IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 1 Ser.3 (January. 2023), PP 49-59
www.iosrjournals.org

Basic Biological Mechanisms Impairing Lubrication in severe Cases of Temporomandibular Joint Internal Derangements: Update and Review.

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Abstract
Introduction: *Lubrication is a basic mechanism in musculoskeletal joints andis responsible for smooth friction free movements of the joint. Abnormal lubrication mechanisms are directly related to lubrication failure and the development of osteoarthritis.****Goals:*** *Review the literature about lubrication of the temporomandibular joints and discuss lubrication impairment mechanisms.* ***Methods:*** *Using the descriptors "Lubrication, TemporomandibularJoints, Internal derangements, Osteoarthritis", 60 papers were found in the current literature. However, 20 were discarded based on insufficient information to discuss different aspects about biological mechanisms of lubrication. Thus, 40 papers were used in the current study.* ***Outcome****: Fortypapers were selected and used to discuss different aspects of normal and abnormal lubrication mechanisms in the temporomandibular joints.* ***Conclusion:*** *Hyaluronic acid and lubricin are two major molecules which provide the lubrication capacity of the temporomandibular joints to prevent excessive friction, compensate for excessive loading and protect the articulating surfaces from wear and damage. Large peak loads, excessive friction and poor lubrication of the articulating surfaces facilitate the development of osteoarthritic changes in the joint.*
Keywords: *Temporomandibular Joints. Internal Derangements. Lubrication. Loading. Osteoarthritis.*

Date of Submission: 01-01-2023 Date of Acceptance: 10-01-2023

I. Introduction

The Temporomandibular Joint (TMJ) performsimportant roles in dental occlusion and the neuromuscular system and is one of the most complex joints involved in many functions of the masticatory system [1].TheTMJs are considered by most researchers as ginglymoarthrodial joints as they allow a relative motion of the articulating bones as a reaction to the forces produced by adjacent muscles[2],tendons and ligaments.Assisted by neuromuscular and proprioceptive mechanisms, the TMJs contribute to control loads exerted by mandibular movements. It has been stablished that normal loading is directly associated with tissue remodeling and adaptation[3]. Because the forces are dissipated in other components of the masticatory system (teeth and periodontal membrane), most of the time, the forces that impinge on the internal components of the TMJ, are not significant. Craniomandibular Disorders (CMDs) is a set of terms used in Medicine and Dentistry to describe signs and symptoms occurring in the TMJs, masticatory muscles and adjacent anatomic structures usually of musculoskeletal origin. With the purpose of diagnosis and treatment such disorders are classified in joint disorders, muscle pathological alterations and TMJ osteoarthritis/osteoarthrosis[4].·Clinical observations demonstrate that CMDs present with classic clinical characteristics including a complaint of pain, joint noises, tenderness to palpation of joint and masticatory muscles, difficulties to perform normal jaw movements [5] and headaches. Osteoarthritis (OA) of the TMJs is observed with some frequency [6] in the clinical setting and is characterized by deformation of the articulating surfaces and deficient lubrication of such surfaces.

Internal derangements of the TMJs (TMJs-IDs)are terms coined in the last decades to describe abnormal anatomical and functional relationships of the TMJ disc when related to other joint components including the condylar head, upper joint cavity and articular eminence.These disordersare usually characterized by an abnormal position of the joint condyle when related to the joint disc [7]. The term derangement has the connotation of an alteration in the normal pathways of movement of the condylar head and usually involves abnormal function of the joint disc, for instance, displacement, deformation and inflammation [8].Interesting to note is that this concept also implies abnormal position, function, cartilage deformation and or deformation of the joint disc (disc displacement) in most patients with CMDs [9].

In joints subjected to loading and/or in thoseinvolved in many physiological functions, lubrication of the system provides less friction during loading and function and thus, to a certain extent guarantees the longevity of the system. Long-term function of the system depends heavily on the viscoelastic properties of the synovial fluid and its molecular characteristics [2]. A low friction and wear status of an articulating biological system is a characteristic of a normal joint whereas increased friction and wear can be observed in certain pathological states, for instance, osteoarthritis and rheumatoid arthritis [3] affecting the TMJ. It has been reported that when the metabolic and physicochemical properties of the synovial fluidsin terms of molecular distribution, is significantly altered, the pressure distribution may impair the physiology of TMJ cartilage, leading first to deterioration of its integrity and later to the development of OA [10].

II. TMJ internal derangements

TMJ-IDs are collective terms used to describe a set of inflammatory and positional disorders occurring in the most important components of the TMJs. They are described in terms of positional or anatomical deformation of the joint disc when related to the mandibular fossa, articular eminence and condylar head[7].Such disorders usually involve the presence of inflammation, inflammatory molecules, deformation of the joint disc and desynchronization of the joint disc relative to the condylar head during jaw movements.Thus, inflammation, positional changes, poor coordination between the joint disc and condylar head and deformation, better characterizes TMJ-IDs[11]. TMJ-IDs are the most common inflammatory and noninflammatory abnormalities of the TMJs observed in patients with a complain of TMJ and muscle pain usually characterized by irregular jaw movements [8].

