学位論文　博士（医学）甲

Adaptive change in temporomandibular joint tissue and mandibular morphology following surgically induced anterior disc displacement by bFGF injection in a rabbit model

（外科的に円板前方転位を生じさせた家兎顎関節におけるbFGF投与後の顎関節組織と下顎骨形態の適応変化）

佐藤　桃子

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Adaptive change in temporomandibular joint tissue and mandibular morphology following surgically induced anterior disc displacement by bFGF injection in a rabbit model

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Purpose: The purpose of this study was to examine the effect of injecting basic fibroblast growth factor following surgical induced anterior disc displacement in temporomandibular joints (TMJ).
Materials and methods: Adult male Japanese white rabbits (n = 16; 2.0–2.5 kg; 10 weeks old) were assigned to experimental and control groups. In the experimental group, anterior disc displacement was induced in the bilateral TMJ. Recombinant human basic fibroblast growth factor (rh bFGF) 0.1 μg/1 μL aqueous solution was injected into the left retro-discal connective tissue close to the disc (ADL group), and saline alone was injected into the same site on the right (ADR group). In the control group, a sham operation without disc position change was performed in the bilateral TMJ (CR group and CL group). Four animals from the experimental (ADR and ADL) and control (CR and CL) groups were sacrificed at 1 and 12 weeks postoperatively to evaluate the mandibular morphology and computed tomographic (CT) value of the condylar head, using 3 dimensional computed tomography. Furthermore, cartilage layers and disc tissue were examined histologically.
Results: Regarding CT value at the 0° site of the condylar surface, ADR showed the lowest value after 1 week (P = 0.0325). However, there were no significant differences among the 4 groups regarding CT values at the other degree sites after 1 and 12 weeks. Regarding mandibular length, ADR showed the lowest value after 12 weeks (P = 0.0079). In condylar width, ADR showed the lowest value after 1 week (P = 0.0097).
Conclusion: This study suggested that surgically induced anterior disc displacement could affect condylar morphology in the early stage, and could decrease mandibular length in the late stage. However, bFGF injection into the TMJ might prevent the degenerative change derived from anterior disc displacement and inhibition of sequential mandibular growth.

1. Introduction

Previous clinical studies on mandibular asymmetry or retrognathia suggested that co-existing non-reducing temporomandibular joint (TMJ) disc displacement in adults as well as children and adolescents could affect the maxilla-mandibular morphology (Gidarakou et al., 2004; Isberg and Legrell, 2000; Nakagawa et al., 2002; Nebbe et al., 1988; Schellhas et al., 1993; Yamada et al., 1999).

On the other hand, there are several reports on studies using animals to prove the relationship between anterior disc displacement and mandibular asymmetry or retrognathia (Brymdahl et al., 2011; Hatala et al., 1996; Legrell and Isberg, 1998, 1999).

Osteoarthritis (OA) is usually associated with disc displacement, especially anterior disc displacement without reduction in TMJ (Dias et al., 2012; Gil et al., 2012; Roh et al., 2012). In short, anterior disc displacement can change the quality of the bone and cartilage

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in the condyle. In the treatment of OA, numerous studies have described the efficacy of hyaluronic acid (HA) when injected into superior joint space. However, the effects were limited in the improvement of function and reduction of clinical symptoms. Only Li et al. (2015) reported that the injection of HA into the inferior and superior joint spaces could result in better condylar reparative remodeling.

In a study by Man et al. (2009) using a rabbit model with temporomandibular joint disc perforation, the authors reported that transforming growth factor-β (TGF-β) might be potentially beneficial in protecting articular cartilage during the development of TMJ OA. Previous studies have suggested that the mitogenic effect of basic fibroblast growth factor (bFGF) is a sign of degeneration rather than regeneration (Ellman et al., 2008; Otsuki et al., 2010). In various animal experiments, exogenous bFGF accelerated cartilage repair and subchondral bone formation (Chuma et al., 2004; Deng et al., 2007; Fukuda et al., 2005; Holland and Mikos, 2003; Maehara et al., 2010). However, there are no reports regarding the repair or regeneration of retro-discal connective tissue in anterior disc displacement joint. When anterior disc displacement is induced in the rabbit model, it is assumed that retro-discal connective tissue of the joint can be a loaded site on the condyle. This retro-discal connective tissue consists of loose fibrous tissue that is vascular and mainly innervated. Our hypothesis is that the bFGF can enhance compression stress tolerance in retro-discal connective tissue, and can prevent inhibition of the mandible including TMJ during growth.

The purpose of this study was to examine the changes in TMJ and mandibular morphology by injecting bFGF following surgically induced anterior disc displacement in TMJ.

2. Materials and methods

2.1. Experimental animals

Sixteen Japanese female white rabbits (2.0–2.5 kg, 10 weeks old) were assigned to an experimental group or sham-operated control group.

