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REVIEW ARTICLE

Degenerative changes of articular cartilage in association with mechanical stimuli

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Summary This article was designed to review the association between degenerative changes of articular cartilage and mechanical stimuli. Finite element analysis revealed an induction of large compressive stresses in the anterior and lateral areas on the condyle by the maximum clenching and the prominent increases as the vertical discrepancy became greater. Increase of friction at the articular surface was indicated as a cause of larger stresses and the relevant disk displacement, which further induced an increase in stresses in the retrodiscal tissues, indicating the important role as a stress absorber. Increase in TMJ loading simulated by vertical discrepancy or excessive mouth opening produced a decrease in the thickness of cartilage layers, an increase in the numbers of clast cells and degenerative changes in the condylar cartilage associated with the expression of bone resorption-related factors. Excessive mechanical stimuli, irrespective of compressive or tensile one, induced HA fragmentation, expression of proinflammatory cytokines, an imbalance between matrix metalloproteinases and the tissue inhibitors, all of which are assumed to induce lower resistance to external stimuli and degenerative changes leading to bone and cartilage resorption. It is also revealed that various cytoskeletal changes induced by mechanical stimuli are transmitted through a stretch-activated or Ca^{2+} channel.

Contents

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1. Introduction

Temporomandibular joint disorder (TMD) has become an important disease in the field of dentistry and/or orthodontics. Under such background, various studies have been conducted to elucidate the nature and causes of TMD in association with various etiologic factors [1—4]. As a result, TMD is currently accepted as a multi-factorial disease, however, occlusal parameters have also been speculated to have a certain association with TMD [5,6].

1.1. Background of the present review

As a background of this review article, a series of our studies on TMD and the relevant factors are introduced for better understanding the nature of TMD. These subjects are (1) the nature and prevalence of TMD, (2) association of malocclusion with TMD, (3) association of condylar position with TMD, (4) association of craniofacial morphology with TMD, and (5) influences of TMD, osteoarthritis (OA) in the TMJ in particular, from a clinical viewpoint.

Firstly, prevalence of TMD was examined in an orthodontic patient group. In this survey, the percentage of TMD patients to the total number of patients was approximately 14% [7]. It is surprising to know very high prevalence of TMDs, which are mostly occupied by TMJ internal derangement with various intraarticular pathologic stages, in adolescent patients with malocclusion. It is also of a clinical significance that adult population has higher prevalence [8], and jaw deformity patients exhibit substantially higher prevalence [9] than adolescent patient group and asymptomatic adult volunteers, respectively. Furthermore, it is of a great interest that the prevalence of TMJ-OA is about 18% in all the TMD patients and approximately 2.5% in all the patients [7].

The second topic is the association of malocclusion with TMD. The prevalence of TMD was considerably higher in open bite, deep bite, and posterior cross-bite [10]. Thus, some specific types of malocclusion were significantly associated with the occurrence of TMD in the patient group. It is also speculated from this finding that condylar displacement in the TMJ space may change disk position relative to the displaced condyle and result in the onset of TMJ internal derangement [11,12].

The next topic is the association between condylar position in the TMJ space and intraarticular pathologic status. Condylar position was more posterior in anterior disk displacement with reduction (AWWD), whereas concentric in anterior disk displacement without reduction (ADDWo) [11]. It is indicated that condylar position is directly relevant to the disk displacement and the nature of TMJ internal derangement, or the progress in intraarticular pathologic status from ADDW to ADDWo [2,4,11].

Then, the association between craniofacial morphology and intraarticular pathologic status was examined by means of a Spearman's rank correlation analysis. The size and position of the mandible presented significant negative correlations and the mandibular plane and ANB angles exhibited significant positive correlations with the pathologic stages [7,13,14]. It is shown from these results that the progress in intraarticular pathologic status is highly related to more severe vertical discrepancy of the craniofacial skeleton.

