Mechanisms of Temporomandibular Joint-Osteoarthrosis (TMJ-OA) :Biomechanical, Histological and Biochemical Evidences

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ABSTRACT

Condylar resorption in the TMJ or TMJ-OA has been experienced occasionally in daily orthodontic practice and recognized to induce substantial influences on craniofacial morphology and the treatment outcomes. This study was designed to investigate the mechanisms of TMJ-OA by means of biomechanical, histological and biochemical approaches. Biomechanical study with finite element stress analysis revealed an existence of large compressive stresses in the anterior, middle and lateral areas on the condyle and prominent increases in the compressive stresses in association with vertical discrepancy of the craniofacial skeleton. Such skeletal discrepancy, simulated in growing rats by placing a metal plate on the upper molars, produced a decrease in the thickness of cartilage layers and an increase in the number of TRAP-positive cells, both of which lead to degenerative changes in the articular cartilage of the mandibular condyle. Furthermore, excessive tensile stresses, applied to articular chondrocytes with use of the Flexercell Strain Unit, induced an imbalance between matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs), which is assumed to induce lower resistance to external stimuli and degenerative changes leading to the resorption of bone and cartilage. It is thus shown that excessive or imbalanced mechanical loading on the TMJ components from occlusal and skeletal discrepancies induce various degenerative responses of cartilaginous tissues and articular chondrocytes, leading to the destruction of bone or cartilage in TMJ-OA.

KEY WORDS: temporomandibular joint disorder, osteoarthrosis, condylar resorption, mechanical stress, orthodontic treatment

INTRODUCTION

Temporomandibular joint disorder (TMD) has become an important disease in the field of dentistry and/or orthodontics (Egermark and Thilander, 1992; Greene, 1982; Tanne *et al.*, 1993). Under such clinical background, various studies have been conducted to elucidate the nature and causes of TMD in association with various etiologic factors (Arnett *et al.*, 1996; Artun *et al.*, 1992; Larsson and Ronnerman, 1981; Laskin, 1973; Ozawa *et al.*, 1999; Rinchuse, 1987; Sugiyama *et al.*, 1997). 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 (Riolo *et al.*, 1987; Roth, 1973).

Background of the present study

In order to elucidate the nature of TMD and the causative factors , we have been conducting a series of studies for the TMD-related problems or parameters. These subjects are 1) the nature and prevalence of TMD in orthodontic population, 2) association of malocclusion with TMD, 3) association of condylar position with disk displacement in TMD, 4) association of craniofacial morphology with TMD, and 5) influences of TMD, TMJ-OA in particular, on craniofacial morphology.

Firstly, prevalence of TMD was examined in the patients of our clinic. In this survey, the percentage of TMD patients to the total number of patients was approximately 14% (Ozawa, 1996). It is surprising to know very high prevalence of TMDs, which are mostly occupied by TMJ-internal derangement (ID) with various intra-articular pathologies, in adolescent patients with malocclusion, although most of the patients visited our clinic to undergo orthodontic treatment, without complaining of TMD symptoms. It is also of a clinical significance that adult population has higher prevalence (Nakamoto *et al.*, 1998), and jaw

deformity patients exhibit substantially higher prevalence (Nonoyama *et al.*, 1998) 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 in our clinic (Ozawa, 1996).

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 (Tanne *et al.*, 1993). Thus, some specific types of malocclusion were significantly associated with the occurrence of TMD in the patient group. It is also suggested from this finding that condylar displacement in the TMJ space associated with these malocclusions may change disk position realtive to the displaced condyle and result in the onset of TMJ-ID.