III. Cartilage of the TMJ

Cartilage and fibrocartilage are essential anatomic and physiologic components of the TMJ condylar head and disc, respectively. They constitute articular surfaces that allow soft, unidirectional preplanned joint movements under conditions of extremely low friction in skeletal joints [12]. Articular cartilage in any joint functions as a surface that allows joint movement under conditions of extremely low friction when the joint surfaces are protected by high weight molecular components present in the synovial fluid [4]. Joint cartilage has a crucial role facilitating articulation with the joint disc reducing point loads on the underlying bone. The fibrous, proliferative, mature and hypertrophic zones found in the TMJ articular cartilage are physiologically adapted to resist loadings [2] during joint functions in which the TMJ participates including eating, swallowing, speech and even jaw posture. The collagen fibers of the TMJ cartilage are arranged in several and different zones facilitating their role and providing tensile and shear strength to the cartilage, characteristics needed to protect the joint during function in which direct tension and shear are involved. Collagen fibers arranged in different directions provide stiffness and strength to the articulating surface [7].

IV. Physiological lubrication mechanisms

Physiological lubrication in the TMJs is the mechanism by which friction, deformation, formation of rugosities and even displacement of the joint disc and the TMJ cartilage are prevented to preserve smooth joint movements without mechanical interferences. Many forms of lubrication have been described in the synovial joints including fluid film or boundary lubrication [12|. The lubrication type depends on the intensity and direction of forces applied on the articulating surfaces of the joints. Hydrostatic lubrication occurs at the onset of joint loading for long periods of time in which fluid pressure within the cartilage increases and the fluid is forced into the articular surfaces. Such fluid contributes significantly to the bearing of normal loads providing resistance to shear load and thus, a very low friction coefficient in the joint surfaces[12].The second type of lubrication is known as boundary lubrication in which joint loading is supported by surface to surface contact when lubricating molecules, for instance, hyaluronic acid, lubricin (and possibly other molecules), are interposed in the articulating surfaces reducing the coefficient of friction and preventing wear and deformation. The role of previously mentioned molecules is to prevent direct contact between the articulating surfaces providing a smooth contact surface (bone versus molecules or disk versus molecules) with such molecules rather than bone or cartilage versus joint disc. In both types of lubrication of the joint disc, bone or cartilage coated surfaces are thought to support or dissipate the forces during articular function. The secretion of synovial fluid

in physiological conditions which pushes lubricating molecules in the articulating surfaces provides a higher coefficient of viscosity between the articulating surfaces thus, protecting the head of the mandible and the articulating disc [3]. Loss of boundary lubrication results in subsurface strain or tension and thus, in the formation of surface asperities [13]and local deformation with the development of residues of cartilage, fibers or bone which favors the formation of areas of inflammation. In situations in which the TMJ disc is located in a normal position between the condylar head and the mandibular fossa and there is a normal secretion of synovial fluid and absence of local inflammation, shear loading of the joint disk is considered negligible or absent [14].

V. Molecular mechanisms in physiological lubrication.

The longevity of diarthrodial and other joints depends largely in their capacity to articulate without friction and wear toproduce smooth movements without anatomic and biomechanical interference. Such capacity also depends on the presence of fluid films and the molecules that protect the articulating surfaces of the joint [7]. Lubrication in articulating skeletal joints is facilitated by the presence of synovial fluid [13] in the synovial membrane elaborated by a number of cells of the connective tissue. Such fluid contains water, cytokines, lubricating molecules and cells of various types. A major function of the synovial fluid and the lubricating molecules is to lower the coefficient of friction to prevent wear and the development of OA and osteoarthrosis. An increase of frictional coefficient in any articulating surface is a major factor leading to discdisplacement [3] and probably local inflammation. It has been reported [15] in experimental studies in patients presenting with signs and symptoms of CMDs, that the coefficient of friction is higher as compared with non CMDs controls. Another potential role of the presence of synovial fluid and lubrication molecules is the protection of chondrocytes and collagenous matrix macromolecules found in the articular cartilage.Hyaluronic acid and lubricin (and probably other unknowncomponents) are molecules of high molecular weight found in the synovial fluid and in the articulating surfaces that protect articulating surfaces reducing the friction coefficient and preventing wear and the formation of tissue residues. The role of such molecules is to maintain the biological properties of the joint disc and condylar head complexfacilitating smooth joint movements.

