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Lubrication of the Temporomandibular Joint

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Abstract—Although tissue engineering of the temporomandibular joint (TMJ) structures is in its infancy, tissue engineering provides the revolutionary possibility for treatment of temporomandibular disorders (TMDs). Recently, several reviews have provided a summary of knowledge of TMJ structure and function at the biochemical, cellular, or mechanical level for tissue engineering of mandibular cartilage, bone and the TMJ disc. As the TMJ enables large relative movements, joint lubrication can be considered of great importance for an understanding of the dynamics of the TMJ. The tribological characteristics of the TMJ are essential for reconstruction and tissue engineering of the joint. The purpose of this review is to provide a summary of advances relevant to the tribological characteristics of the TMJ and to serve as a reference for future research in this field. This review consists of four parts. Part 1 is a brief review of the anatomy and function of the TMJ articular components. In Part 2, the biomechanical and biochemical factors associated with joint lubrication are described: the articular surface topology with microscopic surface roughness and the biomechanical loading during jaw movements. Part 3 includes lubrication theories and possible mechanisms for breakdown of joint lubrication. Finally, in Part 4, the requirement and possibility of tissue engineering for treatment of TMDs with degenerative changes as a future treatment regimen will be discussed in a tribological context.

Keywords—Temporomandibular joint, Joint lubrication, Joint tribology, Temporomandibular disorders, Tissue engineering.

INTRODUCTION

Joints are formed between bones during the growth of the skeleton.[122] These so-called diarthrodial joints or synovial joints allow various degrees of relative motion of the bones produced by surrounding muscle forces.[175] The bone ends come together within a fibrous joint capsule. The inner lining of this joint capsule is a metabolically active tissue, known as the synovium. The ends of the bones are covered by a thin and highly deformable layer of dense connective tissue known as articular cartilage.[175] There are two types of articular cartilage; hyaline cartilage and fibrocartilage. The joint cavity, formed by the cartilaginous surfaces and the synovium, is filled with a small amount of synovial fluid. Ligaments, tendons, and other soft tissues inside and outside the joint cavity give stability to the joint and maintain the proper alignment of the articulating bone ends during motion.[175] Daily activity accompanies joint motion, resulting in joint loads. These loads must be sustained by these biological bearings, the diarthrodial joints, with tribological characteristics such as friction, lubrication, and wear.[114]

The temporomandibular joint (TMJ) is one of the diarthrodial synovial joints in human body. Like other synovial joints, the TMJ enables large relative movements between separate bones.[61,128] A dense fibrocartilaginous articular disc is located between the bones in each TMJ. The TMJ disc divides the joint cavity into two compartments (superior and inferior) and is a structure with an important functional role. The disc provides a largely passive movable articular surface accommodating the translatory movement made by the condyle. In fact, the condyle undertakes translatory as well as rotary movement and therefore the human TMJ is also described as a synovial sliding-ginglymus joint.

Since the fibrocartilage covering both the TMJ condyle and articular eminence is avascular, intra-articular synovial fluid provides nourishment to these fibrocartilage cells, which also have limited ability for self-repair.[15,56,158] The fibrocartilaginous nature of the TMJ disc and articular cartilage, along with the lubrication function of the intra-articular synovial fluid, allow the cartilaginous structures of the TMJ to conform under function and ensure that loads are absorbed and spread over larger contact areas.[43,120,133,165,166]

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Like other synovial joints, the articular surfaces of the TMJ are highly incongruent. Due to this incongruency, the contact areas of the opposing articular surfaces in the absence of the TMJ disc would be very small, and upon joint loading this would lead to large peak loads and friction. The presence of the TMJ disc, articular cartilage, and synovial fluid in this joint is believed to prevent these peak loads,[43,120,133,165,166] as the TMJ disc is capable of deforming and adapting its shape to that of the articular surfaces. During jaw movement, the disc moves with respect to both the mandibular condyle and the articular eminence. When the disc slides along the articular surfaces, shear loading of the disc has been considered to be negligible, due to very low friction.[119] Unfortunately, the pristine structures of the articular surfaces often deteriorate with aging, internal derangement, and arthritis, becoming increasingly roughened and eroded, with development of pain and dysfunction, and progressing to osteoarthritis (OA). Internal derangement of the TMJ is defined as an abnormal positional relationship of the disc relative to the mandibular condyle and the articular eminence, and is classified in terms of a series of five stages of increasing severity.[179] It should be noted that internal derangement frequently precedes the onset of TMJ–OA. The process of TMJ–OA is characterized by degenerative joint changes such as deterioration and abrasion of articular cartilage and disc surfaces, and occurrence of thickening and remodeling of the underlying bone. These could lead to a reduction in boundary lubrication between the articular surfaces, resulting in an increase of the frictional coefficient.[120] As a consequence, joint lubrication can be considered of great importance for an understanding of the dynamics of the TMJ. More information about the tribological characteristics of the TMJ are essential for reconstruction and tissue engineering of the joint.

To date, our understanding of diarthrodial joint lubrication is based on knowledge of the structural and deformational characteristics of articular cartilage, the biochemical and biorheological properties of synovial fluid, the topological design and microscopic roughness of the articulating surfaces of the joint, the kinematics of the joints, and the subsequent biomechanical loading on the articular surfaces. This review is divided into four parts. Part 1 will review the anatomy and function of the TMJ articular components, articular cartilage, disc, and synovial fluid. Part 2 will discuss the biomechanical and biochemical factors associated with regulation of joint lubrication: the articular surface topology with microscopic surface roughness and the biomechanical loading during jaw movements. Part 3 includes lubrication theories (boundary lubrication and fluid film lubrication) and possible mechanisms for breakdown of joint lubrication. Finally, in Part 4, the requirement and possibility of artificial replacements and tissue engineering for treatment of TMJ–OA with degenerative changes will be discussed.