As a next, we examined the association between condylar position in the TMJ space and pathologic status of TMJ-ID. Condylar position was more posterior in anterior disk displacement with reduction (AWWD), whereas concentric in anterior disk displacement without reduction (ADDWo) (Sugiyama *et al.*, 1997). It is indicated that condylar position is directly relevant to the disk displacement and the nature of TMJ-ID, or the progress in TMJ-ID from ADDW to ADDWo (Artun *et al.*, 1992; Ozawa *et al.*, 1999; Sugiyama *et al.*, 1997). These findings provide such clinical implication that repositioning of the condyle and disk should be performed as soon as possible in early-stage TMJ-ID, which is featured as a mild disk displacement with reduction associated with a clinical sign of early-type clicking during jaw movement.

Then, the association between craniofacial morphology and pathologic status of TMJ-ID was examined by means of a Spearman's rank correlation analysis. The size (Go-Me, r = -0.39) and position (SNB angle, r = -0.70) of the mandible presented significant negative correlations and the mandibular plane (SN/Mp, r = 0.39) and ANB (r = 0.57) angles exhibited significant positive correlations with the pathologic stages I through V defined by Wilkes (1989) (Ozawa, 1996; Ozawa *et al.*, 1994). It is shown from these results that the progress in pathologic status of TMJ-ID is highly related to more severe vertical discrepancy of the craniofacial skeleton, which is a morphologic feature of Skeletal 2 open bite with small and retropositioned mandible. It is thus speculated that vertical discrepancy of the craniofacial complex with less developed mandible and mandibular asymmetry are highly associated with the degree of TMJ-ID or the progress in pathologic status in the TMJ induced bilaterally and unilaterally, respectively (Nonoyama *et al.*, 1998; Ozawa, 1996; Schellhas, 1998).

The final topic is the influence of TMJ-OA or condylar resorption on craniofacial growth and morphology. The influence has already been demonstrated in the preceding section in terms of the association between craniofacial morphology and TMD. The evidence is examined here in an adolescent patient. This patient came to our clinic at the age of 16-year-old. She had a retrognathic lateral soft tissue profile due to Class II maxillary protrusion with small mandible. Since then, she came to our clinic twice, however, no treatments were performed. At the age of 28-year-old, 12 years after the initial visit, the retrognathic profile became more prominent in association with larger overjet. Changes in lateral soft tissue profile and craniofacial morphology are shown in Fig. 1. Please note backward and downward rotation of the mandible and the subsequent retrognathic profile, which are speculated due to progressive resorption of the condyle for the 12 years. These findings provide us with very interesting and useful clinical implications such that condylar resorption in TMJ-OA produces jaw deforminty with less developed and distally located mandible and affects the outcomes and stability of orthodontic treatment (Arnett *et al.*, 1996; Nonoyama *et al.*, 1998; Ozawa, 1996; Schellhas, 1998).

Another evidence is presented for a 21-year-old female (Tanaka *et al.*, 2000). She had TMJ pain in the left TMJ, muscle tenderness for the left masseter and difficulty in jaw opening. The amount of maximum mouth opening was 33.0 mm. Molar relation was Angle Class II and overjet and overbite were 6.0 mm and -3.0 mm. Open bite was found at the anterior to the premolar region (Fig. 2A). On the tomogram of left condyle, .severe flattening was observed on the anterior surface (Fig. 2B). On the MR images, anterior displacement of the disk without reduction and disk deformity were observed for both TMJs.

From these examinations, this case was diagnosed as ADDWo or stage IV TMJ-ID or TMJ-OA (Wilkes, 1989). Posterior bite splint was first used with manipulation to the TMJ to induce counter-clockwise rotation of the condyle and mandible followed by orthodontic occlusal reconstruction, aiming to reduce TMJ loading in the anterior region where condylar resorption was prominent. As a result of a series of treatment, stable occlusion was obtained (Fig. 3A), although disk repositioning was not achieved as was expected before treatment (Tanaka *et al.*, 2000). It is surprising that the left condyle was reformed or exhibited unexpected adaptive responses (Fig. 3B). It is demonstrated 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 (Arnett *et al.*, 1996; Tanaka *et al.*, 2000).