V. Etiology of CMDs and abnormal lubrication in the TMJ

It is accepted currently that CMDs have a multifactorial etiology in which mechanical factors predominate. In this regard, a combination of chronic oral jaw habits, macro and microtrauma, a sudden blow to the face and joints, motor vehicle accidents, loss of posterior dental support, and orthodontic disorders (for instance and posterior cross bite), are considered etiological factors in the development of CMDs signs and symptoms.Chronic microtrauma from oral jaw behaviors, for instance, chronic, severe sleep bruxing behavior is a common etiologic factor in the development of TMJ-IDs. It is very difficult for clinicians and researcher to identify a common and single etiologic factor causing signs and symptoms of CMDs. More frequently, a combination of factors is responsible for the development of signs and symptoms.The etiology of CMDs and TMJ-IDs is still considered complex and multifactorial. In young and adolescent patients, a combination of oral jaw habits, for instance, chewing gum, postural disorders, tongue, nailand cheek bitingare frequently found during the examination process. Etiological factors are usually classified in predisposing when they increase the risk for the development of signs and symptoms, initiating are those that directly cause the onset of signs and symptoms, and perpetuating are those that directly interfere in the healing process and/or enhance the progression of signs and symptoms [1]. Most common etiological factors for the development of CMDs and TMJ- IDs, include direct trauma to the face, head or joints, chronic microtrauma from repeated and adverse loadingof the masticatory system, abnormal occlusal relationships (for instance, loss of posterior support, posterior crossbite), abnormal posture of the jaw or head and many others [1]. Pathological factors may alter the normal physiology of the TMJs: Some may chronically alter the position and anatomy of the joint disc, others may increase the concentration of inflammatory molecules in the synovial fluid, others may directly cause disk displacement and inflammation and at the molecular level, some may alter the molecular composition and the properties of the articular cartilage, increasing the roughness of the articular surface and facilitating the development of TMJ- OA[8].

The variety of etiological factors (traumatic events), in the development of CMDs signs and symptoms which may be muscular, articular or both, may cause stretching, tearing or rupture of the joint disc, collateral or lateral ligaments and joint capsule[8] and initiate a chronic inflammatory process known as capsulitis, retro discitis, disk-attachment pain, disk displacement, arthralgia and even OA in which signs and symptoms including pain, headache and restricted jaw mobility predominate. Clinical practice demonstrates that many oral jaw behaviors including chewing gum, poor jaw posture, cheek, lip, tongue biting, and severe or extreme bruxing behavior (BB) predominate in CMDs patients presenting with signs and symptoms of TMJ-IDs. Severe BB is considered a potential cause of disc derangements since compressive overloading may alter the connective tissue of the TMJs [16]. A combination of oral parafunctions produces abnormal compression and shear forces capable of initiating disc displacement and degenerative changes in the mandibular head and articular

eminence[11]. Such forces may perpetuate an inflammatory process and directly contribute to the development of OA signs and symptoms. Previous investigations have demonstrated that loss of posterior support, unilateral chewing patterns, and BB were associated with non-physiologicaloverloading of masticatory muscles and TMJs aggravating preexisting TMJ signs and symptoms paving the way for the development of OA and osteoarthrosis[17].

VII.Pathological joint loading

In terms of anatomy and physiology the TMJs are important structures of the masticatory system designed to resist loading to a certain extent. This is so, as such structures are involved in many stomatognathic functions including speech, chewing, swallowing, breathing, and posture. Such structures are not designed to withstand chronic and repetitive loading, for instance, loading associated with multiple and repetitive oral jaw behaviors which in the other hand constitute frequent etiological factors in CMDs patients. Thus, excessive loading causesmany biomechanical changes which ultimately result in disc displacement, inflammation, pain, and dysfunction. Wang and associates [18] assert that overload of the TM is the result of malocclusion, skeletal asymmetry,bone deficiency and muscle overuse. Excessive mechanical loading on normal TMJ cartilage or normal mechanical loading on impaired articular cartilage supposedly initiates disruption of cartilage,matrix homeostasis and other pathological alterations which ultimately result in OA in susceptible individuals [11]. When loading occurs in susceptible individuals, it may lead to large peak loads causing significant damage to the cartilage layers of the TMJ[19] which in the presence of inflammation and disk displacement, is not prevented by the joint disk. The joint disk is to a certain extent capable of deforming and adapting its shape to that of the articulating surfaces [7].However, in cases of significant inflammation,displacement and pain,these pathological alterationstend to perpetuate deformation, dysfunction, pain and displacement of the joint disc. Any form of strain or excessive loading to the anatomic components of the TMJs may cause damage to the joint disc, capsule, and ligaments. Excessive strain from repetitive jaw movements, may disrupt the normal functioning of the anatomic components of the TMJ resulting in inflammation, pain, disc displacement and joint noises. In this regard, abnormal loading to such components, and associated inflammation and orofacial pain have been experimentally simulated in the rodent following repeated mouth opening [20].During mandibular movements, the joint disc may be subjected to many different modes of loading.Overloading associated with compression,tension and shear stress and deformation has been identified [7]. In theory, the joint cartilage is considered weaker as compared to the bone. It has been demonstrated that the application of mechanical loads to bone increases the percentage of cells synthesizing DNA, alter the type of protein being synthesized,induce bone resorption and inhibit osteoblastic differentiation[21].