PART 1: ANATOMY AND FUNCTION OF ARTICULAR COMPONENTS IN THE TMJ (FIG. 1)

TMJ Disc

The TMJ disc is composed of variable amounts of cells and extracellular matrix. It is noteworthy that the characterization data in the literature are derived from a number of animal species (especially rats, rabbits, dogs, cows, and pigs) in addition to humans,[42] and thus inherent interspecies differences are reflected in differences in data sets among related studies. The extracellular matrix is composed of macromolecules and fluid. The macromolecules comprise about 15–35% of the wet weight of the disc, while the tissue fluid comprises about 65–80%.[48,117,118,148] The dry weight of the TMJ disc consists mainly of collagen (68–83%)

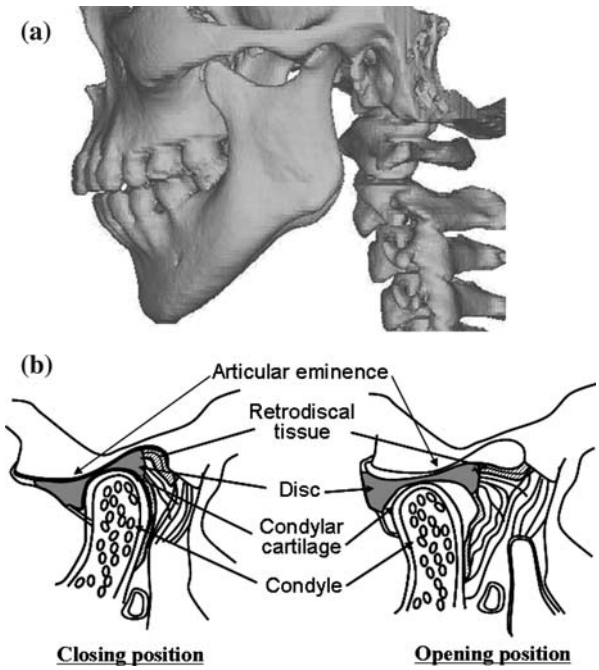

FIGURE 1. (a) Side view of the human skull by means of CT images. (b) Sagittal views of the TMJ. The TMJ consists of the bone components (mandibular condyle and articular eminence) and soft tissues (condylar cartilage, fossa cartilage, joint capsule, articular disc, and retrodiscal tissue). In the healthy joint, the articular disc moves forward and downward when the mandibular condyle moves along the posterior slope of the articular eminence (mouth opening). Both at closing and opening position, the disc is located between the two bone components. The articular surfaces are covered with thin fibrous layers. Synovial fluid inside the joints acts as a lubricant during movement.

and proteoglycans (0.6–10%).[13,19,48,117,118,148] The cells of the TMJ disc are a heterogeneous combination of fibrochondrocytes and fibroblast-like cells, which are distinctly different from chondrocytes of hyaline cartilage [26,47,90,105,106,108,128,133] (Fig. 1).

Collagen fibers maintain the shape of the disc, while elastin is associated with restoration of shape during unloading.[133] Collagen fibers commonly exhibit waviness (''crimping''). When tension is applied to the disc, the first effect is to straighten the crimp; accounting for the initial toe region of the curve.[25,133,155] Beyond this initial phase, the collagen fibers begin to extend and become tensile load-bearing. When further loaded, the collagen network deforms and water is squeezed out of the disc while the orientation of the collagen fibers is rearranged.[25] The rearrangement of the collagen fibers is reversible when the disc is not deformed beyond the physiologic strain range. This enables the disc to continuously adapt its shape to fit in the space between the opposing articular surfaces and to suitably distribute loads in the TMJ. Collagen gives the disc much of its tensile stiffness and strength. The thin surface layers of the disc have a different architecture from the thick inner layer.[134] In the superior and inferior surface layers, the collagen fibers are more or less perpendicularly arranged in an anteroposterior and mediolateral direction.[107] In the inner layer, the orientation of collagen fibers varies markedly in different regions of the disc. The fibers run primarily anteroposteriorly in the intermediate zone and mediolaterally in the anterior and posterior bands. The anteroposterior fibers from the intermediate zone are interlaced with the mediolateral fibers in both bands.[168] In the central region of the bands, the fibers from the intermediate zone flare superiorly and inferiorly and turn medially and laterally, merging structurally with those of the bands.[106,133] In the medial and lateral regions of the disc, near the condylar poles, the anteroposterior fibers of the intermediate zone are attached tightly to the poles of the condyle.[168] These differences in collagen fiber orientation are associated with the regional differences and anisotropy in the mechanical properties of the disc as described afterwards.

Proteoglycans are enmeshed in the network of collagen fibers and are virtually immobile. Several proteoglycans are detected in the disc. Biglycan and decorin belong to the group of small proteoglycans, consisting of a core protein of approximately 38 kDa to which either one (decorin) or two (biglycan) chondroitin/dermatan sulfate side-chains are attached.[35,52] Aggrecan is a large proteoglycan containing both chondroitin sulfate and keratan sulfate.[118] Aggrecan molecules possess high viscosity and large molecular size that reduce their capacity to diffuse through the collagen network, resulting in the retention of large amounts of water.[116] The result is a stiff viscoelastic material surrounding the collagen fibers. Because of its molecular structure, aggrecan is ideally suited to resist compressive loading.

