in vivo *36*: 2126-2133 (2022)
doi:10.21873/invivo.12938

Condylar Resorption Following Compressive Mechanical Stress in Rabbit Model - Association of Matrix Metalloproteinases

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Abstract. *Background/Aim: Idiopathic condylar resorption (ICR) is a morphological change of the condylar head that occurs following orthodontic treatment or orthognathic surgery. This complication is serious, as it can cause relapse after mandible treatment. The aim of this experimental study was to evaluate the mechanism of influence of condylar resorption on compressive mechanical stress in temporomandibular joint following a change in occlusal position by mandible advancement. Materials and Methods: An osteotomy procedure at the midline of mandible was performed in 15 rabbits, with the left side moved forward by 3.5 mm. Advancement of the left side of the mandible resulted in compressive mechanical stress on condylar head on the left side. Samples were subjected to micro-computed tomography, histological staining and immunohistochemistry. Results: The area and depth of anterior condylar resorption at two weeks were significantly different as compared to those at one week ($p<0.05$). TRAP staining confirmed the significantly largest number of TRAP-positive cells after two weeks ($p=0.02$), compared to one week. MMP-3 and MMP-13 immunostaining of the anterior condylar head at two weeks revealed high levels of both proteins from the surface to the deep layer of cartilage. Conclusion: Compressive mechanical stress following mandible advancement results in load on the anterior surface of the condylar head, which leads to bone resorption there, and induces MMP-3 and MMP-13 related to degradation of condylar head cartilage.*

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Key Words: Idiopathic condylar resorption, temporomandibular joint, metalloproteinases, mechanical stress.

Idiopathic condylar resorption (ICR) is known as a type of progressive resorption of the condylar head that occurs following orthodontic treatment or orthognathic surgery for mandibular retrognathism, including sagittal split osteotomy and distraction osteogenesis, and is one of many factors related to mandibular relapse following those treatments. ICR is also considered to be a refractory disease and its occurrence is difficult to predict.

Furthermore, the involvement of other conditions in the mechanism of ICR development as well as management strategies are generally unknown, thus there is an urgent need to elucidate factors related to etiology and pathogenesis. Arnett *et al*. reported that mechanical stress and sex hormones are factors associated with ICR (1, 2). The present authors previously investigated risk factors related to aggressive condylar resorption after orthognathic surgery, and noted a relationship between large advancement of the mandible and ICR (3), thus suggesting that excessive mechanical stress during intraoperative condyle positioning adds load to the temporomandibular joint (TMJ). Mechanical stress includes two types, compression and traction. Compressive force has been shown to induce osteoclastic bone destruction in the TMJ (4), while Gassner *et al*. reported that tractional mechanical stress reversed suppression of proteoglycan synthesis induced by interleukin-1 (IL-1) (5). Therefore, the