As the influences of TMJ-OA from a clinical viewpoint, the morphometric findings mentioned above and the relevant actual TMJ-OA cases provide us with very interesting and useful clinical implications such that condylar resorption in TMJ-OA produces jaw deformity with less developed and distally located mandible and affects the outcomes and stability of occlusal reconstruction [1,7,9,15,16]. On the contrary, it is demonstrated in the treatment cases of TMJ-OA that the sable occlusion achieved by orthodontic occlusal reconstruction has produced biomechanical equilibrium in the TMJ and subsequently provided the condyle with a potential for adaptive or functional remodeling [17].

1.2. Aim of this article

These findings are very useful for understanding the nature of TMD and can be used as a background for the review in this

article to explore the mechanisms of degenerative changes in condylar cartilage. It would also be hypothesized from these findings that various morphological and functional parameters produce an increase in TMJ loading, which further leads to degenerative changes in the articular cartilage of the mandibular condyle and resorption of bone and cartilage expressed as a TMJ-OA.

This article was thus designed to review the association between degenerative changes of articular cartilage and mechanical stimuli in biomechanical, histochemical and biochemical aspects for elucidating the mechanisms of bone or cartilage resorption in the mandibular condyle.

2. TMJ loading from masticatory functions

2.1. TMJ loadings from maximum clenching

There have been various studies on TMJ loading by use of finite element stress analysis [18—24]. Among these studies, a report by Tanaka et al. [23] can be cited as a representative and frontier study for TMJ loading in the field of biomechanics. In the study, a three-dimensional model of the mandible including the TMJ was constructed for stress analysis with finite element method. For loading conditions, the magnitude of muscle forces was determined to exert a resultant force of 500 N, simulating the maximum clenching. Large compressive stresses were induced in the anterior, middle and lateral regions, whereas tensile stresses were found in the remaining areas. In particular, the anterior region of the condyle was loaded the greatest compressive stresses [23].

The results may be compared with previous anatomic and experimental findings. Oberg et al. [25] demonstrated in a study with cadavers that erosion and ruggedness of the bony structures and thinning and/or perforation of the articular disk were more frequently observed in the anterior and lateral areas of the TMJ. Kopp [26] also reported a higher concentration of glycosaminoglycan, which is regarded as a marker of compression, in the anterior and lateral areas of the TMJ. Thus, the greater compressive stresses in the anterior and lateral areas revealed in the above study may account for the various degenerative changes in the articular disk and condyle reported in the anatomic studies [25,26] and clinical cases of TMJ-OA [1,7,15—17].

2.2. TMJ loadings varied by vertical skeletal discrepancy

In previous morphometric and radiographic studies [7,9,13,15], vertical discrepancy was revealed as a key determinant for the intraarticular pathological status of TMD. Thus, the stress distributions were analyzed in association with the discrepancy with an assumption that such morphologic parameter affects the nature of TMJ loading [24]. For stress analysis, the model developed above was modified to represent vertical discrepancies of the craniofacial complex by changing the shape of mandible, maintaining the number of nodes and elements in the standard model. The gonial and mandibular plane angles were changed with a special reference to the means and standard deviations. These stresses were changed in association with varying mandibular plane angles and exhibited more substantial changes than those with varying gonial angles [24]. Changes in the stresses were nonlinear in nature and particularly drastic when the angle became larger than a certain threshold value.

It is thus demonstrated that vertical skeletal discrepancy induces an increase in TMJ loading and lack in biomechanical equilibrium for the TMJ components. These results may help explain a finding that malocclusions with vertical discrepancies have a higher prevalence of TMD than others [5,10]. This may be due to the malposition of condyle in the glenoid fossa in TMD cases with vertical discrepancies [10—12]. Another explanation is that a lack in biomechanical equilibrium in the TMJ induced by the skeletal discrepancies may produce nonlinear and plastic deformation of the articular disk observed in a tensile test of the disk [27] and more extensive degenerative changes in the madibular condyle with articular cartilage. These speculations are to be discussed later in terms of biologic and biochemical responses of articular cartilage examined by *in vivo* and *in vitro* experiments.