Hypothesis

These findings are very useful for understanding the nature of TMD and can be used as a background for the following studies to elucidate the mechanisms of TMJ-OA, indicating that changes in occlusion and the relevant condylar position may produce disk displacement leading to TMJ-ID. It would also be hypothe-

sized from these findings that such occlusal or skeletal discrepancy produces 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 TMJ-OA.

The purpose of this study

This study was designed to elucidate the mechanisms of bone or cartilage resorption in the mandibular condyle in TMJ-OA by means of biomechanical, histological, and biochemical approaches.

MATERIALS & METHODS

Finite element analyses for TMJ loadings in response to vertical skeletal discrepancy

A three-dimensional model of the mandible including the TMJ was constructed for stress analysis with finite element method (FEM) from a young human dry skull (Tanaka *et al.*, 1994). The model is consisted of 2088 nodes and 1105 solid elements (Fig. 4). Hereafter this model is referred to as a standard model. For loading conditions, the magnitude of muscle forces was determined to exert a resultant force of 500 N, simulating the maximum clenching. During loading, the model was restrained at the superior region of the temporal bone to avoid sliding movement of the model. Modeling procedure in detail and the accuracy are described elsewhere (Tanaka *et al.*, 1994).

For stress analysis, the standard model was modified to represent vertical discrepancies of the craniofacial complex by changing the shape of mandible, maintaining the number of nodes and elements for the standard model (Tanne *et al.*, 1995). The gonial angle was changed from 110.1 to 134.1 degrees with a 6.0-degree increment (mean; 122.1 degrees). The mandibular plane angle to the Frankfort horizontal plane (FMA) was similarly varied from 18.5 to 42.5 degrees with a 6.0-degree increment (mean; 30.5 degrees). Stress analysis was executed on a personal computer with the FE software, ANSYS from ANSYS Inc. (Houston, USA). Three principal stresses were analyzed on the standard and modified models for the condyle, disk and glenoid fossa. The stresses were evaluated for five (anterior, middle, posterior, medial, and lateral) areas of the TMJ in association with various skeletal patterns.

Histomorphometric analyses for condylar responses to vertical skeletal discrepancy in growing rats

Thirty 4-week-old male Wistar strain rats were used. Under general anesthesia with sodium pentobarbital, a one mm-thick metal plate was bonded onto the occlusal surface of the maxillary molars to induce a backward and downward rotation of the mandible and to increase the TMJ loading on the concyle (Fig. 5) (Sugiyama *et al.*, 1999). Lateral cephalograms were taken of all the rats using a rat and mouse cephalometer (Asahi Roentgen, Kyoto, Japan) for morphometric analyses of the mandible.

For histological and histochemical examinations, the head of each animal was dissected and cut into serial frontal and sagittal sections of 6 μm thickness. The 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 osteoclasts (Sugiyama *et al.*, 1999).

Biochemical examination of condylar cartilage cells in response to a high magnitude cyclic tensile stress

Chondrocytes were isolated from the surface and middle zones of the knee joint cartilage of 4-week-old Japanese male rabbits. The cells were seeded at a cell density of 5 x 10^4 per 25 mm Flexercell plate dish. A high magnitude tensile stress of 17 kPa was applied, at a frequency of 30 cycles/minute, to the chondrocytes in the Flexercell type I flexible-bottomed dishes using the Flexercell strain unit (Flexcell Corp. Mckeesport, USA) for 12hr or 24hr (Fig. 6) (Honda *et al.*, 2000).

We examined the protein level of cartilage matrixes and the gene expression of matrix metalloproteinases (MMPs), tissue inhibitors of matrix metalloproteinases (TIMPs) and proinflammatory cytokines such as IL-1b and TNF-a in loading with the high magnitude cyclic tensile stress (Honda *et al.*, 2000). Control cultures were cultivated for the same period using Flexercell type II rigid-bottomed dishes.