2.2. Surgical procedure

The surgery was performed under general anesthesia with sodium pentobarbital (60 mg/kg) initiated by injection into the lateral vein in the ear. The hair in the bilateral infra-orbital region was shaved, and about 1.8 ml of 2% lidocaine containing 1/80,000 epinephrine was applied. A 1.5-cm horizontal skin incision was made over the infra-orbital region to expose the condyle and disc in the TMJ. The upper site of the zygomatic arch over the condyle was removed using a #701 fissure bur. Then, the disc was pulled down to the anterior-inferior site and fixed with 4.0 nylon thread at the lower ridge of the zygomatic arch, and anterior disc displacement was achieved. Recombinant human basic fibroblast growth factor (rh bFGF) 0.1 μg/μL solution in distilled water was injected into the left connective tissue close to the disc (ADL group), and saline alone was injected into the right of the same site (ADR group). In the sham surgery of the control animals, the condyle and disc were exposed after an incision was made, and saline was injected into the retro-discal tissue, but disc reposition was not performed in the bilateral TMJ (CR group and CL group). After the joint capsule was closed, the skin was sutured using 4.0 Vicryl (polyglactin 910) (Fig. 1).

2.3. Postoperative morphological and histological evaluation

Gross morphologic and microscopic changes were assessed in both groups. All animals were sacrificed after receiving an injection of sodium pentobarbital into the lateral ear vein. Tissues were initially fixed in saline and then perfused with phosphate-buffered formalin through a catheter placed in the left ventricle of the heart. The heads were fixed with 10% phosphate-buffered formalin for a further 3 weeks. Then CT was performed under the conditions outlined below.

The animals' heads were placed in the gantry with the trag-acanthal line perpendicular to the ground for CT scanning. CT scans were performed in the radiology department using a high-speed, advantage-type CT generator (Aquilion One; Toshiba Medical Systems Corp, Tochigi, Japan) with each sequence taken 0.5-mm apart (120 kV; 130 mA; 0.75 s/rotation; and Pitch Factor 0.641). When the three-dimensional (3D) CT was reconstructed, the threshold of the CT value (Hounsfield units [HU]) was determined as the value where the condylar surface head was seen most clearly (when the condition was FC81, ≥300 was used).

2.4. CT value measurement

Maximum CT values (pixel values) of 4 points of the condylar surface were measured at 1 week and 12 weeks post-operatively. The condylar center-point was determined as the cross point

A B

Fig. 1. Intra-operative photograph. (A) The disc was pulled down to the anterio-inferior site of the zygomatic arch by a thread. (B) The disc was fixed at the anterio-inferior site of the zygomatic arch.

between the most anterior point of the condylar contour surface parallel to the mandibular inferior border line and the most superior point perpendicular to the mandibular inferior border line. The CT value was small at the center of the condyle, but increased at the condylar surface. Therefore, the maximum CT value was determined as the highest value on the line from the condylar center to the condylar surface at the 0, 30, 60 and 90° points (Fig. 2). The measurements were performed 5 times by an author (M.S.) to confirm the reproducibility of the value.

2.5. Distance measurement

A 3D CT image was reconstructed, and the following items were determined and measured with an image software SimPlant O & O (Materialize Dental n.v., Leuven, Belgium). The measurement was performed 5 times by an author (M.S.) to confirm reproducibility of the value (Fig. 3). Measurements were defined as follows:

A) Ramus height: Distance between the most superior point of the condyle and mandibular inferior border line.
B) Mandibular length: Distance between the most anterior point of the condyle and the top edge of the incisor.
C) Condylar length: Distance between the anterior point and posterior point of the condyle.
D) Condylar width: Distance between the most lateral point and medial point of the condyle.

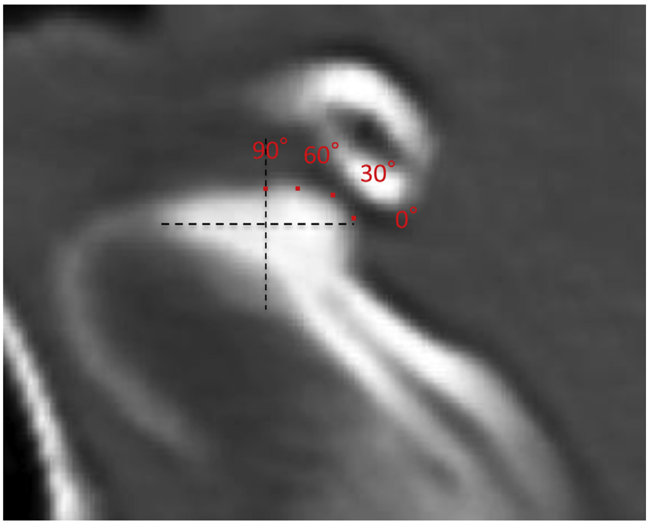

Fig. 2. Measurements on computed tomogram (CT). Maximum CT values at the 0, 30, 60 and 90° sites of the condylar surface were measured.