IIX. Synovial fluid

Hard tissues of the TMJ are anatomically protected from excessive loading by a fibrocartilaginous disc interposed in those components. Further, biochemically, the presence of synovial fluid, guarantees a minimum of friction and wear and the longevity of the joint and its components. The synovial membrane lines the inner surface of the joint capsule [7] and contains a variety of different cells of the connective tissue with phagocytic and immunological properties. The synovial membrane comprises synoviocytes for the production and secretion and even resorption of synovial fluid. Further, some cells of the synovial membrane produces the synovial fluid that provides nourishment and metabolic requirements of adjacent non-vascularized and non-innervatedtissues [7] of the TMJ, for instance, the articular disc. It has been reported [22] that synoviocytes, macrophages, fibroblasts and other cells predominate in the synovial membrane of the TMJ. Inflammation associated neuropeptides including substance P (SP), CGRP, NPY, VIP, serotonin, bradykinin, and other molecules have been identified in the synovial fluid of the TMJ in humans. Analysis of the synovial fluid from the synovial membrane of the TMJ can be extremely useful to evaluate the level of TMJ Inflammation and thus, to establish the best therapeutic approach[23]. Even though, the synovial fluid has a variety of physiological properties, its main function is to protect the joint disc and cartilage from excessive friction and wear. Further,normal secretion of synovial fluid is associated with smooth unidirectional movements of the head of the mandible and joint disc. During jaw movements, the synovial fluid is pushed to the articulating surfaces. Even though the retro discal tissues are not related to jaw movements, but to protection and nourishment, synovial fluid can also be found in those structures since theyare also covered by the synovial membrane[24].It has been reported that the level of 5-HT may be significantly increased and related to pain perceived during jaw movements in patients with CMDs [25]. The synovial tissue is highly innervated and vascularized and has regulatory, phagocytic, and secretory functions being essential to joint surface lubrication [26]. Macro or microtrauma to the articulating surfaces produces and inflammatory reaction in the synovial membrane and capsulitis known as capsulitis-synovitis.

IX Lubricin and Hyaluronic acid

As mentioned before, a major function of the synovial fluid is to provide nourishment to the non-vascularized non-innervated joint tissues and to produce highweight molecules with the function of lubricating, protecting and decreasing friction to a minimum in the articulating surfaces. Hyaluronic acid (HA), is the principal glycosaminoglycan besides chondroitin and keratan sulfate and consists of repeated disaccharide units of glucuronic and acetyl glucosamine[2]. HA is a linear chain, hydrophilic, poly-ionic glycosaminoglycan of high molecular weight found in the extracellular matrix of many types of connective tissues including cartilage and synovial fluid[6].A major characteristic of this material is its high viscosity property, contributing to maintain connective tissue integrity. HA is also present in the synovial fluid where it has been found to have a crucial function in articular joint lubrication. High molecular weight HA provides the viscoelastic property of synovial fluid whereas low weight HA is associated with aging and a reduction of viscoelasticity leading to an impairment of joint lubrication [2]. Synovial fluid of healthy joints containshigh molecular HA. However, studies have found that larger amounts of low molecular weight HA can be found in the synovial fluid of clinical cases of CMDs with OA[3,19].HA is essential in the renewal of cells, for the nourishment of avascular zones of the joint disk and cartilage through its combination with glycosaminoglycans produced by chondrocytes [6]. HA provides the viscoelastic property which generates an environment to separate the hard surfaces of the joint and thus contributes providing smooth joint movements without friction and wear.

Lubricin is another molecule found in the synovial fluid of healthy and dysfunctional CMD patients. Lubricin is normally produced in the synovial joints by synovial fibroblasts and superficial zone chondrocytes. The concentration of lubricin increases under conditions of local stress and compression in experimental studies [13]. Experimental studies have reported that a decrease in the concentration of lubricin can be found in the CMDs subgroup with signs and symptoms of CMDs and OA[15]. Lubricin is a mucinous glycoprotein produced by synovial cells and superficial zone chondrocytes which provides abundant lubrication in the boundary mode which is predominant during periods of high joint loading. In normal articular joints, a layer of lubricin molecules is present in the surface of cartilage and acts as an antiadhesive and boundary lubricant preventing cartilagedamage [13].

X. Pathological Inflammation: Molecular mechanisms

TMJ-IDs are currently viewedviewed as functional disorders in which disc displacement, pain and inflammation resulting in abnormal jawmovements predominate. Inflammatory disorders are frequently observed in those anatomic structures provided with a rich innervation and vascularization. Painand inflammation in the TMJ structures occur in the joint capsule and synovial membrane (capsulitis and synovitis), retrodiscal pad (retrodiscitis), in the collateral ligaments (disk-attachment pain), inthe surface of the bones (arthritis), and in bone and cartilage associated with significant deformation and resorption (osteoarthritis and osteoarthrosis).

When inflammation issevere, inflammatory fluid (TMJ effusion) can be detected in some joint spaces using MRI. It represents the accumulation of joint fluid including water, inflammatory molecules, cells,and components of the immunologic system (pro-inflammatory cytokines)[27]. TMJ effusion represents an inflammatory response to a dysfunctional condyle- disc relationship and is usually associated with the degree of disc displacement [9] and thus, with the severity of joint inflammation. Inflammation of the synovial membrane (synovitis) and joint capsule (capsulitis) is usually not severe when other joint components are not affected and thus, its treatment is very simple. However, in other cases, severe inflammation results in changes in the composition and amount of the synovial fluid resulting in persistent intracapsular pain that is intensified with jaw movements [26]. When treatment is not instituted early, the inflammatory process also occurs in the retrodiscal tissues (retrodiscitis) and in the collateral ligaments (disk-attachment pain).