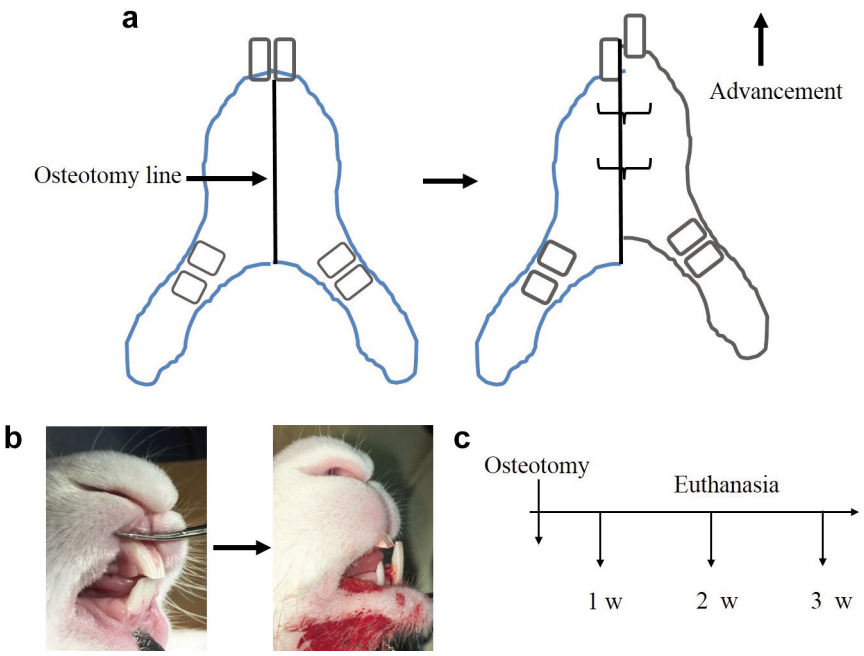

Figure 1. *Schematic diagram of osteotomy in experimental rabbits. The left side of the mandible was advanced, then ligated with a 0.4 mm wire and fixed. (a) Pre- and post-operation photos showing occlusion of part of front tooth (b). Experimental schedule. The rabbits were euthanized at one, two, and three weeks after the operation (c). w, Week(s).*

TMJ is easily influenced by mechanical stresses, including compressive and tractional forces, under several conditions related to changing occlusion. We have previously compared the effects of compressive and tractional stress on the condylar head in model rabbits and showed that excessive compressive mechanical stress has effects on morphological bone resorption (6).

Condylar resorption is considered to be a type of degeneration induced by mechanical stress, as well as inflammatory changes to the synovial membrane and cartilage in the TMJ. It is well known that the extracellular matrix (ECM) consists of collagen type I and type II, as well as proteoglycans (PGs), with aggrecan providing compressibility and elasticity to the articulating surface (7, 8). Metalloproteinases (MMPs) are synthesized intracellularly as inactive zymogens and converted extracellularly to the active form by removal of the amino-terminal propeptide, thus the MMP active form acquires enzymatic activity to cleave specific sites of ECM. Furthermore, MMP-1 and MMP-3 have been found to play important roles in osteoarthritis (OA) progression by degrading the ECM (9-11). Additionally, MMP-13, which shows a high level of degradation activity against type II collagen (12), is also related to OA, as well as MMP-1 and MMP-3. It is considered that clinical features of ICR cause development of OA. With these background issues in mind, the present experimental study was conducted to evaluate the influence of compressive mechanical stress on the TMJ following changing of the occlusal position by mandible advancement using immunohistochemical analysis including MMPs to identify the mechanism of ICR.

Materials and Methods

Animals and experimental procedures. Nineteen Japanese white rabbits, each weighing 2.7-3.0 kg at the beginning of the experiment, were used. The study protocol was approved by the Animal Care and Use Committee of Tohoku University (2016-DnA-042) and all experiments were performed according to the Declaration of Helsinki. All surgical procedures were performed under general anesthesia using intravascular pentobarbital at 0.35 mg/kg and intramuscular ketamine at 60 mg/kg. The mandible was exposed with a submandibular approach, then an osteotomy was performed at the midline and the left side of the mandible was moved 3.5 mm forward, then ligated with a 0.4-mm wire and fixed (Figure 1a and b). The amount of forward movement used was based on previous reports presented by the authors (6, 13). Fifteen rabbits were randomly divided into three groups and euthanized with an overdose of pentobarbital at one, two, and three weeks after surgery (Figure 1c). The left side mandible was moved so that advancement resulted in compressive mechanical stress loaded to the condylar head on the left side, as the disc and glenoid fossa in rabbits are generally located in front of the anterior surface of the condylar head. Front tooth anterior cross-bite on the left side was considered reflect conditions related to loading of compressive mechanical stress to the anterior surface of the condylar head.