Mandibular Condylar Cartilage

The mandibular condyle is covered by a zonal cartilage layer from the articular surface to the underlying bone, which is composed of several zones: the fibrous, proliferative, mature, and hypertrophic zones.[96,109] Essentially, the proliferative zone serves as a separating barrier between the fibrocartilaginous fibrous zone and the hyaline-like mature and hypertrophic zones. The fibrous zone is composed of fibroblast-like cells, which have a flat shape and endoplasmic reticulum surrounded by a dense intercellular matrix of collagen fibrils and ground substance.[87] The proliferative zone plays an important role as a cell reservoir, which has mesenchymal cells distributed heterogeneously as chondrocyte precursors for the underlying zones.[28] Differentiated chondrocytes are found in the mature and hypertrophic zones, where the degeneration of chondrocytes has been noted closer to the subchondral bone.[87] The collagen fibers of fibrocartilage are arranged in several distinct zones,[37] and provide mainly tensile and shear strength to the cartilage, whereas resistance to compressive forces is due to the presence of proteoglycans.[101,155] Regarding the collagen types, collagen type I is found throughout all of the mandibular condylar cartilage zones.[40] Collagen type II and X, commonly found in hyaline cartilage, are abundant in the mature and hypertrophic zones.[170] When cartilage is loaded by compression, the small permeability of the collagen network impedes interstitial fluid flow through the collagen network.[112] These features contribute to the viscoelastic properties of cartilage. In the articular cartilage, collagen forms a three-dimensional network and thus impacts the cartilage form, stability and tensile strength and resistance to shear forces. From MR assessment, the collagen matrix is organized in an arched structure.[63] The fibers curve from a radial orientation at the subchondral bone into a tangential orientation at the articular surface.[63] Then, on the articular surfaces collagen fibers run in parallel. In the mandibular condylar cartilage, collagen fibers mainly run in the anteroposterior direction,[149] which may be an optimized structure concerning resistance to anteroposterior shear forces.

The major proteoglycan in the mandibular condylar cartilage is aggrecan. Aggrecan is mainly located in the hypertrophic and mature zones.[101,130] Aggrecan provides osmotic swelling pressure to the cartilage and enables it to resist compressive loads.[101,130] Versican and decorin have also been reported in the mandibular condylar cartilage.[39,101,130]

Synovial Fluid

Synovial fluid is a viscous gel and contains mostly water. This fluid acts as a lubricant in the upper and lower compartments of the TMJ as well as acting as a vehicle for nutrients as it passes through the surface layers of the disc and articular cartilage layers.[84,165] The collagen and proteoglycans are dispersed in the fluid, making the cartilage a microporous material with a certain permeability. The mechanical response of the disc to compression depends on the permeability.[85] A low permeability means that any significant exchange of fluid between the inside and outside of the disc must take place over a period of time (e.g., minutes) compared to the physiological loading cycle (1 s). As a consequence, the disc maintains its stiffness under compression. In the case of high permeability, a rapid exchange of fluid is possible that results in a substantial decrease in disc stiffness. It should be noted that stress relaxation under compression occurs rapidly in the TMJ disc, with viscoelastic time constants on the order of 5–50 s.[8] By comparison, stress relaxation under tension is much slower.[44,149]

The synovial membrane lines the inner surface of the joint capsule. It contains specialized cell types with phagocytic and immunologic capacity, and produces the synovial fluid that provides the nutritional and metabolic requirements to the avascular tissues of the mandibular condylar and articular eminence fibrocartilage as well as to the disc. It also serves as a joint lubricant.

Hyaluronic acid (HA), 0.14–0.36% of synovial fluid in normal subjects,[156] is one of the principal components determining the rheological properties of synovial fluid, especially the viscosity.[182] Synovial viscosity depends on both the concentration of HA and its molecular weight.[38,88,182] In synovial fluid, HA with high molecular weight released by type B synovial cells is generally believed to be essential for lubrication of joints by reducing friction.[22,129] Meanwhile, in joints afflicted with OA, the synovial fluid has reduced viscosity due to the decrease in both concentration and molecular weight of HA[84,110] (see Part 2).

PART 2: BIOMECHANICAL AND BIOCHEMICAL FACTORS ASSOCIATED WITH REGULATION OF JOINT LUBRICATION

Microscopic Roughness of the Articular Surfaces

The durability of joints depends primarily on their ability to articulate with low friction and wear, which are reduced by pathologies such as arthritis.[51] Fluid films from 0.5–2 μm are required to separate the articular cartilage surfaces with roughnesses on the order of 1 μm.[51,81] These films are only achieved with high-viscosity synovial fluid (see "Biochemical Compositions of Lubricant" section). However, mechanisms other than fluid film lubrication are required to protect cartilage over a lifetime of use. For example, high molecular weight proteins, phospholipids and glycoprotein complexes at the cartilage surface may provide a certain level of lubrication and temporary protection. In addition, models have shown that the highly porous nature of cartilage at its surface is capable of maintaining effective lubrication even in the absence of weeping flow, as only about 1% of the total contact area of cartilage layer interactions consists of solid–solid contacts, where friction occurs.[151] Therefore, the initial friction coefficient following an applied load is decreased by trapped lubricant at the surface, independent of squeeze-film lubrication effects.[151] However, it has been suggested that although compressive stresses prevent the initiation of fissures in a healthy joint, that normal movements in a pathological joint with a thin synovial fluid layer can easily cause fissures.[82]

A classic overview of surface characteristics of articular cartilage was presented in the mid 1970s.[113] To put cartilage roughness dimensions in perspective, typical center line average (CLA) values of surface finishes are 0.05–0.2 μm for superfinishing, 0.1–0.5 μm for polishing, 0.1–2 μm for grinding, and 1–6 μm for milling.[127] The CLA is the arithmetical average deviation from the center line, essentially the average roughness height. In comparison, early studies found the CLA of fetal cartilage to be 1 μm, compared to 2.75 μm for 67-year-old cartilage and 5.25 μm for osteoarthritic cartilage.[181] Average surface roughnesses of bovine femoral cartilages have been measured on the order of 1 μm by interferometry and laser profilometry.[54,60] This roughness was seen to increase from 800 ± 200 to 2100 ± 200 nm when the cartilage was loaded under contact with metal.[54] Roughnesses of loaded articular surfaces of rabbit knees were measured at 10–30 nm, which was less than that observed in unloaded joints.[36] Interestingly, irregularities of one surface had little or no effect on the contour of the opposite surface due to the fluid-containing space in between.[36]

The surface roughness of TMJ cartilages has scarcely been studied. Optical profilometry of cadaveric mandibular condyles revealed roughnesses of 30 ± 5 μm for healthy smooth surfaces and 140 ± 9 μm for remodeled condyles.[49] Using an atomic force microscope (AFM), the superficial zone of mandibular condyles of 7-day-old rabbit exhibited roughnesses varying from 95 to 130 nm.[125]