2.3. Association of friction at the articular surface with TMJ loading and disk displacement

During mouth opening, condylar movement essentially requires cooperative disk motion. When the disk slides on the articular surface, shear stress is induced but negligible because of the very low friction [28]. Furthermore, the presence of synovial fluid decreases the frictional coefficient to almost zero [29]. Meanwhile, under various pathological conditions with intraarticular inflammation and degradation of hyaluronan (HA), an increase in friction at the articular interfaces is generated eventually.

Given these considerations, a biomechanical study with finite element analysis was conducted to assess the stress distribution and disk displacement during mouth opening in association with different frictional coefficients. It is demonstrated that an augmentation in the friction at the articular surface produces an increase in stresses and the subsequent disk displacement, leading to the onset of TMJ internal derangement or the more progressed form with degenerative changes [30]. Changes in stress distribution in the TMJ were also reported in previous studies by Foster and Fisher [29] and Williams et al. [31]. It is also indicated that the amount of friction is increased proportionally to the magnitude and duration of TMJ loading, relating in part to the onset of disk displacement [32].

Thus, friction at the articular surface is a key determinant for maintaining optimal intraarticular environment which allows smooth jaw movement. Therefore, it is of a great significance to eliminate excessive friction at the interfaces between TMJ structures. To this end, various lubricants equivalent to the synovial fluid have been used not to make a progress in intraarticular pathology. HA addition, as an application of lubricant, will be introduced in the following section.

2.4. Friction at the articular surface and lubrication function

When the TMJ disk slides along the articular surfaces during jaw movement, shear loading of the disk can be considered to

be negligible, due to very low friction [28]. Friction in synovial joints, in general, is associated with its lubrication mechanism [33], which in turn is dependent on the rheological properties of synovial fluid.

HA, which occupies 0.14—0.36% of synovial fluid in normal subjects [34], is one of the principal components determining its rheological properties. The amount of viscosity, an essential determinant for the lubrication function, is dependent on the molecular weight [35]. In joints affected with OA, meanwhile, the synovial fluid has a reduced viscosity due to the decline in both concentration and molecular weight of HA [36].

Given these findings, Kawai et al. [37] examined the role of HA in the lubrication of the TMJ. They measured the frictional coefficients in the porcine TMJ after the application of HA with different molecular weights and concentrations. Application of HA resulted in a significant decrease in the frictional coefficient by 50—70%. This study thus reached a conclusion that the addition of HA did reduce the coefficient of friction under the experimental conditions, supporting an assumption that the most superficial layer plays an important role in the adequate lubrication function which apparently cannot be established by the physical action of cartilage alone but by a cooperative function of various TMJ components [37].

2.5. Role of articular disk in buffering or absorbing stresses on the TMJ components

It is well understood that TMJ is one of the load bearing organs in the human body and the disk plays an important role as a stress absorber, resulting in stress reduction and redistribution in the joint [38—40]. For maintaining optimal intraarticular environment, therefore, two major factors can be indicated; *i.e.* healthy disk and optimal positional relation between the disk and bony components.

Mechanical behavior of the disk has already been examined extensively. The elastic and viscoelastic features are described by various parameters such as elastic modulus, instantaneous modulus, relaxed modulus and the strain-relaxation time [27,41—43]. In addition, viscoelastic material model was examined for TMJ disk, demonstrating that a four-mode Maxwell model is more suitable for representing mechanical behavior of the disk during stress absorption [44].

Furthermore, Tanaka and van Eijden [45] published a review about the fundamental concepts of biomechanical behavior of the TMJ disk. In conclusion of the review, they described that the TMJ disk behaves as a viscoelastic structure and can function as a stress absorber and distributor. This means a biomechanical contribution of the disk to prevent stress concentration and excessive stress in the cartilage and bony components of the joint, all of which protect the joint from degenerative and osteoarthritic changes. They also discussed the disk wear in the anterior [26] and intermediate [46] regions. As mentioned in the preceding sections in this article, these phenomena have already been explained in association with excessive loading validated by finite element stress analyses [18—20,23] and histological or histochemical examination which revealed stress concentration by the presence of chondroitin sulfate [47,48]. In addition, it was demonstrated in a previous study [21] that stresses in the retrodiscal tissues were increased by anterior disk displacement and may lead to the thinning and perforation, indicating an important role of the disk as a stress absorber. Finally, it is prudent for us to keep it in mind that the mechanical properties are varied by various intrinsic and extrinsic factors such as aging, trauma and pathologic disease [45].