TMJ-IDs constitute a time dependent chain of events which ultimately results in different disorders with different signs and symptoms and different degrees of disc displacement and inflammation.If inflammation persists, diagnosis is not established and treatment is not instituted, more severe changes including inflammation in the bone and cartilage [20], resorption, deformation and degeneration ensue. In any type of intra-articular inflammation, molecular events associated with inflammation operate in different levels. Neural inflammation causes elevations in cytokine expression and microglia activation. However, proper treatment of injury, compression or displacement (for instance, use of occlusal splints, anti-inflammatory substances and pain killers) may reduce neural inflammation and pain[28].An early pathological and inflammatory process in the TMJ (capsulitis/synovitis or retrodiscal pain) is characterized by a chemical breakdown of degenerative byproducts which in turn stimulatesthe production of inflammatory and pain mediators including prostaglandin E2, leukotriene B_4[26], prostaglandins, serotonin and bradykinin. Some of these components induce changes in the arachidonic acid cascade inducing vasodilation and the release of chemoattractant molecules which attracts neutrophils and monocytes. At the molecular level, an inflammatory process within the joint tissues is characterized by the presence of inflammatory molecules, cells of the inflammatory-immunological system, and

inflammatory cytokines including TNF- alpha, interleukin-1, interleukin-2, interleukin-4. These molecules are very activein the destruction of articular cartilage through regulation of matrix metalloproteinases (MMPs) that affect matrix synthesis [29].

Recent studies[22] indicate that overproduction of inflammatory molecules, is an essential event in mediating the acute and chronic inflammation and tissue destruction in intracapsular pathological conditions. At the molecular, level, the role of interleukin-1 beta, IL-alpha and tumor necrosis factor (TNF) has been emphasized in such investigations [22]. Inflammatory conditions affecting the TMJs are very complex phenomena that involve the participation of many molecules with different origins. Neuropeptides including SP, calcitonin-gene related peptide (CGRP), neuropeptide Y (NPY) and even vasoactive intestinal polypeptide (VIP) have been identified in TMJ tissues and synovial fluid obtained from individuals presenting with signs and symptoms of CMDs [23]. Such neuropeptides are released from activated nerve terminals into surrounding tissue and contribute with an inflammatory response as they activate the release of pro- inflammatory cytokines and arachidonic acid catabolism. These neuropeptides are responsible for inducing vasodilation, stimulate leucocyte migration, margination and adhesion and to function as cell attractants at inflammatory sites [21]. These molecules have the capacity to lower pain threshold of A delta and C fibers and induce local and referred pain in the masticatory system.

XI. Abnormal lubrication in severe clinical cases of TMJ-IDs including OA.

TMJ-IDs are considered by many researchers as functional disorders of the anatomic structures of the TMJs characterized by disc displacement,inflammation,and sometimes structural abnormalities (OA and osteoarthrosis). TMJ-IDs are also considered disorders in which different gradients of inflammation, pain and degenerative disorders can be observed clinically. In the current study, we will consider severe cases of TMJ-IDs, those reported in the current literature, presenting signs, symptoms and/or characteristics of disc displacement without reduction (Stage III according to Nitzan and Dolwick classification), arthralgia and OA/osteoarthrosis (in the same classification system). The synovial fluid has a major role providing blood flow, nutrients, water, and lubricating molecules in areas where innervation and blood supply are very poor.Two high weight molecules (lubricin and HA) have been investigated as major components of the synovial fluid and the lubrication mechanisms in the surface of the condylar head and articular disc.HA is the principal glycosaminoglycan (GAG) found in both the fibrocartilage and hyaline cartilage. Because HA has high viscoelastic properties, this molecule provides the viscoelastic property of lubrication [2] when separating the surface of the joint disc and the articular surface of the condylar head. Lubricin is a mucinous glycoprotein produced by synovial cells and superficial zone chondrocytes in the articulating surfaces. Providing boundary lubrication [13], lubricin protects such surfaces from wear by reducing the coefficient of friction[30] thus, preventing the development of rugosities, cartilage destruction and TMJ-OA. Some TMJ-IDs characterized by localinflammation predispose the cartilage to damage and may trigger the development of OA[30]. Degenerative changes in the TMJ may also be triggered by a decrease in the adaptive capacity of the articulating surfaces or by TMJ overloading[1]. This pathological alteration causes a combination of inflammation and structural abnormalities (resorption, formation of irregularities, and oxidative stress). When the adaptive capacity of major anatomic components of the TMJ is reduced (condylar head, synovial fluid and joint disc), a change in synovial fluid concentration may be observed triggering the synthesis of high molecular weight HA, thus, reducing the lubrication capacity of the system[1] and ultimately resulting in early osteoarthritic changes in the TMJ.

