usually asked to open the mouth and deviate it to the opposite side so as to distract the condyle from the glenoid fossa thereby increasing joint space.

Nagori suggested that custom-made mouth prop is an effective tool to hold the mandible in eccentric position during arthrocentesis **(Nagori *et al.*, 2017**).

•With the patient's mouth open, the first needle is inserted into the superior joint space in the most posterior point directing upward, forward, and inward to a depth of about 20–25 mm, after the tip of the needle has come into contact with the posterior wall of the articular eminence **(Tvrdy *et al* .,2015)**.

•This is followed by administration of irrigating solution (Hartmann solution) [also known as Ringer's lactate solution] or physiological saline, through the first needle with the aim of distending the superior joint space. This compartment will take up to 5 mL of fluid **(Guarda *et al.* ,2008)**.

•Now, the second needle is introduced in the distended compartment, in front of the first needle at the marked point, allowing the visualization of the solution and orienting the flow of the joint lavage solution, as shown in (Figure 14).

Figure 12 : Double-needle arthrocentesis **(Grossmann, 2012)**

Laskin mentioned that it is usually difficult to insert the second needle anterior to the first one, and therefore, he had inserted the anterior needle in the posterior recess of the upper joint compartment by placing it 3–4 mm anterior to the first one and suggested this technique to be much easier than the previous method **(Laskin, 1998).**

However, if the second needle is entered anterior to the first one, it is inserted into a narrower region of the upper joint compartment, and this may cause damage to the articular disc leading to failure of the outflow of irrigating solution.

Recently, a technique using a single needle for both injection and ejection of irrigating solution has been described and gave interesting results over a short period **(Manfredini et al., 2009)**.

2. The single-needle technique

The single-needle approach for the lavage of TMJ was based on the rationale that pumping saline injection into the superior joint compartment with the patient in an open mouth position provides enough pressure to release joint adherences and to allow fluid outflow when the patient closes his/her mouth , as shown in (Figure 15) .The single-needle technique provides the under pressure fluid injection to expand the joint cavity and to break joint adherences that are responsible for the reduced translatory movement of the condyle **(Nitzan, 2001)**. The injection-ejection process must be performed for up to 10 repetitions for a total amount of about 40 ml. This makes the single-needle technique indicated in the case of hypomobile joints with strong adherences or joints with degenerative changes that make the insertion of the second needle difficult **(Guarda *et al.*, 2008)**.

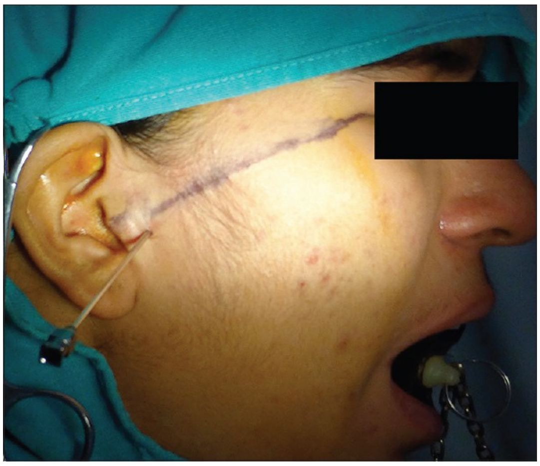

Figure 13 : Single-needle arthrocentesis **(Guarda, 2012)**

The single-needle arthrocentesis technique has several advantages over the traditional two-needle technique which are as follows **(Guarda *et al.*, 2008)**.

•It is a simple, easier, and less invasive technique.

•As the positioning of a second needle could interfere with the stability of the first one in two-needle technique, the single-needle technique provides more sure and stable access to the joint cavity.

•There is reduction in postoperative pain and discomfort to the patient after the procedure which may be attributed to the lesser amount of anaesthetic needed in the single-needle approach. This may further reduce the risks of postoperative facial nerve paresthesia.
•An anteriorly positioned second needle may cause trauma to the facial nerve, that lies anteriorly and medially to the glenoid fossa, which is the site where the second needle is usually inserted; single needle approach reduces the chances of such injuries.
•There is reduction in the execution time for the procedure to perform in single-needle approach
•A single-needle technique might allow full retention of the injected hyaluronic acid within the joint compartment because the risk of hyaluronic acid flowing out through the second point of injection is absent **(Grossmann, 2012).**

1.16 Modifications in Arthrocentesis Techniques

With time, many modifications have been made in arthrocentesis methods to make this traditional procedure even simpler and less invasive.

Double needles in a single cannula **(Alkan and Bas, 2007)** used double needles in a single cannula having two adjacent irrigation and aspiration tubes that allow sufficient irrigation and lavage of the joint with the same device under the desired pressure. It is very safe and does not need another puncture to place the additional needle, such as with classic arthrocentesis. However, the major limitation of this technique is when there are major degenerative changes with decreased joint space and presence of osteophytes; it can be more difficult to enter this instrument into the joint space.