3. Biological responses of condylar cartilage to mechanical stimuli

3.1. Histochemical changes in condylar cartilage from excessive TMJ loading due to simulated vertical discrepancy

In the preceding section, various biomechanical studies have shown the presence of excessive or imbalanced mechanical stresses on the TMJ components. Furthermore, it is noted that TMJ internal derangement with degenerative changes may be relevant to such morphologic characteristics of the mandible as steep mandibular plane and short ramus expressed as vertical discrepancies. Therefore, biological responses of condylar cartilage to enhanced TMJ loading, produced by skeletal discrepancies simulated in biomechanical analyses, are discussed herein with a special reference to the remodeling of cartilaginous tissues on the mandibular condyle.

First, an *in vivo* study with histochemical and morphometric approaches is introduced [49]. They simulated vertical skeletal discrepancies in 4-week-old rats by use of a 1 mm-thick metal plate bonded onto the maxillary molars. In fact, a backward and downward rotation of the mandible was confirmed on serially taken lateral cephalograms, indicating an increase in the TMJ loading on the condyle. The tissue sections were stained with tartrate-resistant acid phosphatase (TRAP) and hematoxylin-eosin (H-E) for histomorphometric analyses of the thickness of cartilage layers, and the number of TRAP-positive cells. During the initial phase of experiment, the thickness of proliferative and maturative/hypertrophic zones in the anterior and superior regions of the condyle was significantly smaller than in the controls. The number of TRAP-positive cells was significantly greater in the experimental group than in the controls at the initial phase of experimental. Morphometric analyses revealed less-developed mandible, decreased ramus height and large gonial angle in the experimental group. From these findings, it is shown that biomechanical changes in the intraarticular environment associated with vertical skeletal discrepancy influences or inhibits cartilaginous growth of the condyle and mandible to a considerable extent, if induced during growing period [49].

Various studies have shown that responses of the condylar cartilage may be altered by changes in the biological and biomechanical environments in the TMJ space [50—52]. Similar changes were demonstrated in experimental animals when the incisors were trimmed or removed [50]. McNamara [53] investigated the influences of increases in the vertical dimension on craniofacial adaptation in growing monkeys, demonstrating that the amount of vertical growth at the condylar head was decreased, which is assumed due to reduced cartilaginous remodeling and growth. From these

studies, it is emphasized that mechanical stimuli acting on the condyle surely reduce cartilaginous remodeling, if excessive, leading to a decrease in the growth of overall condyle and mandible, which in turn produces vertical skeletal discrepancies with small mandible. Subsequently, such morphologic characteristics would produce enhanced TMJ loading and degenerative changes in the TMJ components [49].

3.2. Changes in the condylar cartilage and masticatory muscles from excessive TMJ loading due to forced mouth opening

Another *in vivo* experiment is introduced herein to examine pathological changes in the condylar cartilage from excessive mouth opening, which is speculated to generate an increase in TMJ loading on the condyle and glenoid fossa, and the subsequent masticatory muscle disorders. Kawai et al. [54] examined the association of mechanical loading with the induction of OA-lesion in the rat TMJ and its influence on jaw muscle activity. Mechanical stress was applied to the rat TMJ by forced mouth opening of 3 h/day for 5 days. As a result, the condylar cartilage exhibited OA-like lesions with a decrease in the number of chondrocytes immediately after the experiment. Immediately after the beginning of forced mouth opening, the total duration of muscle activity, defined as a duty time, increased significantly in the masseter muscle, whereas decreased significantly in the digastric muscle at the low activity level. These results suggested that mechanical overloading to the TMJ induced OA-like lesion and the intraarticular pathological status influenced the nature of jaw muscle activity, at the low activity level in particular.