The frictional coefficient (FCO) in the articulating surfaces is thoughtto be very low and depends on the physiologic conditions of the joint disc, articulating surfaces and quality of the synovial fluid. In pathological condition, there may be low secretion of HA and lubricin. Thus, the FCO may increase paving the way for the development of osteoarthritic alterations. Loading is not the cause of osteoarthritic as many researchers believe. Itis merely a mechanism as loading may be caused by a series of pathological conditions in the masticatory system including poor dental anatomy, loss of posterior teeth, posterior cross bite, a combination of oral parafunctions, severe or extreme BB, increased age, pathological alterations caused by rheumatoid arthritis and so forth.

Regarding TMJ-OA, overloading and systemic conditions have been considered as important etiological or mechanical factors associated with the disease. It has been also reported that chondrocytes in the condylar head cartilage are very vulnerable to chronic and repeated overloading causing an increase in metabolic activity and activation of pathological processes resulting in irreversible degradation or destruction of the joint cartilage.[2].These pathological alterations may be mediated by the synthesis of matrix metalloproteinases and aggrecanases. These enzymatic activity results in the degradation of collagen type II and aggrecan (a major proteoglycan in cartilage) [31]. In condylar cartilage in individuals presenting with signs and symptoms of OA, an increase in the number of blood vessels and osteoclasts has been observed in the area directly below the hypertrophic cell layer [32]. Such changes probably indicate a local inflammation, and sites of potential resorptive process associated with areas of pressure or increased loading. TMJ-OA is characterized by degenerative joint changes including deterioration, abrasion, deformation, formation of cavities, and abrasion of

articular cartilage and disc surfaces associated with thickening and remodeling of the underlying bones.These pathological alterations are associated with decreased boundary lubrication[7]. According to Nitzan [33],overloading causes collapse of lubrication in the TMJ as the result of hyaluronan degradation by free radicals released in osteoarthritic joints as a result of continuous friction and deformation in the articulation surfaces. Another mechanism associated with pathological lubrication is one in which increased pressure to the articulating surfaces causes temporary hypoxia. This alteration is thought to release reactive radical species (oxidative stress) in synovial joints leading to inhibition of the biosynthesis and degradation of HA, and ultimately resulting in a significant reduction in viscosity of the synovial fluid, thus directly affecting the quality of lubrication in the joints[11].

XII. Simple modes of therapy versus state of the art treatment or management.

Many modes of treatment have been indicated for the management of signs and symptoms of CMDs. Table I shows the objectives of different approaches in the elimination of mechanisms that lead to pain, inflammation and other signs and symptoms. Tables 1 and 2, shows additional information about the relationship between objectives of treatment, diagnosis and clinical approach.

Table 1: Objectives of modes of treatment and most common approach

Treatment Objectives	Most common approaches	
Reduce pain and inflammation	Pain Killers	Anti-inflammatory drugs
Reduce excessive loading to joints and muscles	Occlusal Splint	Anterior upper splint, repositioning splint, Michigan splint
Reduce muscle tension and anxiety	Muscle relaxants	Anti-anxiety drugs
Reduce depression	Amitriptyline	Sertraline
Increase lubrication in the joints	Viscosupplementation	
Reduce severe inflammation	Arthrocentesis	Arthroscopy, Lysis?
Improve anatomy of the articulating surfaces	Arthroscopy, arthroplasty	Lysis

Table 2: Most common TMJ inflammatory disorders and the corresponding clinical approach from mild to very severe cases:

TMJ-ID	Most common and effective approaches	
TMJ Capsulitis and Synovitis	Occlusal splint, pain killers	Anti-inflammatory drugs
Retro discal pain	Occlusal splint, pain killers	Anti-inflammatory drugs
Disk-attachment pain	Repositioning splint, pain killers	Anti-inflammatory drugs, clonazepam, longer treatment period.
Disk-displacement without reduction	Local anesthesia, jaw manipulation, repositioning splint, pain killers	Muscle relaxants,anti-inflammatory drugs.
Arthralgia and disk-attachment pain	Counseling, anti-inflammatory drugs, clonazepam, jaw stretch exercises, pain killers	Repositioning splint, muscle relaxants, anesthesia of the auriculotemporal nerve.
OA, headache, cervical and facial pain, multiple painful areas adjacent and distant to the masticatory system, difficulties to open the jaw,anxiety and depression.	Pain Killers, anti-inflammatory drugs, jaw exercises, clonazepam, amitriptyline, occlusal splint, counseling, psychotherapy	Local anesthesia for triggerpoints, arthrocentesis, visco supplementation, self-treatment.

XIII. Treatment/management of very severe cases of TMJ-IDs and facial pain.

In this category, we consider cases with the following characteristics: Longer pain duration, inflammation, other clinical complaints duration, patient has been subjected to different treatment modes, presence of multiple disorders, for instance, severe bruxism, myofascial pain, TMJ-IDs, headache, cervical pain, patients that have never been treated using a combination of modes of treatment (for instance, occlusal splints, pain killers, anti-inflammatory drugs, anti-anxiety and antidepressant drugs, presence of anxiety, depression and somatization, presence of multiple internal derangements of the TMJ, for instance, capsulitis, disk-attachment pain and
OA. Clinical approach:
1.Occlusal splint, counseling, jaw exercises, pain killers, anti-inflammatory drugs, antidepressants, clonazepam, physiotherapy (cervical structures)
2.Local anesthesia for trigger points to the masseter and cervical muscles
3.Viscosupplementation: Patients presenting with TMJ-IDs including OA usually demonstrate a higher coefficient of friction as compared to normal individuals indicating abnormal metabolic process and the

presence of anatomic abnormalities in the articulating surfaces. In this cases lubrication of the articular surface withHA is indicated. HA is a normal component of the synovial fluid and is produced in the synovial membrane by specialized cells.