Shepard's single cannula

Rehman and Hall (2009) used a similar device called a Shepard cannula that holds two needles together**.** Nevertheless, the device that keeps two needles together seems to be relatively thick, which has the potential to damage the nerve. Repetitive use of the device may cause the tips of the needles to blunt and increase the risk of infection. In a study conducted by **(Talaat *et al.*, 2016)** they compare single-needle arthrocentesis (Shepard cannula) with double-needle arthrocentesis with viscosupplementation for treating disc displacement without reduction of the TMJ and found that single-needle technique was easier to perform and required a shorter operative time, and therefore, it can be an alternative to the standard technique; however, it might add to the cost of the procedure.

Arthrocentesis technique with automatic irrigation under high pressure **(Alkan and Kilic, 2009)** described a modification of the arthrocentesis technique Nitzan described by in which an irrigation pump from a surgical and dental implant motor was connected to the second needle, and automatic irrigation was initiated under high pressure. They considered that this modification provided the highest hydraulic pressure and made it possible to irrigate the upper joint space in 2 min with saline solution 300 ml. However, complications may develop in the surrounding tissues as a result of the high pressure if the irrigation pump is connected to the first needle without manual confirmation with the second needle. In addition, if the outlet needle suddenly blocks during the procedure, the surgeon must discontinue the irrigation immediately **(Nitzan *et al.*, 1991).**

Concentric needles unit

Öreroğlu suggested the use of a concentric-needle cannula system, i.e., using 2 different gauge needles placed in a concentric manner for SPA in TMJ and found it to be the least traumatic and perhaps the most feasible and cost-effective method for TMJ lavage **(Öreroğlu *et al.*,2011) .**

1.17 Injection Technique of Hyaluronic Acid in TMJ

1.17.1 Single Needle Technique

The injection technique used is the single-needle technique suggested by Guarda-Nardini et al. (2008). The skin surface was disinfected with 10% povidone iodine solution. The needle insertion site was marked on the skin 10 mm anterior to the tragus and 2 mm below the cantho-tragal line. Articaine with epinephrine (1:100,000 ratio) was administered for local anesthesia. The patients' mouths were opened wider for better definition of the glenoid fossa, and a 22-mm gauge needle was inserted into the superior joint space using the anatomical landmarks. While the mouth was open, 2 mL of high molecular weight HA solution was injected into the superior joint space of the TMJ.

1.17.2 Two Needle Technique

After doing the preprocedural considerations regarding the disinfection and anaesthesia. The first needle was inserted 10 mm anterior to the tragus and 2 mm below the cantho-tragal line. The second needle was placed 3 to 4 mm in front of the first needle. Articaine with epinephrine was injected into the superior joint space for local anesthesia. Two 22-gauge needles were used for the arthrocentesis procedure. The joint was irrigated with a minimum of 250 mL Ringer's lactate solution. After the joint lavage was completed, 2 mL high molecular weight HA solution was **(Yilmaz *et al.,* 2019).**

1.18 Effectiveness of HA with arthrocentesis in treatment of Internal derangement

Manfredini et al., 2012 supported the superiority of multiple-injection protocols with respect to single-session joint lavage. Thus, five-session protocol has been used in many studies as the standard of reference when attempting to gain deeper knowledge of the many issues concerning the predictability of HA viscosupplementation at the individual level (**Guarda, et al., 2014).**

However, Arthrocentesis plus HA injection and single HA injection effectively alleviated the signs and symptoms of patients with painful TMJ DDwR or DDwoR except for TMJ sounds. According to many studies, **(Guarda *et al.*, 2010; Tozoglu *et al.*, 2011)** arthrocentesis plus HA injection showed much better outcomes than single HA injection for chewing efficiency and quality of life in patients with DDwR.

The functional and symptomatic improvement in our combined treatment, as shown by numerous researches **(Guarda-Nardini, 2012; Bergstrand *et al.,* 2019; Portelli, 2014)** appears to be linked to:

1. Infiltration of the local anesthetic that is activated at the time of treatment.
2. Use of lavage solution, which removes the intra-articular catabolites.
3. Hyaluronic Acid infiltration, with its analgesic, anti-inflammatory, and lubricant properties.

Chapter Two
Conclusion

Conclusion

Internal derangements are not uncommon. However, they are usually self-limiting and respond well to conservative, inexpensive care. In rare cases, surgical intervention may be indicated, but only in the presence of significant pain and/or dysfunction, despite skillful conservative treatment.

Many authors have reported significant effects of Arthrocentesis with injection of hyaluronic acid in the treatment of TMJ internal derangement is the least invasive procedure with fewest complications. The arthrocentesis studies show satisfactory results in restoration of TMJ functions in patients with TMJ ID, who were refractory to the conservative methods and psychologically depressed due to lack of proper treatment. Thus, it may be the preferred treatment for the patient suffering with TMJ ID who were refractory to conservative methods.

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