RESULTS

TMJ loadings in response to vertical skeletal discrepancy

Mean stresses are shown for the condyle, disk and glenoid fossa (Table 1). Large compressive stresses were induced by the maximum clenching in the anterior, middle and lateral regions, whereas tensile stresses were found in the remaining areas (Tanaka *et al.*, 1994).

Meanwhile, these stresses were changed in association with varying mandibular plane angles (FMAs) and exhibited more substantial changes than those with varying gonial angles (Tanne *et al.*, 1995). Changes in the stresses were nonlinear and particularly drastic when the angle became more than 36.5 degrees. Mean stresses on the condyle and glenoid fossa were almost constant within the range from 18.5 to 36.5 degrees, and increased substantially in the anterior and posterior regions with FMAs greater than 36.5 degrees (Fig. 7).

It is shown that the maximum clenching produces large compressive stresses in the anterior and lateral areas of the condyle, where idiopathic condylar resorption is observed most frequently. It is also

demonstrated that vertical skeletal discrepancy induces an increase of TMJ loading and lack in biomechanical equilibrium for the TMJ components.

Histomorphometric changes in rat condylar cartilage layers from simulated vertical skeletal discrepancy

At the end of the experiment, decreased ramus height and large gonial angle were found in the experimental group, demonstrating an appearance of vertical skeletal discrepancy with less developed mandible (Sugiyama *et al.*, 1999).

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 (Table 2). The number of TRAP-positive cells was significantly greater in the experimental group than in the controls at the initial phase of experimental, and then adaptive responses were induced up to the end of experiment (Fig. 8) (Sugiyama *et al.*, 1999).

From these findings, it is shown that biomechanical changes in the intra-ariticular environment associated with vertical skeletal discrepancy influences or inhibits cartilaginous growth of the condyle or mandibular growth to a considerable extent, if induced during growing period.

Responses of condylar cartilage cells to a high magnitude cyclic tensile stress

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 subjected to high magnitude cyclic tensile stress (Fig. 9). Furthermore, PCR-Southern blot analysis showed that the high magnitude cyclic tensile stress increased mRNA levels of MMP-1, MMP-3, MMP-9, IL-1b, TNF-a and TIMP-1 in the cultured chondrocytes, while the levels of MMP-2 and TIMP-2 were unchanged (Fig 10) (Honda *et al.*, 2000).

It is 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. It is also 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 on the mandibular condyle.

DISCUSSION

TMD has been regarded as one of important diseases in dentistry. In the fields of orthodontics, TMD has become an important topic in terms of the substantial influences on stomatognathic functions, craniofacial morphology and orthodontic treatment outcomes (Roth, 1973; Janson and Hasund, 1981; Ozawa, 1996; Riolo *et al.*, 1987; Sadowsky and BeGole, 1980; Tanaka *et al.*, 2000).

Among TMDs, internal derangement of the TMJ is the most prevalent in orthodontic population during growing period (Ozawa, 1996), therefore, it is of a great significance to elucidate the causative factors, while TMD is a multi-factorial disease in nature. According to our previous studies, 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 (Sugiyama *et al.*, 1997; Weinberg, 1979). Another explanation for TMJ-ID, 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-ID (Kawai *et al.*, 2004; Tanaka *et al.*, 2004 and 2005a).

As a result of the present study, it is shown that excessive TMJ stress, induced by vertical discrepancy of the occlusion and craniofacial skeleton, directly changes the metabolism of cartilage by reducing the matrix components and causing a quantitative imbalance between MMPs and TIMPs. It is also confirmed that excessive mechanical loading is essentially responsible for degenerative change and the subsequent resorption of bone and cartilage in the TMJ, whereas optimal mechanical stresses of 7 and 10 kPa significantly enhanced cell proliferation and syntheses of collagen and proteoglycan (Tanaka *et al.*, 2005b).