2.6. Microscopic condylar cartilage changes of the condyle

After the CT examination, the heads including the mandibular bone and TMJ were demineralized in ethylene diamine tetra-acetic acid (EDTA) for 4 weeks, embedded in paraffin, serially sectioned in the horizontal plane at a thickness of 5 μm and stained with hematoxylin-eosin. The histological features of the condyle were assessed by light microscopy. Thickness of disc, fibrous articular zone, cell-rich proliferation and hypertrophic chondrocytes zone were measured at the 0, 30, 60 and 90° sites. The measurements were performed 5 times by an author (M.S.) to confirm reproducibility of the values (Fig. 4).

2.7. Statistical analyses

Data were analyzed with SPSS software (SPSS Japan Inc., Tokyo, Japan). The Kruskal–Wallis test was performed to analyze the differences among the groups in each period. The Wilcoxon signed rank test was performed to compare 1 week and 12 weeks in each group. The differences were considered significant at $p < 0.05$.

3. Results

The CT values showed no significant difference in all the sites (0–90°) among the groups. There was significant difference between the groups at the 0° site after 1 week ($P = 0.0323$); however there were no significant differences between the groups in the other sites after both of 1 and 12 weeks. Moreover, there was no significant difference between week 1 and week 12 in all the sites in each group (Figs. 4 and 5).

In the all distance measurements, there were no significant differences between 1 and 12 weeks, although the values after 12 weeks tended to be higher than those after 1 week. In the mandibular length after 12 weeks, there was a significant difference among the groups ($P = 0.0079$). This indicated that the largest group was CL, the second was CR, the third was ADL and the smallest group was ADR. In the condylar width after 1 week, there was a significant difference among the groups ($P = 0.0097$). This indicated that the largest group was CL, the second was CR, the third was ADL and the smallest group was ADR (Figs. 7–10).

Histological examination showed no degenerative change in the fibrous layer or cartilage layer in all the groups. Perforation or tear of the disc or retro-discal tissue was not observed in the groups with surgically induced anterior disc displacement (see Fig. 6).

In the statistical results, the Kruskal–Wallis test revealed that for disc thickness, fibrous articular zone, cell-rich proliferation and hypertrophic chondrocytes zone, there was significant difference at the 0° site regarding thickness of cell rich proliferation and hypertrophic chondrocytes zone after 1 week between the groups

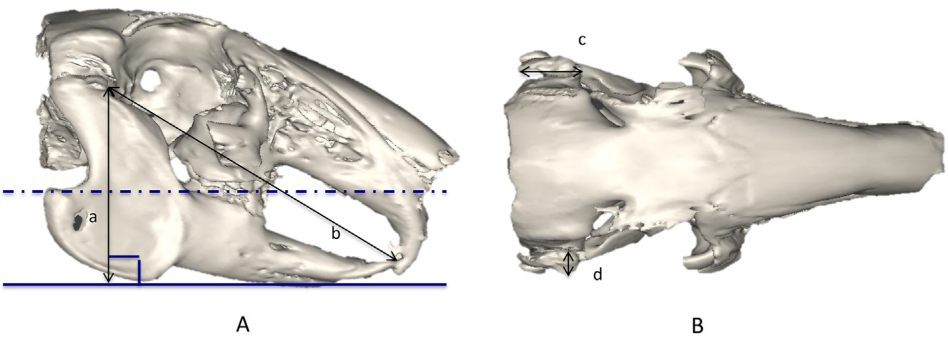

Fig. 3. Measurements on 3D computed tomogram. (A) Lateral view. (a) ramus height, (b) mandibular length. (B) Superior view: (c) condylar length, (d) Condylar width.