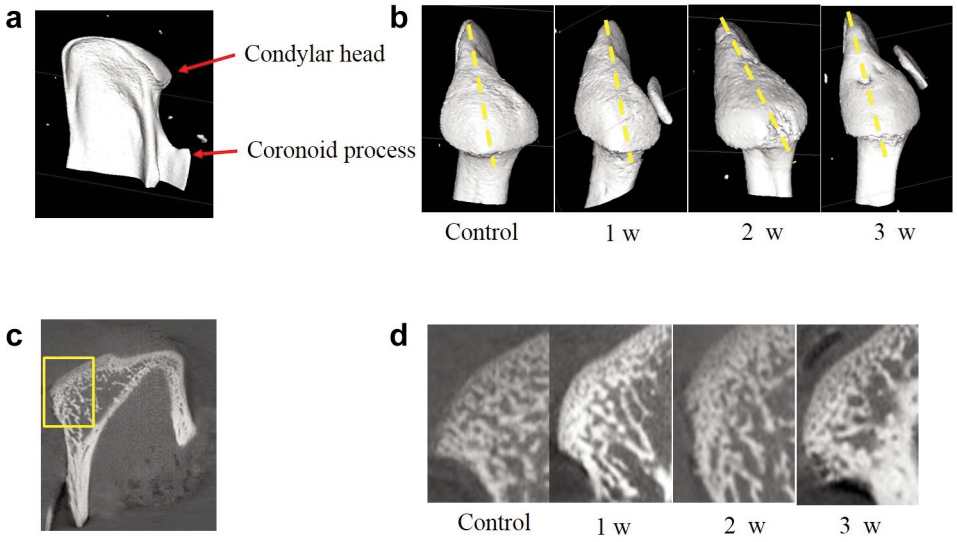

Figure 2. *Representative 3D micro-CT image of ramus of mandible on left side (a). Evaluation and scoring of area of bone resorption shown by 3D micro-CT (b). Evaluation and scoring of depth of bone resorption using cross-sectional sagittal images positioned on plane along line linking anterior surface of condylar head and top of coronoid process (c). Evaluation and scoring of depth of bone resorption using cross-sectional sagittal images (d). w, Week(s).*

As for the rabbits in the control group (n=4), none of the joints received treatment, with the left sides selected as control samples. All rabbits in both groups received normal food and water, with diet consumption and body weight checked each week until euthanasia.

Resorption area and depth shown by micro-computed tomography (micro-CT). The area and depth of resorption on the anterior surface of the condylar head were evaluated using a scoring method presented in our previous studies (6,13). Briefly, micro-CT (Comscantechno, Co., Ltd., Yokohama, Japan) examinations (65 μA and 80 kV) were performed to determine the area and depth of condylar head resorption immediately after euthanasia using samples from the mandible ramus placed parallel to the floor under standard imaging conditions. The findings were evaluated using the Image J software package, ver. 1.52 (NIH, Bethesda, MD). Scoring was performed as follows: 0=normal, 1=1/3 of anterior surface of condylar head shows resorption, score 2=1/3 to 2/3 of anterior surface of condylar head shows resorption, score 3=more than 2/3 of anterior surface of condylar head shows resorption (Figure 2a and b). Additionally, cross-sectional sagittal images were obtained by positioning the plane on a line from the condylar head anterior surface to top of the coronoid process, then resorption depth was scored as follows: 0=normal, 1=cortical bone resorption, 2=cancellous bone resorption (Figure 2c and d). Continuous slice surfaces were used to judge bone resorption visually clear and easy to understand. Two of the authors (Y.K., M.I.) examined the scores for areas and depth in a blinded manner: then, all imaging findings were compared and discussed. In cases of discordance, consensus was obtained after discussion.

Histopathological analysis. Hematoxylin and eosin (HE) staining was performed using the protocol noted in our previous studies (6, 13). Briefly, unilateral specimens were sliced in a sagittal direction with a thickness of 5 μm, then stained using HE. Differences between morphological changes shown by micro-CT and histopathological changes were then noted.

For tartrate-resistant acid phosphatase (TRAP) staining, we used the protocol noted above: osteoclasts were identified using TRAP staining and positively stained multinucleated cells (nuclear number >3) in each well were counted. Two of the authors (S.N. and K.I.) evaluated the results in a blinded manner.

Immunohistochemistry. Sections of articular surfaces of condylar head were air-dried for 30 min and washed 3 times for 5 min with PBS. Endogenous peroxidase was inactivated by incubating the sections in a 0.3% hydrogen peroxide/ethanol solution for 30 min. Deparaffinized sections were incubated with specific antibodies against MMP-3 or MMP-13 (1:200 dilution; Kyowa Pharma Chemical Co, Toyama, Japan), or collagen II (1:200 dilution; Cosmo Bio Co, Tokyo, Japan), followed by fluorescently labeled secondary antibodies. Observations with a Leica DM 250 optical microscope (Leica Microsystems AG, Wetzlar, Germany) were then used to evaluate the intensity of immunostaining on the condylar anterior surface, including the cartilage area. Chondrocytes and the surrounding ECM were graded as negative (-), positive (+) when sporadically or weakly positive, and strongly positive (++) when diffusely and intensely positive. The samples were microscopically evaluated to assess the condylar anterior surface area at ×40 magnification. Two authors (Y.K., Y.Y.) performed calibration of the examinations in a blinded manner.