Similar study was conducted in growing rats subjected to forced mouth opening to increase mechanical stress on the mandibular condyle [55]. As a result, marked OA-like lesions were observed in the condyle. In addition, vascular endothelial growth factor (VEGF) was detected in the chondrocytes of the mature and hypertrophic cell layers of the intermediate and posterior regions of the condyle. The percentage of VEGF immunopositive chondrocytes significantly increased with longer application of excessive TMJ loading. Furthermore, TRAP staining of the condylar cartilage showed a significant increase in the number of osteoclasts in the mineralized layer subjacent to the hypertrophic layer where high VEGF expression was detected, suggesting an important role of VEGF in the progression of TMJ-OA [55].

These findings were also found in previous studies [56,57], demonstrating the expression of VEGF with an ability to induce osteoclasts in association with excessive mechanical stress. Freemont et al. [58] reported that VEGF expression in chondrocytes is induced by high-intensity stress and acts in cartilage as an autocrine inducer of matrix metalloproteinases (MMPs). Furthermore, Forsythe et al. [59] described that VEGF induction in chondrocytes by excessive mechanical stimuli is linked to activation of the hypoxia-induced transcription factor-1 (HIF-1), which is well known to bind to hypoxia response element in the human VEGF gene promoter. It may be a conclusion from these studies that VEGF is probably induced in chondrocytes by excessive mechanical stimuli, facilitating hypoxia to mediate degenerative or destructive processes with the induction of MMPs as an autocrine factor [55].

4. Cellular responses of articular cartilage to mechanical stimuli

4.1. Biological and biochemical responses of articular chondrocytes to excessive mechanical stress

Articular cartilage contains a large amount of matrix macromolecules such as proteoglycan and type II collagen. These molecules contribute to the flexibility of cartilage and protection of the joint components from various mechanical stimuli. It is indicated that mechanical load of appropriate magnitude is essential for the growth and differentiation of chondrocytes. On the other hand, excessive loads influence harmfully the articular cartilage and induce various degenerative joint diseases [60]. It is suggested that excessive or imbalanced mechanical loads induce deformation of the articular cartilage and the subsequent degradation of the cartilage matrices. Jeffrey et al. [61] reported a loss of matrix components depending on the degree of mechanical stimuli when articular cartilage biopsy samples were subjected to a single impact load.

In order to elucidate the mechanisms of degradation of the cartilage matrix, various studies have been conducted and demonstrated that proteolytic enzyme, MMP, is a major factor to degrade the macromolecules of connective tissue matrices at neural pH [62,63]. A lack in balance between MMPs and the tissue inhibitors, TIMPs, was indicated as a cause of matrix degradation [64]. Proinflammatory cytokines such as IL-1beta and TNF-alpha were also demonstrated to have a close relation to the expression of MMPs [58,65,66]. In addition, HA fragmentation or reduced HA synthesis, induced by hyaluronidases and inflammatory cytokines respectively, was demonstrated as an important event for pathologic and degenerative changes in chondrocyets and synoviocytes [67—70].

Furthermore, Honda et al. [71] designed a series of studies for biological and biochemical responses of articular chondrocytes to an excessive tensile stress. Chondrocytes, isolated from the knee joint cartilage of 4-week-old rabbits, were subjected to a high magnitude tensile stress of 17 kPa at a frequency of 30 cycles/min for 12 h or 24 h. They examined the protein levels of cartilage matrices and the gene expressions of MMPs, TIMPs and proinflammatory cytokines. A change in cell morphology from a polygonal to spindle-like shape was observed. Toludine blue staining, type II collagen immunostaining, and an assay of the incorporation of [^{35}S] sulfate into proteoglycans revealed a decrease in the level of cartilage specific matrices in chondrocyte cultures. Finally, the cyclic tensile stress increased mRNA levels of MMP-1, 3, and 9, IL-1 beta, TNF-alpha and TIMP-1 in the cultured chondrocytes, whereas the levels of MMP-2 and TIMP-2 were unchanged [71].