Based upon these findings, the mechanisms of TMJ-OA are summarized as a sequence depicted in the flow chart (Fig. 11). It is well understood that condylar resorption substantially affects the occlusion and maxillo-mandibular relation and produces jaw deformity in extreme cases, as was demonstrated in an adolescent case shown in Fig. 1 (Arnett *et al.*, 1996; Ozawa, 1996; Qzawa *et al.*, 1999; Schellhas, 1989). Condylar resorption, if induced by various factors at once, affects intra-articular mechanical environment which further induces degenerative changes and condylar resorption in a progressive manner. If such a sequence is interrupted by a certain treatment with an aid of sufficient host remodeling capacity, a functional and adaptive remodeling may be achieved as shown in Fig. 3 (Arnett *et al.*, 1996; Tanaka *et al.*, 2000).

For the treatment of TMJ-OA, we firstly have to perform appropriate and accurate examinations enough for differential diagnosis (Ozawa, 1996; Ozawa and Tanne, 1997). 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

(Imada *et al.*, 2003; Tanimoto *et al.*, 2004). During a series of treatment after differential diagnosis, we have to achieve TMJ unloading or the biomechanical equilibrium by means of condylar repositioning and orthodontic occlusal reconstruction, although disk repositioning may not be succeeded in most cases. Thus, orthodontic approach is confirmed as an effective tool for the achievement of optimal intraarticular environment secured by stable occlusion, if performed appropriately without producing adverse influences on TMJ structures and functions (Artun *et al.*, 1992; Rendell *et al.*, 1992; Wyatt, 1987).

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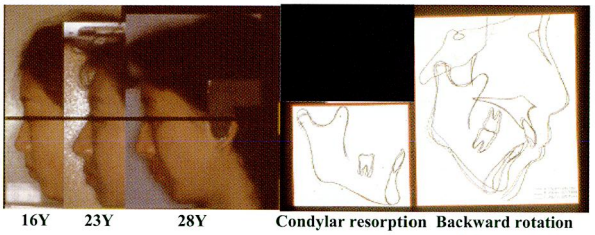

Fig. 1 A clinical evidence of TMJ-OA in adolescent female of 16-year-old and the changes in the lateral profile and craniofacial morphology for 12 years

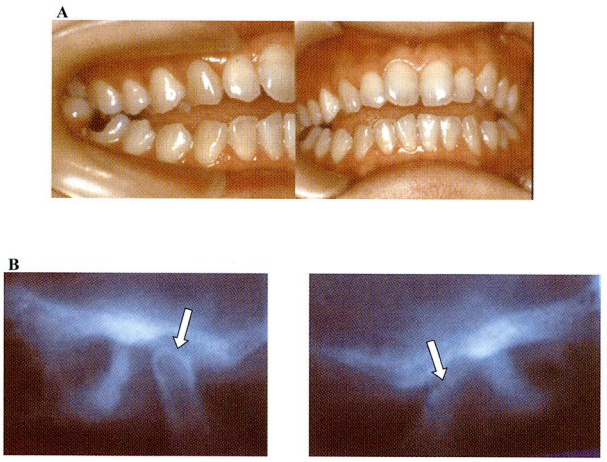

Fig. 2 An adult open bite case with TMJ-OA before treatment
A: Intraoral photos
B: Lateral tomograms, arrows indicate resorption of the condyle