Essentially, there is a cause and effect cycle between surface roughness and joint function, as the

roughness will influence friction and wear, and degenerative joint pathologies will adversely affect roughness. In macrosystems, roughness is the main controlling factor of friction.[137] Macroscale friction is chiefly the result of mechanical interlock caused by the roughness of the contacting surfaces, whereas nanoscale stick/slips are caused by atomic roughness.[137] Adhesion and friction forces have an inverse relationship with roughness, both increasing as roughness decreases.[137] In the presence of synovial fluid, the rougher the surface, the smaller the contact area, and decreasing contact area decreases friction due to a lower probability of liquid bridging. However, if synovial fluid is absent, macroscale friction force increases with roughness as a result of mechanical interlock.[137]

The first study to relate microscale AFM measurements of the friction coefficient of articular cartilage with measurements at the macroscale level found that the microscale AFM friction coefficient correlated well with the macroscale equilibrium friction coefficient, representing the friction response in the absence of cartilage interstitial fluid pressurization.[124] However, the articular surface roughness of bovine humeral heads (462 ± 216 nm) was not found to correlate significantly with friction coefficients, as measured with AFM.

Recently, a model was developed for understanding the effects of both surface roughness and couple stresses on synovial joint lubrication.[31] It was found that roughness increased load carrying capacity relative to a smooth surface, which was attributed to a rougher surface reducing the leakage of lubricant and increasing the pressure in the film region.

In summary, we are aware that micro-scale roughness and porosity of the articular cartilage surface provide for better lubrication than if the cartilage were a completely solid and smooth surface, and we are also aware that degenerative diseases appear to increase the apparent roughness. This apparent paradox can be explained by the number of other factors that lead to the breakdown of the lubrication system in these pathological cases. For example, a biphasic poroviscoelastic model has shown that a significant increase in permeability results from the absence of the superficial zone, as when damaged or fibrillated from arthritis or impact trauma.[147] Moreover, pathological cases are accompanied by a reduction in synovial fluid viscosity[181] and the presence of inflammatory cytokines. The micro-scale roughness is an integral part of the functioning tribology of healthy mandibular condylar cartilage, although its contribution in pathological cases is overshadowed by predominant factors that lead to the breakdown of the lubrication mechanisms.

Biomechanical Loading in the TMJ During Jaw Movements

Mandibular motions are divided into continuous and intermittent motion. These motions, sometimes combined together, result in static and dynamic loading in the TMJ, respectively. Static loading occurs, for example, during clenching, grinding, and bruxism; dynamic loading occurs during, for example, talking and chewing. Mechanical loading in the TMJ is necessary for the growth, development and maintenance of the joint tissue. Generally, dynamic loading is likely to lead to an anabolic effect for the joint tissues, while static loading, if prolonged or excessive, induces a catabolic effect. As both sliding and rotating with slightly lateral excursion occur simultaneously between articulating surfaces, the TMJ is subjected to a multitude of different loading regions during mandibular movements. Basically, three types of loading can be distinguished: compression, tension, and shear. Obviously, during natural loading of the joint, combinations of these basic types of loading do occur on the articulating surfaces. During every type of loading, the joint tissues such as articular cartilage and fibrocartilaginous disc undergo a deformation (strain) commensurate with their material properties, while internal forces are produced within the tissue.

Numerous works have focused primarily on calculating the absolute magnitude of TMJ loading with finite element models. Previously reported magnitudes of TMJ loading, however, differ significantly from one another because of different simulated conditions such as jaw geometry and musculature. For this reason, and due to large discrepancies in direct measurements as well, there is currently no universally agreed-upon value of TMJ loading. Our understanding is that the loading distribution produced by masticatory muscle forces during various mandibular movements is largely dependent on the biomechanical properties of the joint tissues, and that these properties are in turn dependent on the loading environment.

As described in our previous reviews,[43,165,174] the TMJ disc and condylar cartilage are viscoelastic, being frequency-, region-, direction-, and time-dependent in nature. For evaluation of the basic biomechanical characteristic of a tissue, the elastic modulus or relaxed modulus is commonly used. This elastic modulus is defined as the slope of the elastic region of the stress–strain curve. With respect to the disc, tensile studies have shown that the disc is stiffer and stronger in the anterior and posterior bands than in the intermediate zone in the mediolateral direction.[43,169] Furthermore, through its center, the disc is stiffer under tension and shear in the anteroposterior direction than in the mediolateral direction. For example, the tensile

modulus of the porcine disc was 76.4 MPa in the anteroposterior direction, whereas it was 3.2 MPa in the mediolateral direction (strain rate, 500 mm/min[24]). This is due to the orientation of collagen fibers of the disc. Also in shear, the elastic modulus of the disc was about one-third smaller in the mediolateral direction than in the anteroposterior direction.[160] Under compression, regional studies of the disc are contradictory, but more evidence suggests that the disc is stiffer in the center than in the periphery.[7,43] The resistance to compression is mainly dependent on the density of proteoglycans, especially of the large chondroitin-sulfate molecules. Since the distribution and amount of the proteoglycans are different in various regions of the disc and articular cartilage, regional differences in its compressive modulus can be explained. Although the results of the various studies cannot be easily compared due to the large interspecies variation and different experimental protocols, the compressive modulus of the disc is considered to be smaller than its tensile modulus.

Of the three types of loading, shear loading is the most important from a tribological perspective. Shear can result in fatigue, damage, and irreversible deformation of cartilage.[152,183,184] Furthermore, shear stress is associated with a breakdown of joint lubrication through a reduction of HA molecular weight (see Part 3). Previously our works have demonstrated that the shear behavior of the discs was dependent on the frequency and direction of shear load.[160,162] In other studies it was reported that the shear stress in cartilage was very sensitive not only to the frequency and direction of the loading, but also to the amount of shear and compressive strain.[115,152,183] This implies that the shear stress induced in the disc may be dependent on the compressive strain when the frequency and direction of the shear loading are kept constant. The dynamic shear properties of the disc are anisotropic. That is, the dynamic shear modulus of the disc is significantly larger in anteroposteriorly than in mediolaterally applied shear strain.[160] The anisotropic behavior of the disc is mainly dependent on the orientation of collagen fibers as well as the tensile modulus. This implies that upon mediolateral shear deformation the collagen network bears a larger part of the loads and therefore, could be more vulnerable to damage.