Malek and Izumo [72] reported that endothelial cells in loading with fluid flow stress changed to spindle shape and aligned in the flow direction. The mechanism is also assumed to be dependent on tyrosine kinase activity, intracellular calcium and an intact microtubule network. It is thus sug-

gested that the stretched load may affect the cell morphological change but not affect the cell alignment.

With respect to the expression of MMPs, TIMPs and proinflammatory cytokines, cytoskeletal deformation induced by cellular changes in morphology was indicated [73]. Furthermore, the cytoskeletal deformation was indicated to be associated with regulation of the gene expression for ECM properties [74]. Meanwhile, it is speculated if the expression of MMPs is a direct effect of excessive mechanical stimuli or an indirect effect through the stimulation of various cytokines such as IL-1 beta and TNF-alpha. With respect to this question, Honda et al. [71] derived an interesting finding that the gene expression of MMP-1, 3, and 9 was observed in the loaded cultures treated with cycloheximide, indicating that the induction of MMP mRNA is not pertinent to the stimulation of cytokines and other inflammatory products. It is also reported that the gene expression of MMP-1, 3, and 9, but not MMP-2 is regulated by the activation of protein kinase C (PKC) in vascular smooth muscle or chondrocytes [75,76] and that a cyclic tensile load activates PKC in chondrocytes [76].

It is thus shown that excessive stresses induce changes in cartilage cell morphology, reducing a synthesis of cartilage matrices such as type II collagen and proteoglycan, leading to lower resistance of cartilage tissues to external stimuli. Direct effects of the excessive mechanical stress were observed for the induction of MMPs even in the absence of protein synthesis through the recognition of cytoskeleton and activation of PKC following cellular changes in shape. Finally, it is demonstrated that induction of MMPs and proinflammatory cytokines and quantitative imbalance between MMPs and TIMPs directly produce the destruction of cartilage matrices leading to bone or cartilage resorption in the mandibular condyle.

4.2. Effects of mechanical stimuli with different frequencies on the metabolism of chondrocytes

In the preceding discussion, the influences of excessive mechanical stimuli on the metabolism of articular cartilage have been well documented with the speculated mechanisms. The remaining parameters of mechanical stimuli, *i.e.* compressive or tensile, static or dynamic, high or low frequency, and so on, have to be taken into considerations with a special reference to biologic and cellular responses.

Mechanical loading is classified into static and dynamic ones by its frequency. Various studies conducted using cartilage tissue explants have demonstrated that sustained loading induced the reduction of cartilage metabolism [77,78], whereas intermittent mechanical stimulation enhanced cartilage metabolism irrespective of the loading type, tension and compression [79—81].

From these considerations, influences of loading frequency on the metabolism of chondrocytes were examined [82]. Intermittent tensile stress upregulated the syntheses of DNA and proteoglycan in chondrocytes at the proliferating stage and matrix-forming stages, respectively. Especially, an intermittent tensile stress with 30 cycles/min or the higher frequencies increased significantly the chondrocyte metabolism. Intermittent compressive stress also significantly enhanced the syntheses of DNA and proteoglycan in chondrocytes, whereas sustained compression significantly decreased these syntheses. These findings suggest that the proliferation and differentiation of growth plate chondrocytes are regulated by the mechanical loading and that the chondrocyte metabolism is enhanced with an increase in the frequency.

One possible mechanism for the cell recognition about mechanical stimuli may be explained by a fact that changes in the level of intracellular calcium ions ($[Ca^{2+}]i$) is caused by the fluid flow [83], which may be generated by cyclic loading and release of osmotic pressure to the collagen gel. Therefore, intermittent stresses might induce the intra- or extracellular Ca^{2+} mobilization, resulting in the promotion of chondrocyte metabolism.