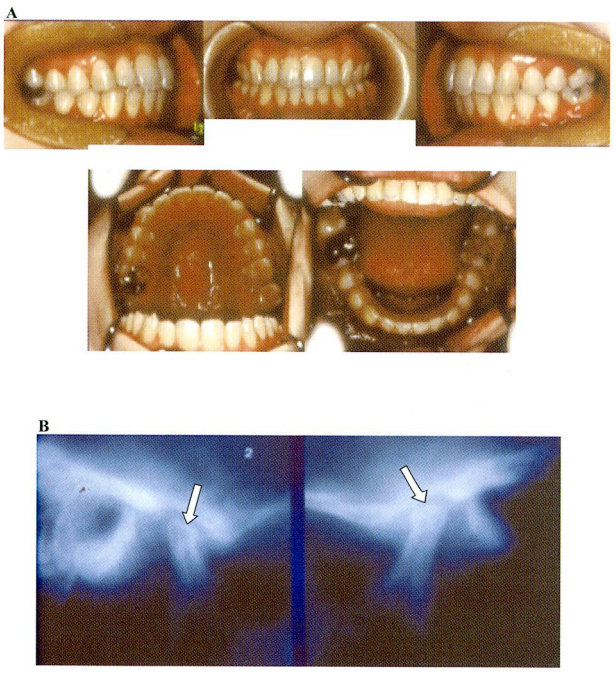

Fig. 3 An adult open bite case with TMJ-OA after treatment
A: Intraoral photos, stable occlusion is obtained.
B: Lateral tomograms, arrows indicate functional and adaptive remodeling of the condyle

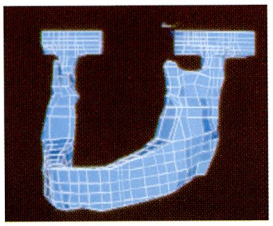

Fig. 4 A three-dimensional finite element model of the mandible including the TMJ

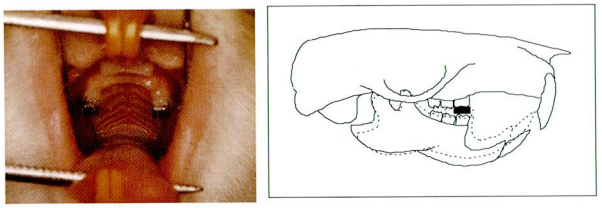

Fig. 5 Experimental appliance to induce backward and downward displacement of the mandible, simulating vertical skeletal discrepancy which is assumed to increase the TMJ loading

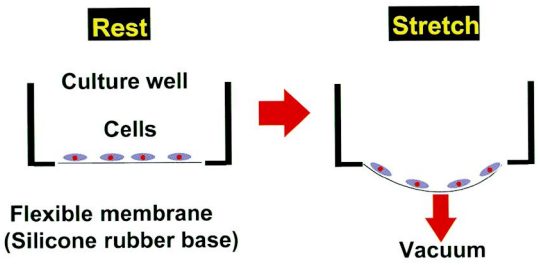

Fig. 6 Vacuum-induced flexion cycling with a Flex I culture plate membrane to apply a high magnitude cyclic tensile stress on cultured articular chondrocytes

Mean Stresses in the TMJ

	Anterior	Middle	Posterior	Lateral	Medial
Condyle	-1.642	-0.543	0.664	-1.017	0.521
Glenoid fossa	-0.440	-0.410	0.445	-0.351	0.103
Articular disk	-0.403	-0.200	0.258	-0.342	0.041

(Unit : MPa)

Table 1 Mean stresses on the TMJ structures

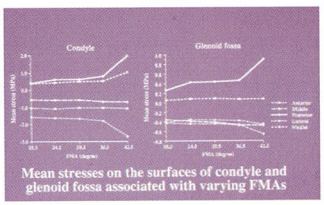

Fig. 7 Changes in the mean stresses on the condyle and glenoid fossa in association with vertical skeletal discrepancy simulated by varying mandibular plane angles

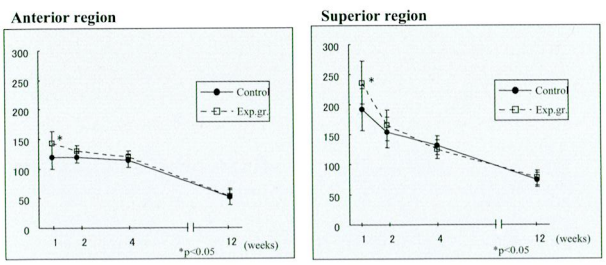

Fig. 8 Changes in the number of TRAP-positive cells in the cartilage layers on the mandibular condyle in response to vertical skeletal discrepancy, which is assumed to increase TMJ loading