The mandibular condylar cartilage is a nonlinear viscoelastic material, as is the TMJ disc. Anisotropy of the mechanical properties in mandibular condylar cartilage is confirmed by greater average tensile strength, tensile stiffness, and energy absorption in the anteroposterior direction than in the mediolateral direction. The reported Young's moduli in the anteroposterior and mediolateral directions were, respectively, 9.0 and 6.6 MPa.[83] Under dynamic compression, the dynamic elastic and viscous moduli were 1.36 and 0.34 MPa at a frequency of 1.0 Hz, respectively.[166] Significant regional differences in the dynamic properties were detected, and the anterior area revealed significantly higher moduli than the posterior area.[166] These findings were in agreement with the nanoindentation findings of Hu *et al.*[76] The resistance to compression is mainly dependent on the density of proteoglycans, especially of the large chondroitin-sulfate molecules. As the distribution and amount of the proteoglycans are different in various regions of the mandibular condylar cartilage, regional differences in its compressive modulus can be explained. With respect to the dynamic shear modulus in the anteroposterior direction, the dynamic elastic and viscous moduli were, respectively, 1.56 and 0.34 MPa at a frequency of 2.0 Hz[164] and these values were almost the same as those in dynamic compression.[166] In contrast, the dynamic shear moduli in the mediolateral direction were about 30% of those in the anteroposterior direction (data not published), which implies that the dynamic shear behavior of mandibular condylar cartilage is also anisotropic. As described above, shear loading can induce a breakdown of cartilage. Therefore, the shear characteristics suggest that mandibular condylar cartilage has a weak resistance to mediolateral shear stress, which might lead to degradation of articular cartilage and synovial fluid.

Biochemical Compositions of Lubricant

HA in synovial fluid has been believed to be a crucial factor in articular joint lubrication.[30,150] The rheological property of HA in solution is characterized by remarkably high viscoelasticity.[21,57] High molecular weight HA plays an important role in maintaining the viscoelasticity of synovial fluid, whereas the increase of low molecular weight HA results in a reduction in the viscoelasticity, leading to the deterioration of joint lubrication[88] (see Part 3).

HA imparts viscoelastic character to the solution due to its specific structure, which is generally explained as random coil-entanglement. HA is a glycosaminoglycan consisting of repeated disaccharide units of D-glucuronic acid and *N*-acetyl-D-glucosamine and with high molecular weight (800–1900 kDa) in its native state.[91] The secondary and tertiary structures of HA in solution have been examined by means of rotary shadowing-electron microscopy[143] and NMR.[66,145,146] The HA forms reversible and ordered aggregates, extensively branched networks at physiological temperature in solution.[143] This dynamic network formation is affected both by its concentration and molecular weight, resulting in changes in its

viscoelastic behavior.[30,88,111,143,144] Increasing the molecular weight more effectively enhances the HA network formation than the concentration.[88] High molecular weight HA strands in solution have no ends, whereas low molecular weight HA forms islands of meshworks under similar conditions.[143] The enzymatic digestion of HA resulted in lower stability,[145] suggesting that stable intermolecular interactions can be achieved by high molecular weight HA. In contrast, low molecular weight HA disrupts the intermolecular network formation by high molecular weight HA.[177]

The accumulation of lower molecular weight HA in synovial fluid has been suggested to be due to various mechanisms such as depolymerization with reactive oxygen species (ROS),[93,102] enzymatic cleavage[123] and newly synthesized low molecular weight HA.[167] IL-1β, TNF-α, and IFN-γ are highly distributed in the synovial fluid of joints with degenerative disease such as OA and rheumatoid arthritis (RA).[75,138,176] A number of previous *in vitro* studies supported cytokine-induced HA synthesis, and the accumulation of low molecular weight HA in cultured synoviocytes.[32,64,77,89,104] Low molecular weight HA modulates immune or inflammatory processes[71,89] and decreases the viscoelasticity of synovial fluid.

Several molecules locally present in synovial fluid have been reported to contribute to joint lubrication, especially boundary lubrication.[53,78,132,140] Among them, surface active phospholipids (SAPLs) are considered to be mostly responsible for the boundary lubrication of the articular cartilage surface by reducing the kinetic friction.[53,69,132] Surface active phospholipids have been suggested to be coupled with HA under healthy conditions.[53,121] Dipalmitoyl phosphatidylcholine (DPPC), the predominant surface active component, synergistically enhanced lubricating ability when mixed with HA.[53] In addition, SAPLs are protected by adhesion to the high-molecular weight HA from phospholipase A_2 (PLA_2), with the SAPL-lysing enzyme secreted in synovial fluid[121] (see Part 3).

A mucinous glycoprotein called lubricin, also known as PRG4[78] or articular cartilage superficial zone protein (SZP),[140] is found in the synovial fluid. Lubricin provides boundary lubrication of articular surfaces under high contact pressure and quite low sliding speed.[80] Since the boundary lubricant needs to be adsorbed to the surface before it exerts its ability, lubricin may contribute to boundary lubrication as a water-soluble carrier of SAPLs,[70,142] although the detailed lubrication mechanism associated with lubricin is still unclear.

From these findings, it is suggested that the various contents of synovial fluid contribute to articular joint lubrication, and maintain the lubrication ability by synergistic interactions. Overloading and subsequent deterioration of these lubricants may cause high friction in joints, resulting in degenerative diseases.