In conclusion of this section, the metabolism of chondrocytes is significantly enhanced by the intermittent mechanical stress even if the magnitude is lower, suggesting that the frequency of mechanical stress may be the most important factor for modulating the metabolism of chondrocytes.

4.3. Signal transmission of mechanical stimuli through cell surface ion channels

Association of biologic and cellular changes with mechanical stimuli has been well documented in the preceding sections. Therefore, based on an evidence that mechanical stress regulates chondrocyte proliferation and differentiation via some cell surface ion channels [84], Tanaka et al. [85], examined if a specific ion channel is involved in the cascade during the induction of PTHrP by mechanical strain. Cyclic mechanical strain, applied to rat growth plate chondrocytes at a frequency of 30 cycles/min, significantly increased PTHrP mRNA levels in chondrocytes. The induction of PTHrP was inhibited by nifedipine, a Ca^{2+} channel blocker, but not by the blockers of stretch-activated channel.

Yellowley et al. [86] showed that the fluid flow caused mobilization of intracellular Ca^{2+} in articular chondrocytes by the activation of G-protein. Furthermore, it was reported that either intra- or extracellular Ca^{2+} mobilization was highly associated with regulation of chondrocyte proliferation and maturation. Therefore, when the cyclic mechanical forces are applied to the bottom of the Flexercell dishes, the cells are exposed to fluid flow stress [82,83], which may consequently up-regulate the expression of PTHrP mRNA through a signal transduction pathway via the mobilization of Ca^{2+}.

Meanwhile, Motokawa et al. [87] examined the influences of Gd^{3+} (gadolinium), an S-A channel inhibitor, and nifedipine as a L-type calcium channel blocker for the expression of VEGF and M-CSF in osteoblastic cells with mechanical stimuli. Gadolinium treatment reduced the amount of mRNA and protein concentration but nifedipine had no effect. These findings suggest that cyclic tensile forces increase the expression of VEGF and M-CSF in osteoblastic MC3T3-E1 cells via S-A channel. They explained these findings by a hypothesis that mechanical stress activated cellular mechanotransducers such as mechanosensitive ion channel, cytoskeleton and integrins. S-A channel is a membrane stretch-activated ionic channel, which is localized in osteoblast-like cells [88]. Naruse and Sokabe [89] showed that stretching cellular membranes increased intracellular Ca^{2+} concentration in human umbilical endothelial cells, and that the Ca^{2+} response

disappeared when extracellular Ca^{2+} was removed or treated with Gd^{3+} which is a potent blocker for the S-A channel. It was also demonstrated that cell orientating and elongating responses of cultured endothelial cells to cyclic stretch were inhibited by the removal of external Ca^{2+} or by adding Gd^{3+} [90]. These findings suggest that cell orientating and elongating are mediated by Ca^{2+} permeable S-A channels that exist on the membrane of endothelial cells. Recently, the eukariotic gene (Mid1) encoding S-A channel was identified from yeast. It was revealed that Mid1 acts as a calcium-permeable, cation-selective stretch-activated channel [91]. Thus, it may be confirmed that mechanical stretch to osteoblastic MC3T3-E1 cells might cause them to express VEGF and M-CSF mediated by the S-A channel, indicating that the signal transmission of mechanical stimuli to osteoblasts is different from that to chondrocytes, elucidated previously by Tanaka et al. [85]. This may require further investigation in detail in near future.

5. Clinical implication and concluding remarks

TMD has been regarded as one of important diseases in dentistry. Among TMDs, internal derangement of the TMJ is the most prevalent in adolescent subjects [7]. It is emphasized that a certain type of malocclusion with a lack in occlusal stability produces condylar displacement in the TMJ space, and then disk displacement is induced as the condyle occupies concentric position [11,12]. Another explanation for TMJ internal derangement, derived from biomechanical studies on joint friction and synovial lubrication, is that pathologic changes in the TMJ space generate reduced viscosity of synovial fluid and greater friction, which finally induce disk displacement in TMJ internal derangement [30,32].