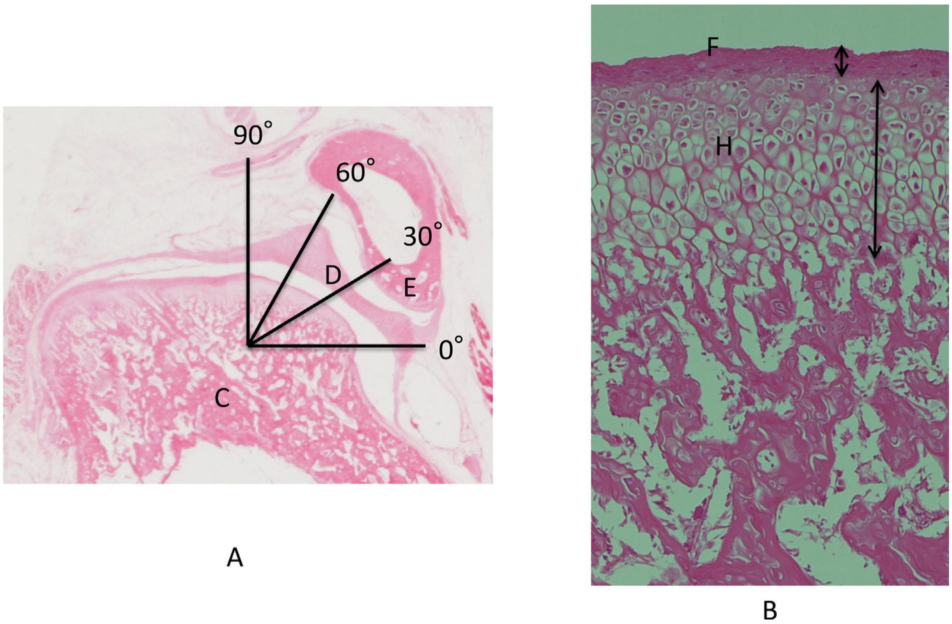

Fig. 4. Computed tomographic results after 1 week. Median and error bars (maximum and minimum values) are shown. *At the 0° site of the condylar surface, values in the ADR group were significantly lowest among all the groups after 1 week (P = 0.0325).

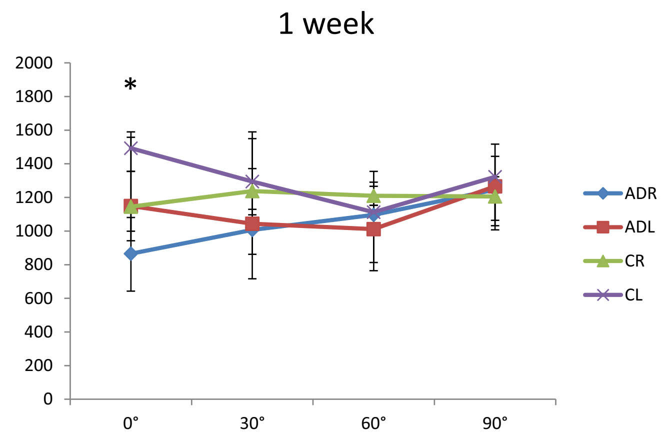

Fig. 5. Computed tomographic results after 12 weeks. Median and error bars (maximum and minimum values) are shown.

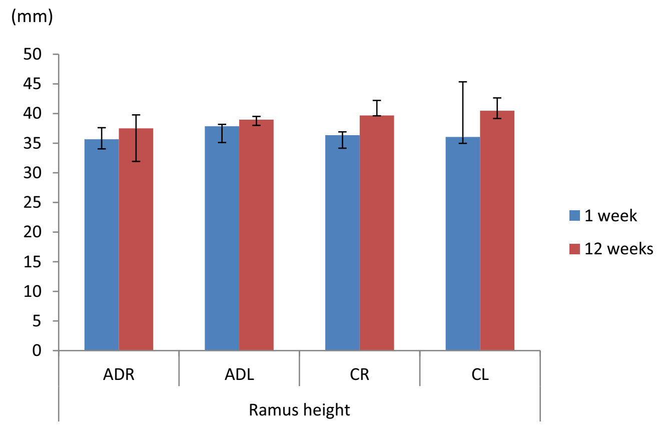

Fig. 7. Mandibular length. Median and error bars (maximum and minimum values) are shown. *The ADR group values were significantly lowest among all groups after 12 weeks (P = 0.0079).

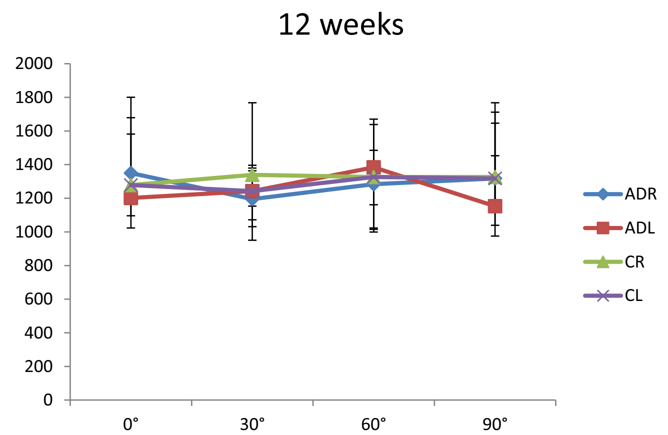

Fig. 6. Ramus height. Median and error bars (maximum and minimum values) are shown.

