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Review
Biomechanical and biochemical characteristics of the mandibular condylar cartilage

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Summary

The human masticatory system consists of a mandible which is able to move with respect to the skull at its bilateral temporomandibular joint (TMJ) through contractions of the masticatory muscles. Like other synovial joints, the TMJ is loaded mechanically during function. The articular surface of the mandibular condyle is covered with cartilage that is composed mainly of collagen fibers and proteoglycans. This construction results in a viscoelastic response to loading and enables the cartilage to play an important role as a stress absorber during function. To understand its mechanical functions properly, and to assess its limitations, detailed information about the viscoelastic behavior of the mandibular condylar cartilage is required. The purpose of this paper is to review the fundamental concepts of the biomechanical behavior of the mandibular condylar cartilage. This review consists of four parts. Part 1 is a brief introduction of the structure and function of the mandibular condylar cartilage. In Part 2, the biochemical composition of the mandibular condylar cartilage is summarized. Part 3 explores the biomechanical properties of the mandibular condylar cartilage. Finally, Part 4 relates this behavior to the breakdown mechanism of the mandibular condylar cartilage which is associated with the progression of osteoarthritis in the TMJ.
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Introduction

The so-called diarthrodial joints allow relative motion of the articulating bones in reaction to the forces produced by the surrounding muscles[1]. Furthermore, they act as growth centers for the skeleton[2]. The articulating ends of the bones are covered by a thin and highly deformable layer of articular cartilage, a dense connective tissue[1]. The joint cavity, the space between the cartilaginous surfaces, is filled with a small amount of synovial fluid which serves as a lubricant. The articular capsule, augmented with ligaments, tendons, and other soft tissues inside and outside the joint compartment, provides stability to the joint. It helps to maintain a proper alignment of the articulating bone ends during motion, and prevents the synovial fluid from flowing away[1]. Generally, daily activity is coupled with joint motion and joint loading. Diarthrodial joints then act as biological bearings, with tribological characteristics such as friction, lubrication, and wear[3].

The human masticatory system consists of a mandible which is able to move with respect to the skull, guided by two temporomandibular joints (TMJ) through contractions of the masticatory muscles. Like many other synovial joints, the TMJ enables large relative movements[4,5]. As the mandibular condyle undertakes both translatory and rotary movements, the TMJ can be described as a sliding-ginglymus joint. Very unlike most other joints, in the TMJ the articular surfaces are separated by a cartilaginous articular disc with nonuniform thickness[6,7]. This disc is able to move smoothly together with the mandibular condyle along the articular eminence while it is simultaneously rotating underneath[5]. The TMJ disc is connected superiorly to the temporal bone and inferiorly to the mandible by relatively loose fibrous structures that make up the articular capsule. It is reinforced laterally by the temporomandibular ligament, which is the only capsular structure that runs directly between the temporal bone and the mandible[7].

The articular surfaces of the TMJ are highly incongruent. If these surfaces would be in contact directly the contact area would be very small, which would lead to large peak loads and friction. The presence of the TMJ disc in combination with the articular cartilage of this joint is believed to prevent these peak loads[8−12], as they are capable to adapt their shape to that of the bony articular surfaces by deformation. Unfortunately, the pristine structures of the articular surfaces often deteriorate with aging by internal derangement, and arthritis. Then they erode and become increasingly roughened, leading to pain and dysfunction. Eventually, this may progress into osteoarthritis (OA).

Degradation is frequently preceded with internal derangement of the TMJ characterized by an abnormal positional relationship of the disc relative to the mandibular condyle and the articular eminence. Ultimately, TMJ-OA is characterized with deterioration and abrasion of articular cartilage, and thickening and dysfunctional remodeling of the underlying bone[13]. This results in painful and impaired function with limited movement characteristics.