Statistical analysis. Statistical analyses were performed using the JMP software package, ver. 10 (SAS Institute Japan, Tokyo, Japan). Scores for resorption area and depth were determined using micro-CT findings, TRAP-positive osteoclast numbers, and MMP-3 and MMP-13 immunohistochemistry at each time point were statistically

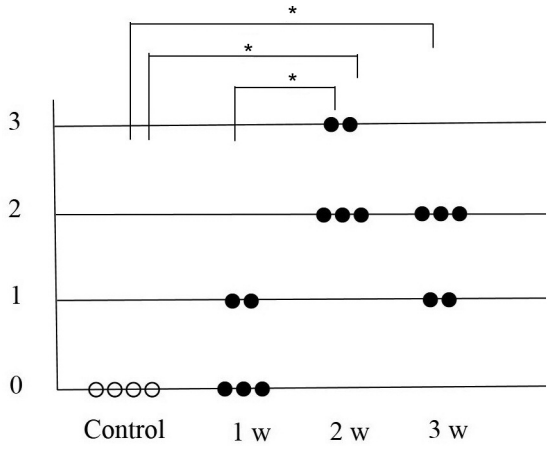

Figure 3. *Area of resorption shown by micro-CT imaging at 1, 2, and 3 weeks (w) after mandible advancement. Each circle represents one animal. 0=normal; 1=cortical bone resorption; 2=cancellous bone resorption; *p<0.05.*

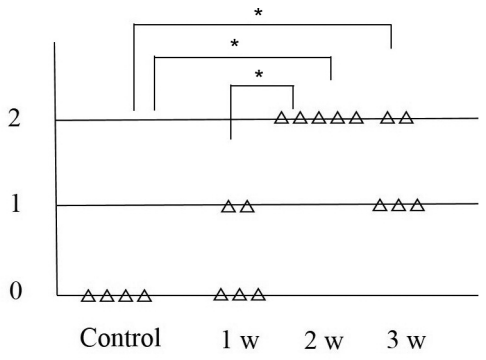

Figure 4. *Depth of anterior condylar head resorption shown by micro-CT imaging at 1, 2, and 3 weeks (w) after mandible advancement. Each triangle represents one animal. 0=normal; 1=cortical bone resorption; 2=cancellous bone resorption; *p<0.05.*

compared using a Steel-Dwass test for multiple comparisons after ANOVA with a Kruskal-Wallis test. The level of significance for all statistical analyses was set at $p<0.05$.

Results

Morphological changes of anterior condylar head. Representative micro-CT findings showing the area of anterior condylar head resorption are presented in Figure 3. The greatest level of anterior condylar head resorption was noted at two weeks after mandible advancement. Bone resorption continued until three weeks after mandible advancement, though the score for the area of anterior condylar head resorption was lower as compared to that at two weeks. Furthermore, there was a statistically significant difference in the area of anterior condylar head resorption at two weeks as compared to that at one week ($p=0.02$) and in the control group ($p=0.02$), and also at three weeks as compared to the control ($p=0.03$).

Figure 4 shows representative micro-CT findings for the depth of condylar head resorption. At two weeks after mandible advancement, the greatest level of bone resorption of the anterior condylar head resorption reached cancellous bone, while reached cortical bone at three weeks. There were statistically significant differences for depth of anterior condylar head resorption at two weeks as compared to that at one week ($p=0.03$) and in the control group ($p=0.04$), and also at three weeks as compared to the control ($p=0.02$).