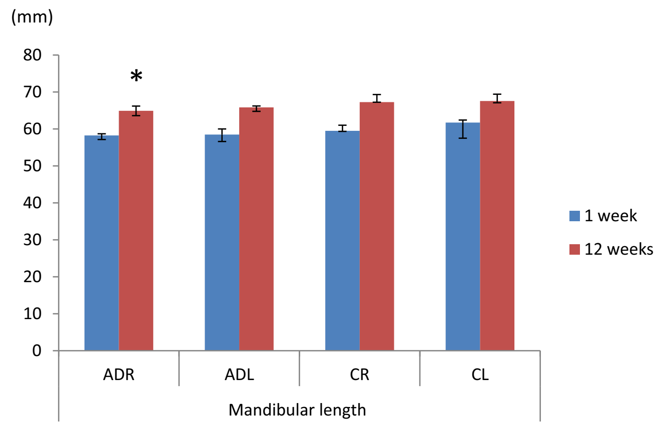

Fig. 8. Condylar length. Median and error bars (maximum and minimum values) are shown.

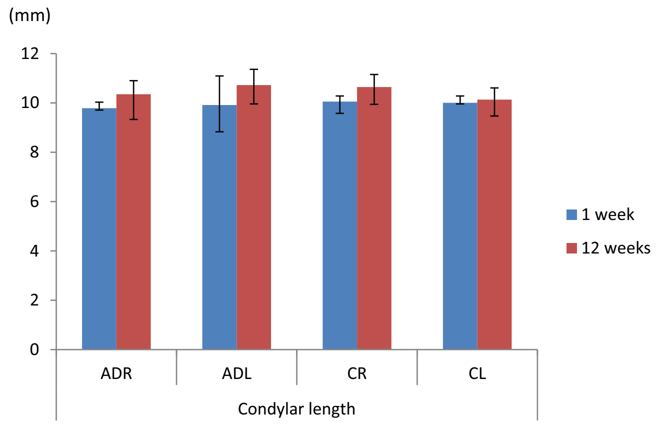

Fig. 9. Condylar width. Median and error bars (maximum and minimum values) are shown. *ADR group values were significantly lowest among all groups after 1 week (P = 0.0097).

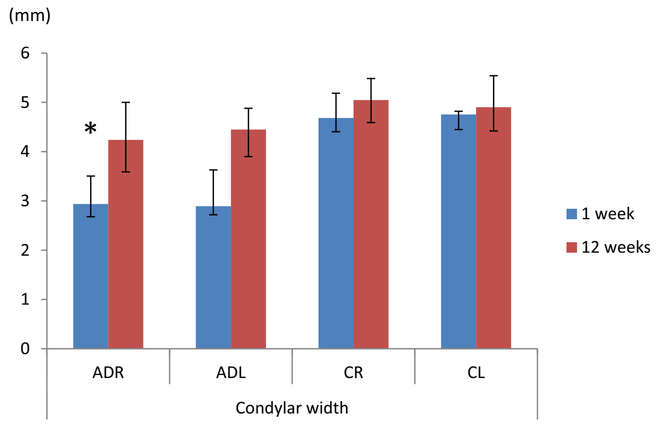

Fig. 10. Photomicrographs of the control group after 1 week. (A) Hematoxylin-eosin staining, original magnification × 10. The thickness was measured at the 0, 30, 60, and 90° sites. (B) Hematoxylin-eosin staining, original magnification × 100. Abbreviations: E = articular eminence, D = disc, C = condyle, F = fibrous articular zone, H = cell-rich proliferation and the hypertrophic chondrocyte zone.

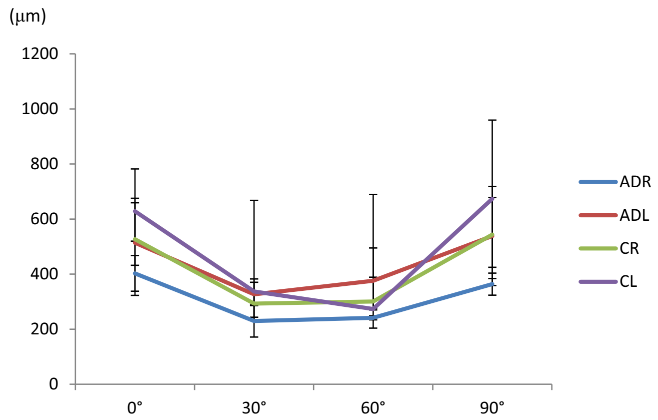

Fig. 11. Thickness of the joint disc after 1 week. Median and error bars (maximum and minimum values) are shown.

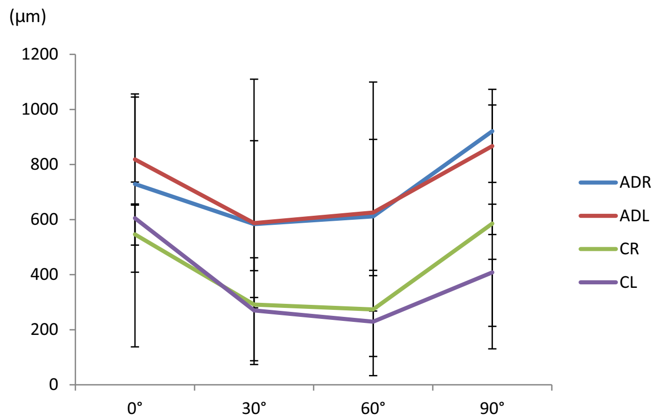

Fig. 12. Thickness of the joint disc after 12 weeks. Median and error bars (maximum and minimum values) are shown.