HA lubricates the joint, resulting in less friction and stress on the joint cartilage[18], improving joint movements and increasing the longevity of the cartilage and joint disc. Exogenous HA via intra-articular injections following arthrocentesis has been indicated as a treatment for joint diseases being effective in relieving signs and symptoms [34]. Sodium hyaluronate (SH) is effective, clinically safe and is indicated in the management of the following clinical conditions: Disk displacement without reduction, OA and degenerative joint disease.

4.Arthrocentesis: This mode of treatment is invasive to the TMJs even though many clinicians view it as safe and non-invasive. This method of treatment can be implemented with intraarticular injection of other drugs including analgesics and anti-inflammatory material to increase its effectiveness [35]. Arthrocentesis is recommended in severe cases of TMJ-IDs including arthralgia, adhesions, OA, and disc displacement without reduction. This mode of treatment should not be used indiscriminately in moderate cases of TMJ-IDs, for instance, in cases of disk-attachment pain as this disorder can be treated more conservativelyusing jaw exercises, occlusal splints, pain killers and anti-inflammatory drugs.

5.Surgery Surgery is not a common mode of treatment in patients withCMDs and Craniofacial Pain. Because many modes of therapy are currently available for the treatment of pain, inflammation, and muscle disorders, very rarely a clinician or specialist refers a patient for surgery.Wang and colleagues [18] argue that surgical interventions such as joint replacement with autologous bone or an artificial joint, may restore joint function to some extent in severe cases with impaired joint function, severe muscle disorders and difficulties to open the jaw and chew. In many cases, a poor prognosis, and difficulties to completely restore joint function may not indicate the use of surgery.

6.Longer period of treatment management, more frequent consultations.

Many cases of CMDs are chronic and at first sight seem to be refractory to treatment. It seems to us that these cases have been conditioned indirectly and behaviorally to make patients believe that their cases are difficult, refractory to treatment or even untreatable. Some risk factors responsible for such refractoriness are the following:

1.Presence of non-identified psychological factors namely anxiety, depression and somatization.
2.These cases have been treated using simple modes of treatment usually more frequently pain killers, anti-inflammatory drugs, and muscle relaxants usually for a short period of time.
3.A comprehensive examination is usually not carried out, thus, other concomitant disorders for instance, myofascial pain in the neck and cervical structures are not addressed during treatment.
4.Patients usually present a combination of TMJ-IDs, including arthralgia, OA and disk-attachment pain.
5.Treatment period has been usually short
6.Patients usually take their medication when some anatomical structures are painful pain rather than on regular basis.

Clinical Approach?

1.A comprehensive examination is necessary and usually take 2-3 hours of evaluation.
2.The clinician should be capableof making all the diagnosis in each individual patient, for instance, the type of TMJ-ID, type of headache (tension-type headache, combination headache, migraine). Further, the diagnosis and location of myofascial pain should be determined. In clinical practice is very common to evaluate patients presenting with signs and symptoms of tension-type headache, disk-attachment pain, severe BB and difficulties to open the mouth. Thus, using gentle palpation the clinician should evaluate the cervical structures to determine the location and site of trigger points and how they produce referred pain to the head. Because cervical trigger points are responsible for referred pain to the anterior region of the head, local anesthesia for trigger points should be incorporated in the treatment plan.
3.The clinician should compare previous modes of therapy with the effectiveness of treatment in the course of time. If some muscle relaxants, for example, Flexeril has been effective to a certain extent and according to patient's report, the clinician should suspect of myofascial pain as one of the diagnosis.
4.Because the clinician should control and assess all modes of therapy being used, for instance, he needs to eliminate pain from trigger points, control proper use of pain killers, antidepressants and occlusal splints. Thus, it seems clear that the period of treatment should be longer;
5.The time elapsed between each single appointment should be shorter in order to increase the effectiveness of those modes of treatment being used.
6.Sometimes it is necessary to shift from a SSRIs antidepressant to the use of cyclobenzaprine as this drug has antidepressant properties whereas some SSRIs cause very severe BB.

7.If occlusal splint use is clinically working well in the patient, the clinician should then focus on the treatment of multiple trigger points that cause headache and joint pain.