During normal and abnormal function the joints are loaded. This causes its cartilaginous structures to deform. The magnitude of deformation and the resulting stress is, besides the nature of the applied loads, primarily determined by the biomechanical properties of the cartilage, such as stiffness. An understanding of these properties is important for several reasons. First, they determine the role of the cartilage as a stress-distributing and load-absorbing structure[12,14]. Second, mechanical stress and strain affects the extracellular matrix synthesis in the cartilage[15,16], resulting in an adaptation of stiffness. Third, the mechanical properties of the cartilaginous structures and their alterations by joint loading will also influence the stresses and strains that occur in the subchondral layers, which are of critical importance for damages on the short term and bone remodeling on the long term. Fourth, precise information about the biomechanical properties of the articular cartilage is required to develop suitable joint simulation models, with which the distribution of stress and strain in the structures of the joint can be estimated[17]. This will enable prediction of the effects of mechanical manipulation of the joints in the process of prevention or treatment of joint derangements. Finally, information on the biomechanical properties of the articular cartilage is indispensable for the development of tissue-engineered replacements for damaged TMJ components.

In this paper, the fundamental concepts of the biomechanical behavior of the mandibular condylar cartilage are reviewed. The review is divided into four parts. The first part introduces the structure and function of the mandibular condylar cartilage. Part 2 relates the biomechanical behavior to the biochemical composition of the mandibular condylar cartilage. In Part 3, the biomechanical properties of the mandibular condylar cartilage are summarized. Finally, Part 4 relates this behavior to the breakdown mechanism of the mandibular condylar cartilage associated with the progression of OA in the TMJ.

Structure and function of the mandibular condylar cartilage

Mandibular condylar cartilage plays a crucial role in TMJ function. It facilitates articulation with the TMJ disc and reduces point loads on the underlying bone[14]. It is of the fibrous type and is therefore structurally different from the generally applied hyaline articular cartilage.

The cartilage layer on the mandibular condyle is from the articular surface to the underlying bone, composed of several zones: the fibrous, proliferative, mature and hypertrophic zones[18,19]. 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. Their endoplasmic reticulum is surrounded by a dense intercellular matrix of collagen fibrils and ground substance[20]. The proliferative zone plays an important role as a cell reservoir. It has mesenchymal cells distributed heterogeneously as chondrocyte precursors for the underlying zones[21]. Differentiated chondrocytes are found in the mature and hypertrophic zones. Here an increase of degenerated chondrocytes

has been noted close to the subchondral bone[20]. The collagen fibers of the fibrocartilage are arranged in several distinct zones[22], and are considered to provide mainly tensile strength to the cartilage. Shear strength has been suggested to originate from cross-links between the collagen fibers[23]. Mandibular condylar cartilage differs from general articular cartilage by the presence of type I collagen[24]. This is dominant in the superficial zone, though type II collagen (the dominant type in hyaline cartilage) is dominant in the mature and hypertrophic zones. In addition collagen type III is observed in the superficial zone[25], while collagen type X, which is also commonly found in hyaline cartilage, is present in the mature and hypertrophic zones[26,27]. In articular cartilage, collagen forms a three-dimensional network and thus impacts its form, stability and tensile strength and resistance to shear forces. When cartilage is loaded by compression, the low permeability of the collagen network impedes the interstitial fluid to flow through the collagen network[28]. This feature contributes to the viscoelastic properties of cartilage. The collagen matrix is organized in an arched structure[29]. The fibers curve from a radial orientation at the subchondral bone into a tangential orientation at the articular surface[29]. These fibers run predominantly in parallel. In the mandibular condylar cartilage, collagen fibers run mainly in the antero-posterior direction[14], which is suggested to be an optimized orientation to resist antero-posterior shear forces.

Resistance to compressive forces is due to the presence of proteoglycans which are embedded in the collagen network[30,31]. Proteoglycans are able to bind the interstitial fluid. Under compression this fluid may pressurize to bear the actual compressive forces, especially at high strain rates[32]. Versican and decorin are among the proteoglycans present in the mandibular condylar cartilage, but the major proteoglycan in this structure is aggrecan. The latter is mainly located in the hypertrophic and mature zones[31,33]. It provides osmotic swelling pressure to the cartilage which also contributes to resistance to compression[31,33].

The fibrocartilage covering both articular surfaces in the TMJ is avascular. Consequently, for nourishment these structures are dependent on the intra-articular synovial fluid. Partially thanks to the presence of this fluid the fibrocartilaginous cells even have limited ability for self-repair[34–36]. The fibrocartilaginous nature of the condylar cartilage along with the lubrication function of the intra-articular synovial fluid allow the TMJ to conform under function and ensure that loads are absorbed and spread over larger contact areas[8–12].