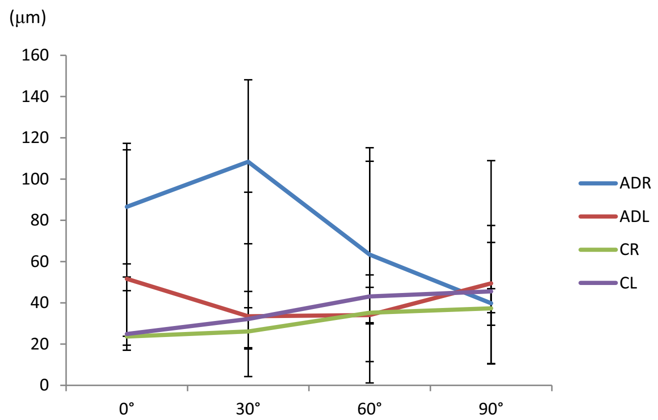

Fig. 13. Results on thickness of the fibrous articular zone after 1 week. Median and error bar (maximum and minimum values) are shown.

(P = 0.0343). However, there were no significant differences in the other measurements (Figs. 11–16).

4. Discussion

Articular disc displacement is a clinical sign often observed in patients with symptoms of temporomandibular disorders (TMD). Some studies have focused on the relationship between internal disorders and occurrence of osteoarthrosis, primarily in cases of anterior disc displacement without reduction (Dias et al., 2012; Gil et al., 2012; Roh et al., 2012). Furthermore, the internal derangement of TMJ has been presumed to have an impact on mandibular growth. A close relationship between acquired facial asymmetry and TMJ disc displacement has been reported in pediatric patients and adults (Gidarakou et al., 2004; Isberg and Legrell, 2000; Nakagawa et al., 2002; Nebbe et al., 1988; Schellhas et al., 1993; Yamada et al., 1999). However, whether mandibular asymmetry predisposes for the development of TMJ disc displacement or whether the displaced disc can cause deviant mandibular growth is unknown.

Hatala et al. (1996) showed that internal derangement induced by transecting the posterior attachment could produce altered growth in the rabbit mandible. Legrell and Isberg (1998, 1999) showed that surgically induced disc displacement could cause mandibular asymmetry in growing rabbits, including shortening of the mandibular ramus and excessive inferiorly directed bone growth along the lower border of the mandible.

On the other hand, histological and immuno-histochemical findings have been examined after surgical induced disc displacement in a rabbit osteoarthrosis (OA) model, although mandibular

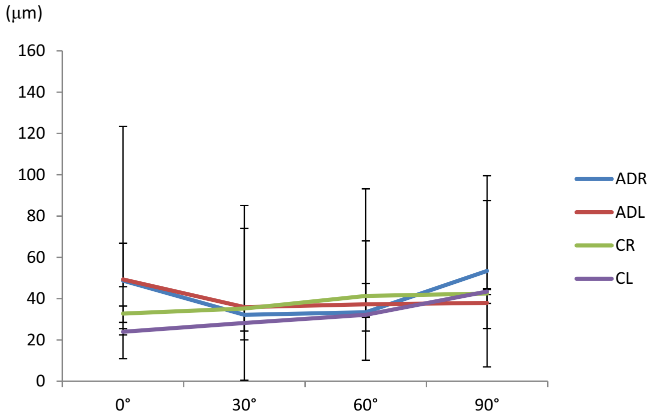

Fig. 14. Thickness of the fibrous articular zone after 12 weeks. Median and error bar (maximum and minimum values) are shown.

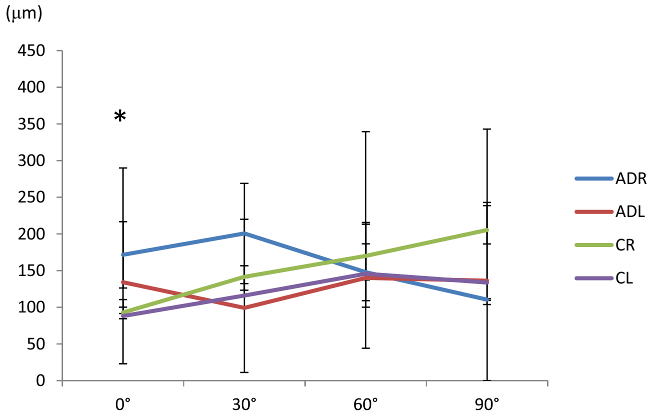

Fig. 15. Thickness of the cell-rich proliferation and hypertrophic chondrocyte zone after 1 week. Median and error bars (maximum and minimum values) are shown. *There was a significant difference among the groups at the 0° site after 1 week (P = 0.0323).