For the treatment of TMJ-OA, we firstly have to perform appropriate and precise examinations enough for differential diagnosis [7,92]. In addition to the conventional examinations, a highly advanced biochemical examination of urinary bone resorption markers (pyridinoline and deoxypyridinoline) has recently been used for the detection of bone or cartilage destruction in TMJ-OA [93,94]. During a series of treatment after differential diagnosis, we have to achieve TMJ unloading or the biomechanical equilibrium by means of condylar repositioning, if indicated, and the subsequent occlusal reconstruction without producing adverse influences on TMJ structures and functions [2,95].

As a summary of this review article, a schematic illustration is depicted for the mechanisms of TMJ-OA and the sequence (Fig. 1). An induction of large compressive stresses in the anterior and lateral areas on the condyle was recognized as an initial factor. Increase of friction at the articular surface was indicated as a cause of larger stress and the relevant disk displacement. Excessive stresses on the condyle induced a decrease in the thickness of cartilage layers and an increase in the numbers of clast cells. Degenerative changes in the condylar cartilage and the expression of bone resorption-related factor were also observed. In a biochemical aspect, excessive mechanical stimuli, irrespective of compressive or tensile one, induced HA fragmentation, expression of proinflammatory cytokines and VEGF, an imbalance between MMPs and TIMPs, all of which are assumed to induce lower resistance to external stimuli and degenerative changes leading to bone and cartilage resorption. Furthermore, condylar resorption affects intraarticular mechanical environment which further induce degenerative changes in a progressive manner. If such a sequence is interrupted by an appropriate therapeutic system with an aid of sufficient host remodeling capacity, a functional and adaptive remodeling may be achieved [1,17], as noted by a dotted arrow in Fig. 1.

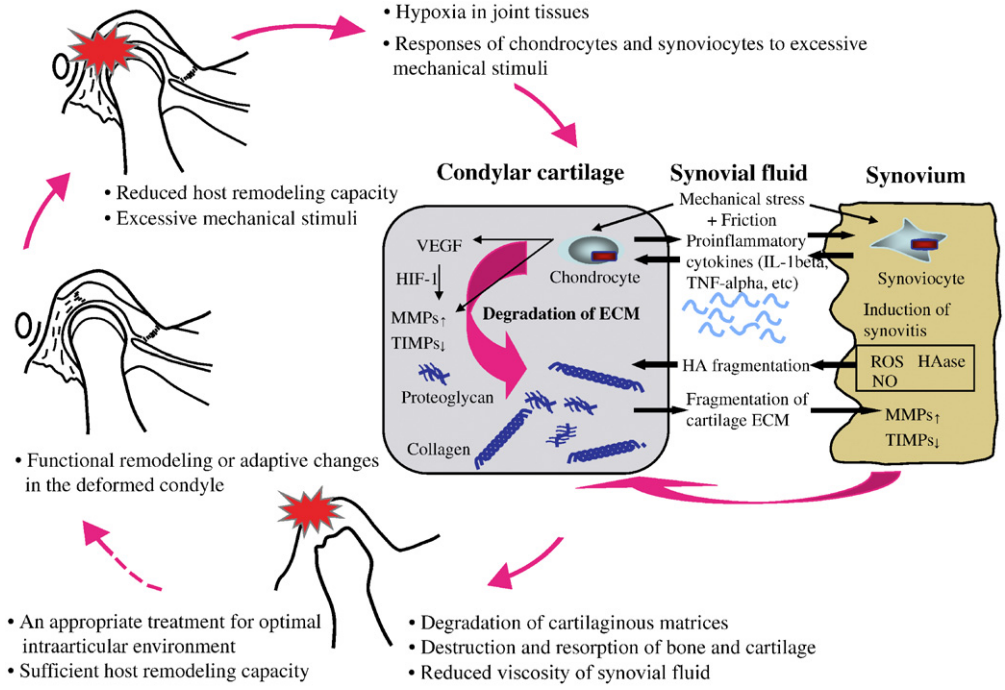

Figure 1 Schematic illustration for the mechanisms of degenerative changes in the articular cartilage on the mandibular condyle.

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