Histological findings. HE staining confirmed bone resorption on the anterior surface of the condylar head at two and three weeks after mandible advancement (Figure 5). Additionally, it was noted that type II collagen had already begun to decrease at one week after mandible advancement, with the articular cartilage layer beginning to show destruction at this time point (Figure 6). TRAP staining findings confirmed the largest number of TRAP-positive cells at two weeks after mandible advancement, with significant differences at two ($p=0.02$) and three ($p=0.03$) weeks, as compared to one week after mandible advancement (Figure 7a, b and c). Additionally, immunostaining of the anterior condylar head at two weeks after mandible advancement showed the greatest levels of intensity for MMP-3 and MMP-13 both on the surface and in deeper layers (Figure 8, Figure 9, Table I). MMP-3 and MMP-13 expressions were first noted at one week after mandible advancement and reached their peak at two weeks, though there were not statistically significant differences at any postoperative time point.

Discussion

ICR is a morphological change of the condylar head that occurs following orthodontic treatment or orthognathic surgery. This complication is serious, as it can cause relapse after mandible treatment (1, 2). A deeper understanding of TMJ condition before treatment is important. In particular, the techniques used by oral maxillofacial and plastic surgeons can dynamically change occlusion, as they perform intraoperative condylar positioning at the same time. On the other hand, the condylar position is maintained before and after surgery in order to stabilize occlusion (3). When performing intraoperative condylar positioning during orthognathic surgery, condylar head can receive excessive mechanical stress. In our previous experimental study, occlusion in a rabbit model was gradually changed and morphological changes of the condylar head were examined (6). Those results indicated that the greatest amount and depth of condylar resorption occurred under the condition

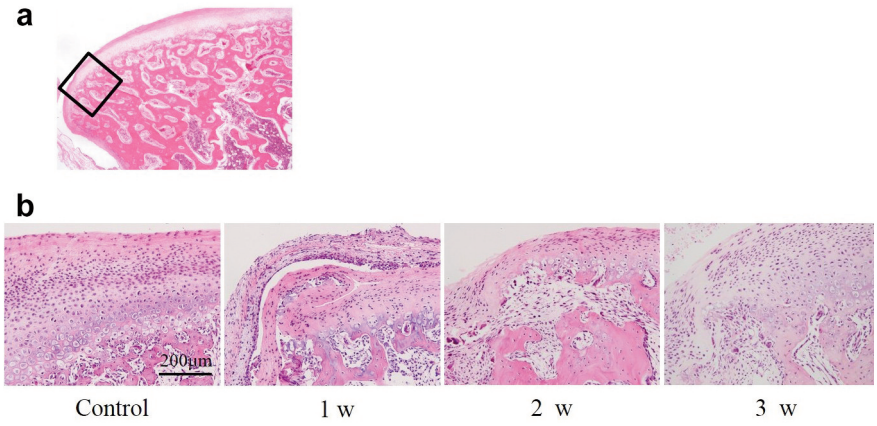

Figure 5. *Representative image of temporomandibular joint with hematoxylin and eosin staining (original magnification, ×12.5) (a). Representative image of temporomandibular joint with hematoxylin and eosin staining (original magnification, ×40) (b). w, Week(s).*

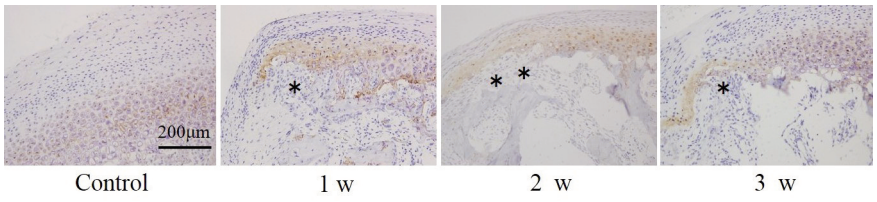

Figure 6. *Representative images of temporomandibular joint with type II collagen staining (original magnification, ×40). *Type II collagen had already begun to decrease, and the articular cartilage layer had been beginning to destruct.*

of compressive mechanical stress rather than tractional mechanical stress. Additionally, the relationship between estrogen and condylar resorption was examined using a rabbit model following an ovariectomy, which indicated that condylar head resorption in the ovariectomy group developed earlier than that in the non-ovariectomy group. Thus, it was concluded that there may be a relationship between estrogen and aggressive condylar resorption (13). Those results identified excessive mechanical stress and estrogen as risk factors for ICR. However, the mechanism of condylar head resorption was not evaluated because of lack of immunostaining analysis. In the present experimental study, we focused on the condylar head cartilage, with the aim to identify the mechanism of ICR using immunostaining analysis, including type II collagen, MMP-3, and MMP-13.