Biochemical composition of the mandibular condylar cartilage

Articular cartilage contains chondrocytes and a large amount of surrounding matrix macromolecules such as proteoglycans, glycosaminoglycans (GAGs) and type II, IX, and XI collagens[37,38]. These molecules contribute to the flexibility of cartilage and protection of the joint components from mechanical threats originating from, for instance, compression, shearing and stretching loads. The load-bearing functions of cartilage are mainly provided by the viscoelastic property of collagen fiber network and the osmotic pressure due to the presence of proteoglycans[39].

Condylar cartilage of the TMJ is macroscopically similar in structure to articular cartilage in other synovial joints, and also similar regarding pathological changes. For instance, TMJ arthritis resembles knee or hip arthritis largely[40]. Microscopically, mandibular condylar cartilage is dissimilar to articular cartilage, especially regarding its constituents. Where articular cartilage in general is composed

of hyaline cartilage, the mandibular condylar cartilage consists largely of fibrocartilage (Fig. 1), with thick multi-layers composed of several collagen fiber zones[41]. The surface of the mandibular condylar cartilage contains primarily type I collagen where primarily type II is present in articular cartilage in general. The latter is also present in mandibular condylar cartilage, in its matured layer located beneath the fibrous layer[42]. An immunohistological study revealed that type IX and XI collagens are also present in the condylar cartilage of neonatal mammalian[43]. The functional consequences of the differences between fibrocartilage and hyaline cartilage due to the collagen composition, however, remain unclear.

The proteoglycans consist of a protein core to which GAGs are attached. In aggrecan, these are large strands of negatively charged polysaccharides. Due to their charge they enable the proteoglycans to trap water. They are a major extracellular matrix component, which exert a key function by contributing to both the structural and functional integrity. They intertwine creating large proteoglycan aggregates to give the material viscosity.

Both in fibrocartilage and hyaline cartilage hyaluronic acid (HA) is the principal GAG, besides chondroitin and keratan sulfate[38]. It is a GAG consisting of repeated disaccharide units of D-glucuronic acid and *N*-acetyl-D-glucosamine and with varying, but high molecular weight (800−1900 kDa) in its native state[44]. The rheological properties of HA in solution are characterized by a remarkably high viscoelasticity[45,46]. HA imparts the viscoelastic character of the solution due to its specific structure, which is generally explained as random coil-entanglement. HA forms reversible and ordered aggregates and extensively branched networks at physiological temperatures in solution[47]. The large size and high negative charge of HA contribute to the physiological features associated with its structural fluid dynamics, and the homeostasis and maintenance of connective tissue integrity. HA in cartilage has been demonstrated to change with aging. The molecular weight of HA in human articular cartilage decreases from 2000 to 300 kDa between the ages of 2.5 and 86[48]. As HA in cartilage is essential to maintain viscosity such decrease in molecular weight can be considered to lead to reduction of its biorheological properties.

Furthermore, HA is also present in synovial fluid, where it is believed to have a crucial function in articular joint lubrication[49,50]. The function of HA is highly dependent on its molecular weight. High molecular weight HA is associated with viscoelasticity of synovial fluid. Increase of low molecular weight HA, as in aging, appears to result in a reduction of viscoelasticity, leading to impairment of joint lubrication[51].

Lubricin, a high molecular mass (∼345 kDa) mucinous glycoprotein with small amounts of keratan and chondroitin sulfate substitution, also known as proteoglycan 4[52] or articular cartilage superficial zone protein is detected in the superficial zone of articular cartilage[53]. This molecule plays a major role in the boundary lubrication of articular surface with high contact pressure and low speed sliding[54].

From these findings, it is suggested that the various contents of cartilage and synovial fluid contribute to the function of articular joints: to enable skeletal movement under more or less heavy loads. Overloading and subsequent deterioration of the metabolism and simultaneous remodeling processes in the underlying bone may result in degenerative diseases in TMJ.