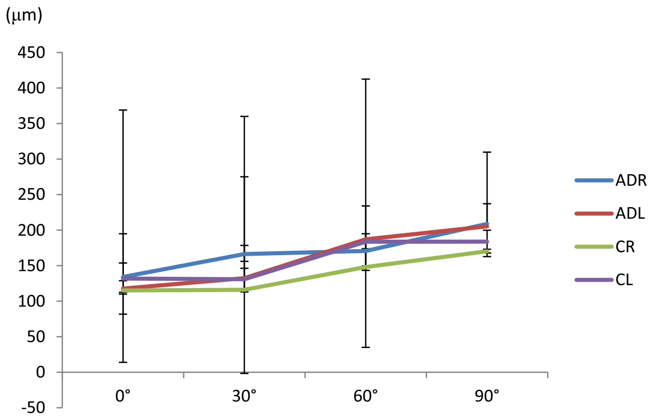

Fig. 16. Thickness of the cell-rich proliferation and hypertrophic chondrocytes zone after 12 weeks. Median and error bars (maximum and minimum values) are shown.

length or ramus morphological changes were not described. Ali and Sharawy (1995c) concluded that surgical induction of ADD in rabbit CMJ causes enlargement of the condyle, which is in part caused by hyperplasia of the condylar cartilage.

Glycosaminoglycans (GAGS), mainly keratan sulfate (KS), chondroitin-4-sulfate (C4S), chondroitin-6- sulfate (C6S), hyaluronic acid (HA), and link protein (LP) are essential components of condylar cartilage and discal fibrocartilage (Milam et al., 1991; Mills et al., 1988; Poole, 1986; Sharawy et al., 1991). Ali and Sharawy (1996) concluded that surgical induction of ADD in rabbit CMJ leads to alterations in the KS, C4S, C6S, HA, and LP contents, which is consistent with similar changes accompanying osteoarthritis of other synovial joints.

Ali and Sharawy (1995a) have reported previously that ADD causes fragmentation and loss of fibronectin. Fibronectin degradation products initiate chondrolysis (Homandberg et al., 1992), partial degradation of GAGs (Shiozawa et al., 1984), and inhibition of GAG synthesis (West et al., 1984). In addition, loss of GAGS is attributable to ADD, and could be the initiating factor for the loss and degradation of type II (Ali and Sharawy, 1995b), types VI and IX (Sharawy et al., 1991), and collagen in osteoarthritic condylar cartilage as GAGS bind to type II collagen (Goetinck et al., 1990). Loss of GAGS in osteoarthritic cartilage may contribute to the fibrillation observed in the ADD model (Ali and Sharawy, 1995a). Furthermore, the loss of GAGS could be attributable to the transformation of cartilage chondrocytes into undifferentiated mesenchymal cells under loading. The newly formed cells produce type I collagen instead of type II collagen and elastic fibers (Ali and Sharawy, 1995b). Furthermore, Ali and Sharawy (1996) proved that surgical induction of ADD in rabbit CMJ leads to alterations in its type III, VI and IX collagens.

Brymdahl et al. (2011) reported that surgically induced nonreducing displacement of the TMJ could produce histological and macroscopic changes. The severity of cartilage changes was inversely corrected to the magnitude and direction of mandibular growth, which resulted in a retrognathic growth pattern (Brymdahl et al., 2011). Kubota et al. (2001) reported that artificial disc displacement in the rabbit caused osteoarthritic changes that were reversible as the displaced disc was restored within 2 weeks. Their study suggested that repositioning of the anterior displaced disc could reduce overloading on the condyle, and recover the condylar cartilage. Progressive osteoarthritic change was induced by disc displacement. Articular disc perforation at 5 weeks after the first operation was accompanied by subchondral bone exposure (Kubota et al., 2001). Brymdahl et al. (2011) reported that 12/37 joints had severe cartilage changes and 1/37 joint had destructive changes following surgically created anterior disc displacement in rabbits.

On the other hand, the histological evaluations in this study showed that the severe degenerative change of fibrous layer and cartilage layer were not observed in all the groups, and the hypertrophic chondrocyte zone was thinner in the surgical induced anterior disc displacement group after 1 week. However, after 12 weeks, no significant difference was seen. Adaptive response to altered biomechanics was considered to have occurred in the condyle histologically. In the other measurements, there were no significant differences among the groups, although the sample size was small. Changes in disc thickness and the fibrous layer varied so greatly that any significant difference went undetected. There might be a difference in the degree of disc displacement compared with the previous study (Kubota et al., 2001).