PART 3: DEVELOPMENT THEORY AND BREAKDOWN MECHANISM FOR TMJ LUBRICATION

Lubrication Theory

A number of physicochemical modes of lubrication occur in synovial joints and have been classified as fluid film and boundary. The former mainly depends on a synovial fluid, and the latter on articular components such as articular cartilage and the fibrocartilaginous disc. One type of fluid-mediated lubrication mode is hydrostatic. At the onset of loading and after a prolonged loading, the interstitial fluid within cartilage becomes pressurized, due to the biphasic nature of the tissue; fluid may also be forced into asperities between articular surfaces through a weeping mechanism.[139] Pressurized interstitial fluid and trapped lubricant pools may therefore contribute significantly to the bearing of normal load with little resistance to shear force, facilitating a very low friction coefficient.[17] In addition, at the onset of loading and/or motion, squeeze film, hydrodynamic, and elastohydrodynamic types of fluid film lubrication occur, with pressurization, motion, and deformation acting to drive viscous lubricant from and/or through the gap between the two surfaces in relative motion.[139] The normal frictional coefficient between the cartilage surfaces of synovial joints is reported to be within a range of 0.001–0.1 (Fig. 2).[54,94,97,98] This coefficient may increase due to deterioration in the lubrication mechanism.[16,18,94] This mechanism is primarily dependent on the synovial fluid, where HA is considered to be the primary effective constituent.[98,141] However, the composition of the lubricant may change upon joint loading, because then it mixes with water, which is exuded out of the cartilaginous tissue when it is compressed.[55]

A number of studies are available concerning joint lubrication, which strongly suggest that SAPLs provide highly efficient boundary lubrication and act as protectors of the articular surfaces (Fig. 3).[68,142] SAPLs are associated with lubricin. According to Nitzan,[120] SAPLs are polar lipids that bind to the articular surface by their polar ends, thus orientating their non-polar moieties outward. The latter impart a hydrophobic surface, which has a relatively low surface energy that is much less conductive to friction than the articular surface without SAPLs. The hydrogen bonds between the phospholipid molecules provide excellent cohesion, a factor on which load bearing is dependent.[68] In contrast, HA is a multipotential, high

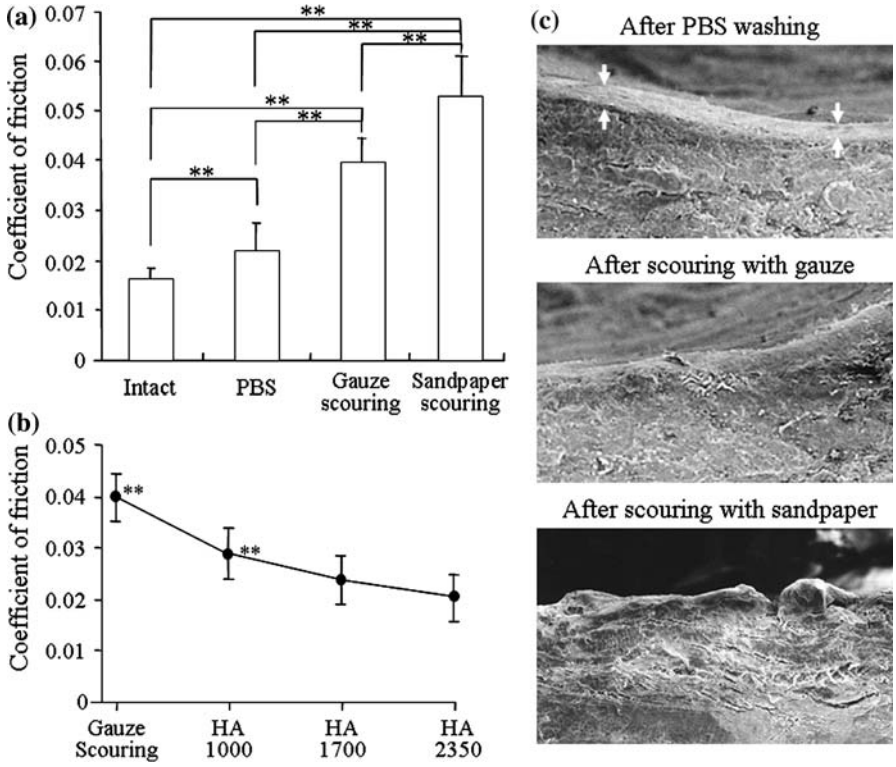

FIGURE 2. (a) Frictional coefficients of the TMJ measured by a pendulum type friction tester. Means and standard deviations of frictional coefficient are provided for the TMJ, as measured in the intact joint and after washing with PBS and scouring with gauze and sandpaper. Double asterisks indicate a significant difference between the groups at 1% of confidence.[84,159,161] (b) Frictional coefficients of the TMJ after scouring with gauze, and the effect of the application of HA with different molecular weights and concentration in the TMJ with experimentally reduced lubricating ability. The error bars indicate standard deviations. Double asterisks indicate a significant difference between the groups at 1% of confidence.[84,159,161] (C) Microscopic observations of the cartilage surfaces by scanning electron microscopy after PBS washing and scouring with gauze and sandpaper. After PBS washing, the amorphous layer (arrows) still existed. After scouring with gauze, the amorphous layer collapsed in part although the congruent articular surface still existed. After scouring with sandpaper, the amorphous layer was completely disrupted and the inner layer exposed as an irregular surface.[84,159,161]