Biomechanical properties of the mandibular condylar cartilage (Table I)

Mandibular motions can be continuous or intermittent . These motions, sometimes combined together, result in static and dynamic loading in the TMJ[11]. 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 in the joint tissues, while static loading, especially if prolonged or excessive, induces a catabolic effect. As both sliding and rotating movements occur simultaneously between the articulating surfaces, the TMJ is subjected to a multitude of different loading regimen during mandibular movements. Basically, three types of loading can be distinguished: compression, tension, and shear. During natural loading of the joint, combinations of these basic types occur on the articulating surfaces. During joint loading, its articular cartilage layers and the fibrocartilaginous disc undergo deformations (strain) dependent on their material properties. These strains are accompanied by internal forces (stress) within the tissue.
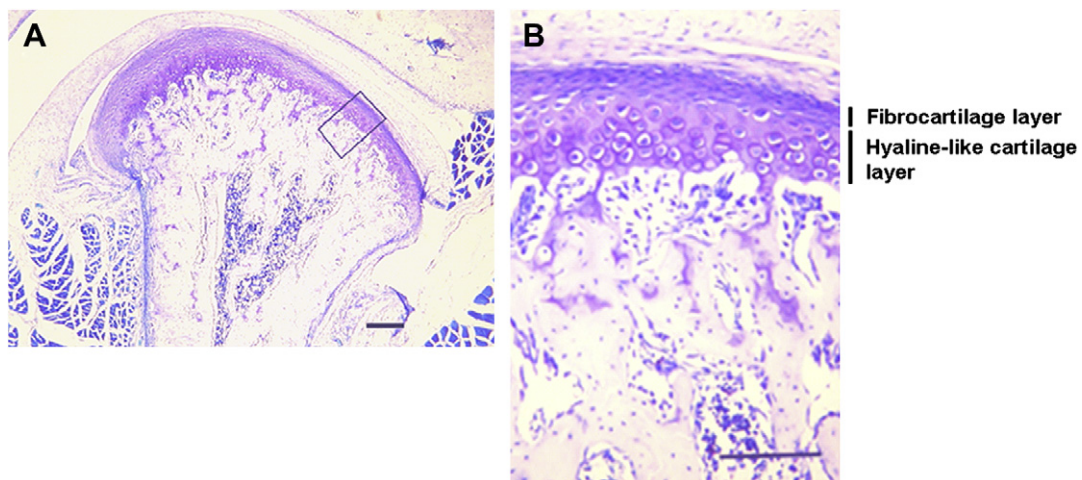

Fig. 1. Photomicrographs of the TMJ and the articular cartilage layer. Cartilage layers of condyle in 16-week-old male rats were visualized by toluidine blue staining. Bar indicates 200 μm (A) and 100 μm (B).

Table I
Summary of elastic moduli (in MPa) of mandibular condylar cartilage

	Species	Loading motion	Loading direction†	Region				
				Cent*	AM*	AL*	PM*	PL*
Tension								
Kang et al.[57]	Pig	Static	A-P	9.04				
			M-L	6.55				
Singh and Detamore[14]	Pig	Static	A-P	12.2 (7.4)‡				
			M-L	6.5 (3.8)‡				
Compression								
Kuboki et al.[60]	Pig	Static (sustained)		2.68−4.75§				
		Static (intermittent)		3.36−6.621§				
Hu et al.[59]	Rabbit	Dynamic			2.34	1.53	1.11	0.95
Patel and Mao[58]	Rabbit	Dynamic			0.95			1.02
Tanaka et al.[12]	Pig	Dynamic			1.36	1.12	0.79	0.72
					(0.34)‖	(0.24)‖	(0.16)‖	(0.16)‖
Shear								
Tanaka et al.[64]	Pig	Dynamic	A-P	1.50−2.03 (0.41−0.51)‖				
Tanaka et al.[65]	Pig	Dynamic	M-L	0.33−0.55 (0.09−0.15)‖				

*Central (Cent) region, anteromedial (AM), anteorolateral (AL), posteromedial (PM), and posterolateral (PL) regions.
†Antero-posterior (A-P) and medio-lateral (ML) direction.
‡Relaxed modulus.
§Equilibrium modulus.
‖Viscous modulus.