XIII. Discussion

Lubricin and HA

Even though an interarticular joint disc is found in the TMJ, the disk by itself does not guarantee that the joint surfaces are not subjected to loading in such a way that friction, erosion and destruction occur. For this reason, two major molecules (lubricin and HA) are synthesized, secreted in the synovial fluid and pushed during jaw function to the articulating surfaces. Lubricin, a mucinous glycoprotein produced by synovial cells and superficial zone chondrocytes provides the so called "boundary lubrication" in the articular components of the TMJ.[13] Lubricin secreted by the synovial fluid of the TMJ protects joint surfaces from wear by reducing friction [30]. Recent investigations point out that lubricin may be degraded and its synthesis may be reduced in pathological conditions in the major components of the TMJ, for instance, disc and cartilage due to a loss of joint lining cells which produce the molecule [4]. Lubricin synthesis may also be reduced by the action of inflammatory cytokines, thus paving the way for the development of osteoarthritic changes in the TMJs.

HA, is a non-sulfate glycosaminoglycan and one of the principal components of synovial fluid playing a major role in the biomechanical properties protecting the synovial joints[3]. HA increases viscosity of the synovial fluid forming a protective film on the joint articulating surfaces[14]. The physiological function o HA is highly dependent on its molecular weight [2].It has been reported that changes in the synovial fluid composition resulting in a high molecular weight HA may eliminate the protective capacity of the articular surfaces increasing erosion and friction[1].

Pathological overloading and failed lubrication

Compressive mechanical stress to the TMJs (overloading) is caused by many factors including loss of posterior teeth, parafunctional behaviors, oral jaw habits and systemic factors affecting the TMJs, for instance, the presence of rheumatoid arthritis. Compressive mechanical stress interferes with the production and secretion of glycosaminoglycans in the TMJ articular disk[36]. Recent studies[18] indicate that excessive mechanical loading on normal articular cartilage supposedly initiates the disruption of cartilage matrix homeostasis resulting in signs and symptoms of TMJ OA. Pathological loading, excessive friction and wear lead to the accumulation of tissue residues or free radicals that initiate molecular events that ultimately result in inflammatory changesleading to OA signs and symptoms [16]. Basically, three types of loading occur in the TMJ: Compression, tension and shear. Isolated or combined jaw motions result in dynamic and static loading. Static loading can be observed during clenching, grinding and bruxism whereas dynamic loading is observed during talking and chewing [11].From a tribological standpoint, shear loading is the most important and when excessive can lead to fatigue, damage to cells and molecules and irreversible deformation of cartilage. Additionally, shear loading is associated with a breakdown of the normal lubrication mechanism in the articular surfaces altering the molecular weight of HA. Frequent and directional shear stress seems to be a particular factor increasing friction and wear and decreasing the capacity of HA to lubricate articular surfaces [11]. Further, the loss of the viscoelasticity of HA is a key element reducing the lubrication capacity of the synovial fluid resulting in deterioration of the joint surfaces [7]. Deterioration of the articulating surfaces is a complex process in which many mechanisms including increased pathological loading,hypoxia, free radicals production, local inflammation,increasedproduction of inflammatory cytokines [21] and altered cell proliferation and function are intermingled.

Management of refractory cases in patients with TMJ-IDs

As explained before, many times, the specialist in CMDs and Orofacial pain is confronted with difficult cases in which longer duration of pain, a combination of disorders, poor diagnosis and history of many consultations and treatments predominate.Such cases are classified under the umbrella of "refractory cases". These cases should be evaluated comprehensively and are better treated using a combination of modes of therapy, longer period of treatment, counseling, antidepressants and sometimes referral for psychological intervention may be necessary. Such cases are usually characterized by the presence of multiple etiological factors including increased loading to the joints,severe BB and other oral jaw habits, severe trauma, anxiety, depression, and somatization. Chronic long-standing pain and dysfunction result in physiological changes and remodeling events leading to significant difficulties in providing treatment[37]. Surgery is recommended only in the most complex cases which cannot be treated by anon-specialist in the field[38]. Clinical cases in which patients report the presence of long-standing and severe pain and dysfunction of the TMJs indicate a significant risk for poor recovery and the need for interdisciplinary intervention and longer treatment period[39].Many of these cases indicate the need to use a multidisciplinary treatment team including longer treatment period, non-conventional modes of therapy including surgery, psychological intervention, arthrocentesis and viscosupplementation[40].

Conclusions

Based on the review of the literature to carry out this investigation, the following conclusion can be drawn: The normal functioning of the TMJs depends largely in the capacity of the articulating surfaces to contact with a minimum of friction and wear. Excessive loading in the interphase joint disk-mandibular condylar is one of many mechanisms responsible for disk displacement and inflammation in the innervatedand vascularized surfaces of the TMJ. Large peak loads in the articulating surfaces of the TMJ cause significant damage to the cartilage layers of the mandibular condylar paving the way for the development of osteoarthritic changes, poor lubrication, oxidative stress, and the transformation of lubricating low molecular weight to high molecular weight molecules. HA and lubricin are two major molecules produced in the synovial fluid of the TMJ by synoviocytes and other cells of the connective tissue in the synovial membrane of the TMJ.

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Bruno R Simiao, et. al. "Basic Biological MechanismsImpairing Lubrication in severe Cases of Temporomandibular Joint Internal Derangements: Update and Review.." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 22(1), 2023, pp. 49-59.