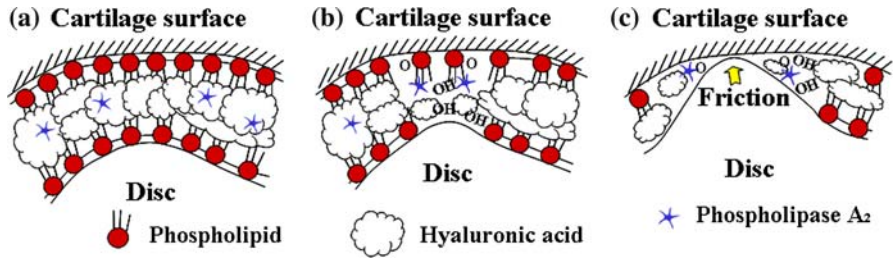

FIGURE 3. Concepts of a breakdown of TMJ lubrication. (a) According to Nitzan,[120] SAPLs are polar lipids that bind to the articular surface by their polar ends. In the healthy joint, the hydrogen bonds between the phospholipid molecules provide excellent cohesion. PLA_2 poses a constant threat to the continuity of SAPL layers, and HA adheres to the SAPLs, protecting their continuity from lysis by PLA_2. (b) Overloading may impair the lubrication by biochemical reaction. The excessive loading decreases the blood flow and causes hypoxia in the joint. On reperfusion, xanthine oxidase generates reactive oxygen species (ROS) in the presence of re-supplied oxygen with hypoxanthine as a substance. ROS in joints inhibits the biosynthesis of HA and degrades it. Reduction of HA causes not only a decrease in viscosity of synovial fluid, but also an inability to protect phospholipids from PLA_2. (c) On lysis of the SAPLs, the articular surfaces are stripped of their lubricants, and as a result, friction is generated between the exposed surfaces of the disc and articular eminence.

molecular weight, viscous component of the synovial fluid that has a negligible load-bearing capacity.[79,92] To date, an important indirect role in the lubrication process has been assigned to HA especially with high-molecular-weight. PLA_2, which is secreted by the synoviocytes, chondrocytes, and osteoblasts into the synovial fluid, poses a constant threat to the continuity of SAPL layers.[173] An *in vitro* study showed that

dose-dependent inhibition of PLA_2 activity occurred in the presence of increasing concentration and molecular weight of HA.[121] It has also been shown that the high-molecular-weight HA actually adheres to SAPLs, protecting their continuity from lysis by PLA_2.[121]

Breakdown Mechanism

The major cause of breakdown of the joint lubrication is overloading.[55,120,163] The lubrication of synovial joints generally accepted is the multimodal, including fluid film and boundary mechanisms. Fluid film lubrication is the dominant mechanism and joints can withstand dynamic and static loading by this lubricating mechanism as long as the loading is not excessive. However, fluid film lubrication exists only during short periods of overloading. After prolonged overloading, only solid contact may exist between the articular surfaces, and then there is probably no longer any fluid film lubrication but only boundary lubrication.[97,163] That is to say, the fluid film lubrication of synovial joints achieves low friction only when the articular surfaces are kept apart; then the lubricating mode is changed to boundary lubrication, because the squeeze film mechanism is disrupted due to the thinning of the fluid film and the solid contact of articular surfaces.

Overloading also impairs lubrication by biochemical reaction. The loading pressure that exceeds the capillary perfusion pressure decreases blood flow and causes hypoxia in the joint.[29] Under hypoxia, adenosine triphosphate (ATP) is degraded to hypoxanthine. When the joint is released from the loading pressure, blood flow recovers and oxygen is supplied to intracapsular tissues. On reperfusion, xanthine oxidase generates superoxide in the presence of re-supplied oxygen with hypoxanthine as a substance. This mechanism is hypoxic-reperfusion injury and it explains the production of ROS in the joint on overloading (Fig. 3).[29] ROS in joints inhibits the biosynthesis of HA and degrades it.[62] Articular surfaces are covered with a phospholipid that is attached to HA as a fluid film, and HA in the joint space protects phospholipids from PLA_2. Reduction of HA causes not only a decrease in viscosity of synovial fluid, but also an inability to protect phospholipids from PLA_2.[121] As a result, the lubrication of the joint breaks down.

Friction in synovial joints is associated with its lubrication mechanism, and breakdown of the joint lubrication increases friction in joints.[16,94] It is generally accepted that increased friction in the joint is a major contributing factor in disc displacement.[120] Tanaka *et al.*[159,161,163] and Kawai *et al.*[84] investigated the association between friction in the porcine TMJ and the condition of the joint lubrication by using a pendulum-type friction tester. To experimentally mimic pathology, the joint space and disc surface were washed with phosphate-buffered saline (PBS) to replace the synovial fluid with PBS, and the cartilage and disc surface were scoured with PBS gauze or sandpaper to remove the fluid film. The frictional coefficient of the TMJ increased with the duration of loading because the fluid film got thinner and fluid film lubrication was damaged. The more the TMJ was damaged, the more friction in the TMJ was increased. Therefore, it is likely that overloading the TMJ increases the friction by damaging fluid film lubrication, and in the impaired TMJ, friction increases markedly because of reduction in viscosity of the synovial fluid and damage to the fluid film. The articular disc is important to the lubrication. The frictional coefficient of the TMJ was increased significantly by removal of the TMJ disc.[159] This means that the friction in the diseased TMJ, especially in which the disc is displaced, is large and the damage of the TMJ may progress to OA under large shear stresses. As described above, HA has an important role in lubrication, but HA in the synovial fluid of the damaged TMJ can be degraded.[157] The addition of HA to the damaged TMJ was proven effective in reducing the friction.[84,159,161] However, the frictional coefficient did not recover to the level of the intact TMJ.

In a clinical setting, HA injection into the TMJ has been attempted for use as a treatment remedy of TMDs with severe pain and movement disability, although HA injection has not yet been FDA approved for use in the TMJ. In double blind studies in other joints after 2–12 months, HA has been shown to provide significantly better results than saline. However, no significant differences were noted in radiographic progression of the disease.[95] In the TMJ, Bertolami *et al.*[27] reported that when using HA in TMJ–OA cases, there were no differences in outcomes among the placebo and saline control group measured variables. Meanwhile, Alpaslan and Alpaslan[14] reported that arthrocentesis with the addition of HA revealed superior results compared to that without HA addition, although arthrocentesis both with and without HA provided beneficial results. Consequently, the effectiveness of HA injection into the TMJ is still controversial.