The functional role of mandibular condylar cartilage is similar to articular cartilage in general. It plays an important role as stress absorber during function, and enables functional joint movements[11,55]. However, the more fibrous nature of TMJ cartilage is responsible for some differences. As determined from its embryologic origin, this cartilage cannot be classified as a primary growth center. It is characterized as secondary cartilage, primarily associated with membrane bone[56]. The biological composition and histochemical content of the mandibular condylar cartilage, therefore, differ from articular cartilage in the synovial joints as described in Part 2.

The mandibular condylar cartilage behaves as a nonlinear viscoelastic material, just like the TMJ disc. Anisotropy of its mechanical properties is characterized by larger average tensile strength, tensile stiffness, and energy absorption in the antero-posterior direction than in the medio-lateral direction. The reported Young's moduli in the antero-posterior direction were 1.5−2 times larger than those in the medio-lateral direction[57]. Furthermore, both the instantaneous and relaxed moduli have been reported about twice as large in the antero-posterior direction[14]. These findings are correlated well with the predominantly antero-posterior fiber orientation in the fibrous zone of condylar cartilage.

Under dynamic compression, the dynamic elastic modulus was significantly larger than the dynamic viscous one[12]. These dynamic properties, however, varied significantly between antero-posterior regions[12,58]. For instance, the anterior area revealed significantly larger moduli than the posterior area[12]. These findings were in agreement with the nano-indentation findings of Hu et al.[59]. The resistance to compression is mainly dependent on the density of proteoglycans[60]. As the distribution and amount of these aggregates are different in various regions of the mandibular condylar cartilage, the observed regional differences in the compressive modulus can be explained accordingly.

Of the three types of loading, shear loading is the most important in a tribological aspect. During joint loading the cartilage layers are sheared to adapt their shape to the incongruent articular surfaces. Excessive shear, however, can cause a fatigue, which irreversibly may lead to damage of cartilage[61−63]. Furthermore, excessive shear stress is associated with a breakdown of joint lubrication through a reduction of HA molecular weight. Previously, our work has demonstrated that the shear behavior of the mandibular condylar cartilage was dependent on the frequency and amplitude of the applied shear strain[64]. The dynamic shear moduli increased nonlinearly with the frequency irrespective of the shear strain amplitude[64]. 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[53,61]. Our recent study indicated that the condylar cartilage had direction-dependent dynamic shear characteristics[65]. The resistance to shearing is larger in anterior−posterior than in medio-lateral direction, but the viscous properties are not dependent on the direction[65]. This may indicate that the former might be attributed to anisotropy of collagen cross-links.

With respect to the dynamic shear modulus in the antero-posterior direction, the dynamic elastic modulus was also larger than the dynamic viscous one[64] and these values were almost the same as those in dynamic compression[12]. In contrast, the dynamic shear modulus in the medio-lateral direction was about 30% of the antero-posterior one, which implies that the dynamic shear behavior of the mandibular condylar cartilage is also anisotropic[65]. As described above, excessive shear loading can induce a breakdown of cartilage. Therefore, the shear characteristics suggest that the mandibular condylar cartilage has a weaker resistance to medio-lateral shear stress, which more easily might lead to degradation of articular cartilage and synovial fluid.

Breakdown mechanism of the mandibular condylar cartilage

The dominant factor in relation to cartilage wear is age. Both frequency and severity of the cartilage breakdown appear to increase with aging. For example, degenerative joint disease occurs typically in the fifth and sixth decades of life when articular cartilage usually starts to lose its cellular density and

herewith its adaptive capacity[66]. Age-related changes have also been detected in the TMJ components. For example, the calcium content of the human TMJ disc increases progressively with aging[67,68]. Furthermore, the amount of GAGs in the disc increases markedly from newborns to mature adults[69]. This increase will elevate the osmotic swelling pressure and hence the cartilaginous stiffness.