Recently, experimental research has shown that unbalanced occlusion created excessive mechanical stress on the TMJ, leading to TMJ osteoarthritis (14, 15). In our previous studies, occlusion was gradually changed, with a slow process of mechanical stress loading on the condylar head (6, 13), while, in the present investigation, occlusion was dynamically changed. In both conditions, the greatest amount of resorption occurred at two weeks after the operation.

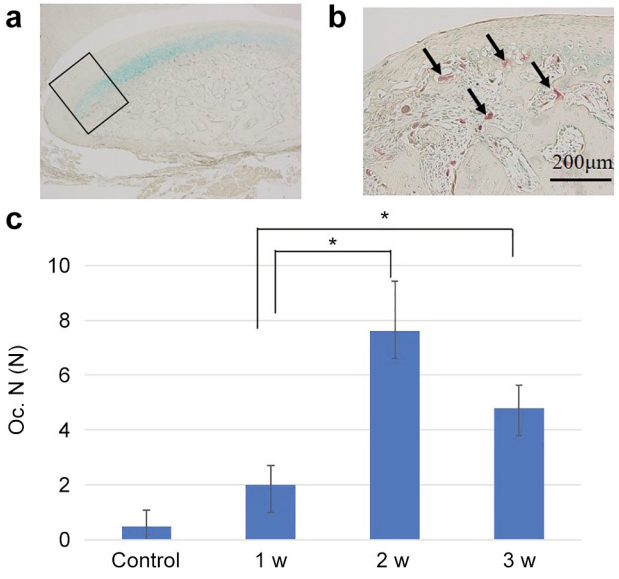

Figure 7. *Osteoclast activity in condylar subchondral bone of temporomandibular joint (TMJ). Tartrate-resistant acid phosphatase (TRAP) staining in subchondral bone of TMJ (original magnification, ×12.5) (a). TRAP-positive osteoclasts with more than three nuclei (b). Comparison of the number of TRAP-positive cells (Oc. N) at 1, 2, and 3 weeks (w) after mandible advancement (c). *p<0.05.*

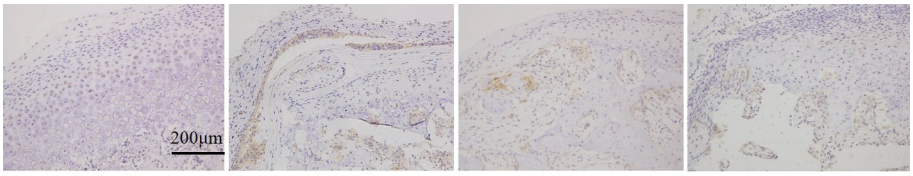

Figure 8. *Representative images of temporomandibular joint with matrix metalloproteinase-3 staining (original magnification, ×40). w, Week(s).*

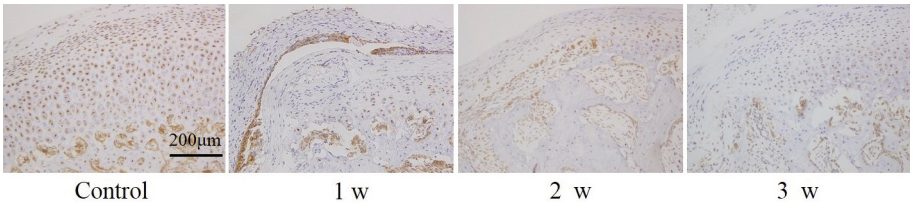

Figure 9. *Representative images of temporomandibular joint with matrix metalloproteinase-13 staining (original magnification, ×40). w, Week(s).*

Table I. *Immunoreactivity for matrix metalloproteases (MMPs). Immunohistochemical reactivity: (–) negative, (+) positive, (++) strongly positive.*

		MMP-3			MMP-13		
	No. of rabbits	(–)	(+)	(++)	(–)	(+)	(++)
Control	4	4	0	0	3	1	0
1 week	5	1	3	1	1	4	0
2 weeks	5	0	1	4	0	3	2
3 weeks	5	1	3	1	1	3	1