PART 4: LOOKING TO THE FUTURE

Requirement and Possibility of Artificial Replacement and Tissue Engineering for TMJ

Joint Lubrication in Tissue Engineering Strategy

It is clear that as a result of a breakdown in the lubrication system of the TMJ the tissues may be

irreparably destroyed. While more conservative treatments are preferred when possible, in severe cases or after multiple operations, the current end stage treatment is total joint replacement. There are now long-term studies available in the literature that support the safety and efficacy of total joint replacement under appropriate circumstances.[103] The next generation of joint replacements will incorporate live tissues in an effort to reconstruct the joint to its normal state. However, with a few exceptions, orthopedic and craniofacial tissue engineering technology have not yet reached the point where joint lubrication has become an integral part of design strategy. One notable exception is a recent study that proposed a strategy to promote joint lubrication by layering PRG4-secreting superficial zone chondrocytes at the articular surface of an engineered construct.[86] In addition, a recent review of tissue engineering and biomechanics in the knee joint by Ateshian and Hung[17] highlighted the need to match the material properties of the native articular cartilage in tissue engineering to maintain not only the function, but also the lubrication of the joint as well. In another example of considering joint lubrication in tissue engineering, Sander and Nauman[131] have summarized mathematical relationships between microstructure and permeability, with the emphasis that controlling the permeability of a scaffold or engineered construct may assist in providing the desired hydrodynamic lubrication of the joint. Strategies such as these may be essential for successful implementation of engineered constructs. It should be clear from the preceding sections that even with a "good as new" engineered joint, that without a functioning lubrication mechanism the engineered tissues may befall the same fate as the ravaged tissues they replaced.

TMJ Disc Tissue Engineering

The TMJ disc and the mandibular condyle have been the focus of tissue engineering efforts for the TMJ. In the long term, TMJ tissue engineering strategies may need to combine both of these structures into a single implant, perhaps along with other TMJ tissues such as the retrodiscal tissue.[46] Thorough reviews of TMJ disc tissue engineering are available in the literature,[7,9,42,43,59] which describe the structure and function of the TMJ disc in comparison to other cartilages and summarize previous TMJ disc tissue engineering studies. TMJ disc tissue engineering efforts date back to 1991,[171] although the majority of related studies were not published until 2004 or later. Early studies focused on cell source, biomaterials, and shape-specific scaffolds.[58,126,153,171] More recent studies have supported the use of polyglycolic acid (PGA) over agarose,[12] promoted the spinner flask as the preferred seeding method with PGA scaffolds,[12] demonstrated the importance of using growth factors such as platelet-derived growth factor (PDGF)-BB[65] and insulin-like growth factor (IGF)-I,[6,11,41] revealed the detrimental effects of passaging and pellet culture,[5,6] recommended 25 μg/mL as a preferred ascorbic acid concentration,[23] and investigated the effects of hydrostatic pressure[10] and rotating wall bioreactors.[45]

Overall, the TMJ disc tissue engineering studies to date have utilized various cell sources and biomaterials, evaluating the effects of different bioactive signals and bioreactors. The next major investigations into TMJ disc tissue engineering will be the incorporation of stem cell sources and the evaluation of *in vivo* performance of engineered TMJ discs.

Mandibular Condyle/Ramus Tissue Engineering

Although mandibular condyle/ramus tissue engineering studies were not published until this decade, several publications have appeared in the past 5 years, with comprehensive reviews available in the literature.[99,100] The largest contributions, thus far, have come from the groups of Hollister[50,72–74,135,136,180] and Mao.[2–4] Hollister and colleagues have developed a solid free-form fabrication (SFF) method for producing patient-specific condyle-shaped scaffolds based on CT and/or MRI, allowing for precise control over overall shape, internal architecture, pore size, porosity, permeability, and mechanical integrity. Their *in vivo* studies have collectively demonstrated substantial bone ingrowth and glycosaminoglycan (GAG) formation.[73,135,136,180] Mao's group has taken another approach, encapsulating marrow-derived mesenchymal stem cells (MSCs) in a polyethylene glycol diacrylate (PEG-DA) hydrogel to create stratified bone and cartilage layers in the shape of a human condyle. After 12 weeks *in vivo*, it was shown that collagen type II and GAGs were localized in the chondrogenic layer, and osteopontin, osteonectin, and collagen type I were localized in the osteogenic layer.[4]

Beyond these two primary groups, various different approaches have been employed, most of which were *in vivo* studies using only histology and/or imaging to validate engineered constructs. One approach was to mold coral into the shape of a human condyle, seed them with MSCs, and implant with bone morphogenetic protein (BMP)-2 to demonstrate osteogenesis in rats and angiogenesis in rabbits.[33,34] Another approach was to implant acellular poly (lactic-co-glycolic acid) (PLGA) based constructs with growth factors in rat mandibular defects, either demonstrating the efficacy of transforming growth factor (TGF)-β1 and IGF-I[154] or the lack of efficacy of BMP-2[172] under the respective study conditions. In another study, osteoblasts were

seeded into condyle-shaped PGA/polylactic acid (PLA) scaffolds and chondrocytes were painted on the surface prior to implantation in mice, after which positive histological results were observed.[178] In a related study, porcine MSCs seeded in condyle-shaped PLGA scaffolds were cultured under osteogenic conditions in a custom-built rotating bioreactor, which also yielded positive histological results.[1] Another approach examined a new cell source, comparing human umbilical cord matrix MSCs with porcine condylar cartilage cells *in vitro*, showing that the umbilical cord matrix stem cells outperformed the cartilage cells with regard to biosynthesis and proliferation.[20]

The next major step for mandibular condyle/ramus tissue engineering will be demonstrating long-term *in vivo* efficacy with osteochondral condyle/ramus replacements in larger animals (e.g., pig), which will require an understanding of the growth and mechanics of the native tissue.[67]

CONCLUSIONS

The lubrication system of the TMJ is an essential function for mandibular dynamics. Understanding the development and breakdown mechanisms of TMJ lubrication may enable us to develop a ''good as new'' treatment remedy for TMDs. Future studies attempting to artificially replace and tissue engineer the TMJ should be aware of the wealth of joint lubrication data, as it will be necessary to incorporate tribological considerations in design criteria as tissue engineered constructs reach clinical application.

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