The major direct cause of mandibular condylar cartilage breakdown is overloading[9,13]. With respect to TMJ-OA, the mechanism of overloading is probably the same as that in the other synovial joints. Chondrocytes − especially hypertrophic chondrocytes− appear to have evolved mechanoresponsive mechanisms[70,71]. They may lead to an increase in metabolic activity and activation of pathological processes which could lead to irreversible cartilage degradation[72]. The key mediators of cartilage degradation include the matrix metalloproteinases (MMPs) and the closely related aggrecanases[73]. Collagen type II is degraded by the first, while aggrecan, the major proteoglycan in cartilage, is degraded by both[74,75]. These proteases, especially aggrecanase-1 and -2, are important mediators of aggrecan loss in cytokine-stimulated normal cartilage and in already-damaged OA cartilage[73]. MMP-1, -3 and -9 are abundantly present in cartilage and synovial fluid in joints under pathologic conditions[76,77].

Cyclic tensile pressure has been demonstrated to up-regulate the expression of MMP-13[16]. Also vascular endothelial growth factor (VEGF) is up-regulated, whereas the expression of tissue-inhibitors of matrix metalloproteinase (TIMP) -1 is down-regulated. Cyclic hydrostatic pressure appeared to have the opposite effect[71]. VEGF expression in OA cartilage appeared to be progressive with mechanical overload. VEGF induction in chondrocytes by mechanical overload is linked to activation of the hypoxia-induced transcription factor-1 (HIF-1) which is known to bind to hypoxia response element (HRE) in the human VEGF gene promoter[78]. After mechanical overload chondrocytes were strongly immunopositive for HIF-1α, resulting in induction of VEGF[79]. VEGF, which is also enhanced by hypoxia and cytokines[80,81] acts mainly on endothelial cells by stimulating proliferation, migration, and induction of various genes involved in tissue remodeling. Recently, its expression in mandibular condylar cartilage was demonstrated abundantly after mechanical overload which indicated its relationship with TMJ-OA[36]. VEGF expression in chondrocytes has been demonstrated to be induced by high-intensity stress[82] and, therefore, may act in cartilage as an autocrine inducer of MMPs (Fig. 2).

In condylar cartilage associated with TMJ-OA, the number of blood vessels and osteoclasts is markedly increased in the area directly below the hypertrophic cell layer. In the same layer VEGF-expressing chondrocytes were detected[36]. It is reported that VEGF played an important role not only in endothelial cell recruitment but also in osteoclast recruitment[83,84]. Macrophage-colony stimulating factor (M-CSF) and VEGF have been demonstrated to have overlapping function in the support of osteoclastic bone resorption[83]. Therefore, VEGF produced by chondrocytes might be responsible for migration, differentiation and stimulation of preosteoclasts and osteoclasts into cartilage. This may induce destruction of cartilage through vascular invasion which is suggested to be an early mechanism to turn cartilage into bone[85].

With overload of a joint, its intra-articular pressure increases. When this should exceed the capillary perfusion pressure, it may cause temporary hypoxia, which in turn is
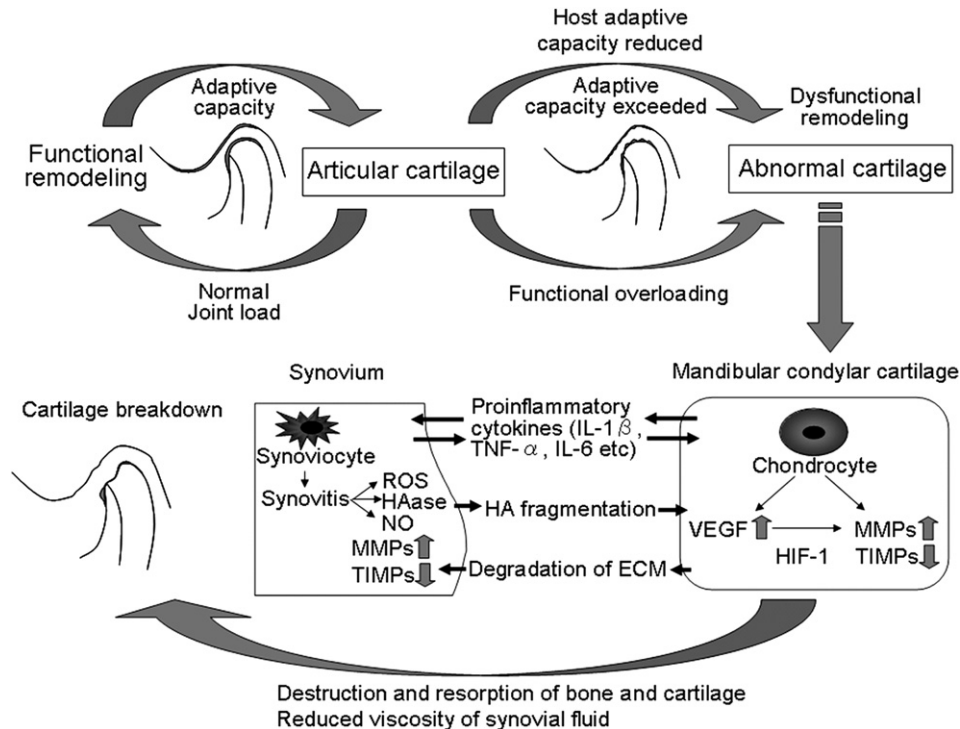