In the present experiments, HE staining showed bone resorption on the anterior surface of the condylar head at two weeks after the operation, while destruction of the cartilage layer on the anterior surface of the condylar head was observed at one week by type II collagen immunostaining. This destruction of the cartilage layer of the condylar head continued until three weeks after the operation. Additionally, the greatest number of osteoclasts was observed at two weeks after the operation, based on TRAP staining results. Osteoclasts are well known as bone resorbing cells, which originate from hematopoietic stem cells (16-18), and also involved in dissolving collagen and some matrix proteins through the process of bone resorption (19). In our study, the greatest amount of condylar head bone resorption in micro-CT imaging was also observed at two weeks after operation. These findings provide support for a relationship between bone resorption and osteoclast formation.

It is well known that osteoclasts are related to bone resorption, which is promoted by activation of several inflammatory cytokines (20, 21). Stimulation by proinflammatory cytokines, such as IL-1 and tumor necrosis factor (TNF) α, induces production of MMP-3 by articular chondrocytes, synovial cells, fibroblasts, and macrophages (22-25). MMP-3 has a lower substrate specificity as compared to other members of the MMP family and considered to be a breakdown enzyme of proteoglycan, a component of cartilage substrate. MMP-3 also induces activation of MMP-1, which dissolves type I and type II collagen, and is well known as an important enzyme responsible for degradation of aggrecan and collagen in cartilage (9, 10). Additionally, MMP-13 is considered to be one of the essential enzymes responsible for degradation of aggrecan and type II collagen in cartilage (12). Therefore, both MMP-3 and MMP-13 are related to breakdown of TMJ cartilage, and considered to be prognostic biomarkers of OA progression. The present results showed the first evidence of decrease in type II collagen at one week after operation, with expressions of MMP-3 and MMP-13 noted at the same time point. Furthermore, MMP-3 and MMP-13

expression levels peaked at two weeks after the operation, at which time a greater number of TRAP-positive cells such as osteoclasts was revealed. Together, these findings suggest that MMP-3 and MMP-13 begin to breakdown components of the extracellular matrix such as type II collagen at one week after a procedure that loads compressive mechanical stress onto the anterior surface of the condylar head for mandible advancement.

A major limitation of the present study is that the origin of MMP-3 and MMP-13, related to dissolving of collagen in cartilage, was not determined. It is speculated that these MMPs are produced from articular chondrocytes and synovial cells, though further investigation such as *in vitro* experiments regarding this point is needed and ongoing. Moreover, IL-17 was not examined in the present study, although there are some reports on its role in osteoclast-mediated bone resorption (26, 27). Hence, the Authors are planning to perform further analysis of synovial fluid from rabbits with ICR, in a future study.

In conclusion, based on the present *in vivo* findings compressive mechanical stress following mandible advancement results in load on the anterior surface of the condylar head, which leads to bone resorption there, and induces MMP-3 and MMP-13 related to degradation of condylar head cartilage. Furthermore, association of MMP-3 and MMP-13 is involved in breakdown of cartilage, which begins at one week after the start of compressive mechanical stress, as well as the progress of bone resorption, which continues until two weeks after a related procedure. Additional studies are warranted to evaluate MMP expression in synovial fluid for prevention of ICR.

Conflicts of Interest

There are no conflicts of interest to declare in regard to the present experimental study.

Authors' Contributions

S.N. and Y.K. were the primary researchers for this study. S.N., Y.K., K.Y., and A.K. performed the experiments and surgical procedures. Y.K., Y.Y., K.I., and H.K. performed the histological analyses, and Y.K., Y.Y., and H.K. evaluated those findings. S.N., Y.K., A.K., and M.I. performed the micro-CT imaging, and Y.K. and M.I. evaluated those findings. S.N., K.I., T.K., M.I., H.K., and T.T. performed a literature review and revisions of the manuscript. All Authors have read and approved the final version submitted for publication.

Acknowledgements

A Grant-in-Aid for Young Scientists (B) (no. 16K20557) and a Grant-in-Aid for Scientific Research (C) (no. 20K09988) were given to Y.K. and T.T. from the Ministry of Education, Culture, Sports, Science, and Technology, of Japan.

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Received March 23, 2022
Revised June 1, 2022
Accepted June 15, 2022