Table 2 Changes in the thickness of articular cartilage layers in the anterior region of the mandibular condyle in response to vertical skeletal discrepancy

	Experimental period (weeks)							
	1		2		4		12	
	Control	Exp. gr.	Control	Exp. gr.	Control	Exp. gr.	Control	Exp. gr.
Fibrous layer	37.0 (11.6)	22.5 * (7.4)	27.8 (8.7)	20.2 (8.2)	26.9 (7.5)	27.0 (7.6)	32.1 (5.5)	31.9 (9.2)
Proliferative layer	44.4 (7.9)	29.2 ** (5.7)	35.9 (2.6)	29.2 ** (4.6)	35.4 (6.0)	29.7 (7.2)	38.8 (8.8)	31.3 (7.3)
Maturative/ hypertropic layer	173.6 (14.5)	147.5 * (21.9)	142.3 (21.8)	112.5 ** (12.0)	105.4 (18.5)	103.8 (9.3)	95.3 (15.7)	85.2 (15.2)
Total	255.0 (24.0)	199.3 ** (31.1)	205.9 (31.1)	161.9 ** (21.0)	168.2 (18.4)	159.8 (21.1)	167.6 (17.3)	148.4 (18.5)

( ); SD, *p<0.05, **p<0.01 (Unit : μm)

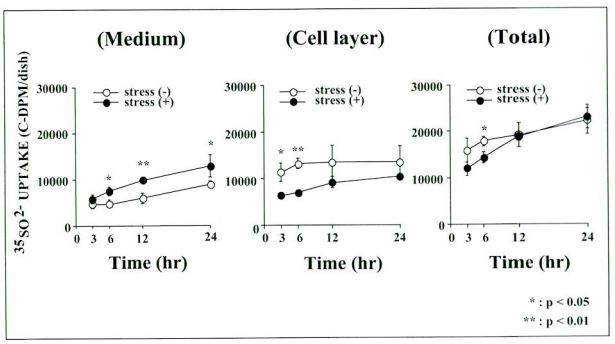

Fig. 9 Effect of a high magnitude cyclic tensile stress on proteoglycan synthesis in cultured rabbit articular chondrocytes

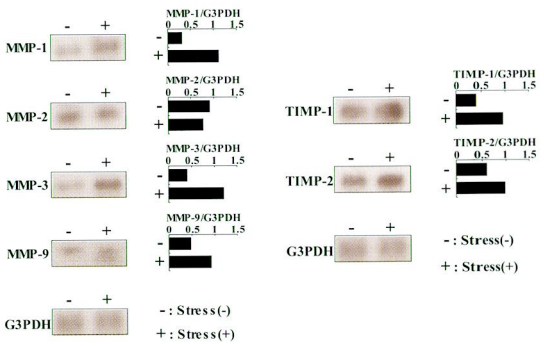

Fig. 10 Effects of a high magnitude cyclic tensile stress on the gene expression of MMPs and TIMPs in cultured rabbit articular chondrocytes

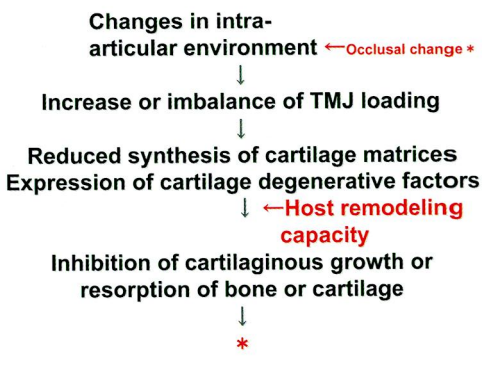

Fig. 11 Mechanisms of condylar resorption