Fig. 2. Schematic illustrations of the concept of mandibular condylar cartilage degradation. Functional overloading can facilitate hypoxia in the TMJ mediate the destructive processes associated with osteoarthrosis as an autocrine factor. VEGF induction in OA cartilage by functional overloading is linked to activation of the HIF-1, leading to hypoxia in the joint tissue. Furthermore, VEGF regulates the production of MMPs and TIMPs which are among the effectors of extracellular matrix remodeling. Overloading also causes collapse of joint lubrication as the result of the HA degradation by free radicals. The regulation of HA production is controlled by various pro-inflammatory cytokines.

corrected by re-oxygenation on cessation of degradation by the overloading. Such a hypoxia-re-perfusion cycle has been reported to nonenzymatically release reactive oxidative radical species (ROS) such as superoxide anions and hydroxyl anions[86]. One of the effects of ROS in synovial joints is inhibition of the biosynthesis and degradation of HA, both causing a marked reduction in viscosity of the synovial fluid[86].

It is suggested that HA degradation occurs in pathologic joints, because of free radical de-polymerization of the HA chain[87,88] or the abnormal biosynthesis of HA by type B synovial cells[89,90]. Free radicals rapidly de-polymerize HA in vitro, which may implicate them in the degradation of HA in vivo. Hereupon the molecular weight of HA in the synovial fluid decreases[91]. Such degradation affects the viscoelastic properties of synovial fluid in arthritic joints, resulting in impairment of joint lubrication[13,87]. In the TMJ this may lead to adhesion of the disc to the glenoid fossa[9]. Furthermore, the fragmentation of HA may lead to cartilage destruction in terms of the enhanced expression of MMPs as well as the up-regulation of CD44[92]. As neither healthy nor inflammatory synovial fluids contain hyaluronidase activity, ROS is assumed to cause HA de-polymerization[88,93].

The process of regulation of HA production is controlled by, among others, cytokines like interleukin (IL)-1β, tumor necrosis factor (TNF)-α, interferon (IFN)γ and transforming growth factor (TGF)β. In rabbit TMJ synovial lining cells it has been demonstrated that TGFβ1 enhances the expression of HA synthase-2 mRNA in synovial membrane fibroblasts[94]. Such may contribute to the production of high molecular weight HA in the joint fluid. Several pro-inflammatory cytokines, such as TGFβ, TNF-α, IL-1β, IL-6, IL-8, IL-10, and IL-12, have been detected in the synovial fluid obtained from patients with TMJ-OA[95−97]. This indicated that cytokines in the synovial fluid might be responsible for progression of the degenerative changes in the TMJ.

Conclusions

TMJ-OA has a similar pathobiology as OA in any other joint in the body. Therefore, in order to eliminate the confusion amongst patients, clinicians, researchers and third party insurance carriers, TMJ-OA should be discussed in the same terms as orthopaedists discuss OA, and not as a separate disease. Mandibular condylar cartilage plays a fundamental role in the TMJ function as a stress absorber. This role is dependent on its biochemical and biomechanical features, which may degenerate with aging and mechanical loading. In fact, the cartilage is indispensable for whole musculoskeletal system[85], while TMJ-OA indicates its collapse. Therefore, an understanding of the pathogenesis of TMJ-OA and current clinical treatment are essential to the successful integration of tissue engineering into the future surgical management of TMJ pathology.

Conflict of interest

The authors have no conflict of interest.

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