Recently, it became evident that joint disc repositioning is not always necessary clinically. If the retro-discal tissue exists on the condyle, it is expected to play the role of a disc, mainly as a shock absorber, in anterior displaced discs with no reduction.

Some growth factors are for the repair and regeneration of the TMJ articular cartilage. Transforming growth factor β (TGF-β) is a 25-kDa disulfide-linked dimer protein and has been shown to be beneficial for that cartilage. That is because it stimulates chondrocytes to induce elevation of proteoglycan and collagen type II production (Goldring and Goldring, 2004; Van der Kraan et al., 1997). An increase in proteoglycan (PTG) synthesis and PTG content of articular cartilage was observed after injecting TGF-β in naive murine knee joints. Man et al. (2009) reported that injection of TGF-β in the OA in rabbit TMJ could show significantly greater expression of aggrecan and collagen type II after 12 weeks. Insulin-like growth factor-1 (IGF-1) is one of the most important anabolic proteins (Hickey et al., 2003; Trippel, 1995). IGF-1 has been shown to induce chondrocyte synthesis of proteoglycan and collagen and its importance in the etiology of osteoarthritis is also confirmed (Nixon et al., 1999; Tyler, 1989). Liu et al. (2011) reported that hyaluron (HA) and IGF-1 injection into a rabbit model of TMJ with OA induced by partial discectomy could induce better histological repair and nearly normal micro-architectural properties of the subchondral cancelous bone. With regard to the amount injected into the rabbit TMJ, it was reported that IGF-1 was 0.5 μg/ml (Liu et al., 2011), and TGF-β was 20 ng/50 μl (Man et al., 2009). We set the bFGF dose at 0.1 μg/μL based on data on the skin injection of bFGF (Fayazzadeh et al., 2016). However, the injection site of bFGF in this study was actually retro-discal tissue, although the descriptions of the injection site in previous studies are very vague (Liu et al., 2010; Man et al., 2009).

FGF1 and FGF2 (basic fibroblast growth factor [bFGF]) stimulate angiogenesis and the proliferation of fibroblasts that give rise to granulation tissue, which fills up a wound cavity early in the wound-healing process. FGF-2 is produced endogenously in cartilage and has been proposed to be sequestered by perlecan, a heparin sulfate proteoglycan (HSPG) located in the extracellular matrix (ECM) of articular cartilage (Vincent et al., 2007). It has been reported that FGF-2 ablation accelerates spontaneous and surgically induced OA development, which can be rescued by the administration of recombinant FGF-2 (Chia et al., 2009). The role of FGF-2 is controversial in both articular and intervertebral disc cartilage, as it has been associated with species- and age-dependent anabolic or catabolic events (Ellman et al., 2013). In this study, bFGF was injected into the retro-discal tissue of TMJ, to preserve the disc- and retro-discal tissues. As previously mentioned, the action of bFGF was unclear at the mandibular condyle cartilage. However, the disc or retro-discal tissue involved fibrous tissue including fibroblast cells. We hypothesized that an increase in fibrous tissue induced by bFGF can increase mechanical strength of retro-discal tissue stretched by anterior displaced discs.

The use of Hounsfield units (CT value) to assess regional bone mineral density (BMD) has recently been described in several subsequent reports (Johnson et al., 2016; Schreiber et al., 2011). Kim et al. (2017) stated that HU values of the proximal femur could be used to assess local bone quality. However, the reports on condylar surface CT value are few. In this study, changes in CT value could be detected, and we could contemplate the trend of dynamic stress distribution. As disc perforation or degenerative changes were not observed histologically, mild adaptation of the condylar surface might occur in all experimental groups. Furthermore, the sample might be too small to detect the accurate CT value. The results of the macroscopic measurements proved that surgically induced anterior disc displacement could inhibit condylar width and mandibular length; however, injecting bFGF had no effect on normal disc position. On the other hand, condylar width decreased after 1 week, and growth of mandibular length was inhibited after 12 weeks in the non–bFGF-treated group. In contrast, condylar width and growth of the mandibular length were not inhibited in the bFGF-treated group. Condylar morphological response is more rapid than that of mandibular morphology overall. As such, the significant difference of the period between the 2 measurements is likely reasonable and valid.

Further studies on biomechanical properties and molecular biological assessment of the joint tissue are necessary, as the morphological phenomenon was observed in only a small sample in this study.

5. Conclusion

This study suggested that surgically induced anterior disc displacement could affect condylar morphology in the early stage, and likely decreases the mandibular length in late stage. However, bFGF injection into the TMJ likely prevents the degenerative change derived from anterior disc displacement and inhibition of sequential mandibular growth.

Conflicts of interest

None declared.

Ethical approval

This study was performed according to the Declaration of Helsinki and was approved by the Ethics Committee of the University of Yamanashi.

Offprint request

Not required.

Sources of support in the form of grants

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2018.11.034.

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◆　Figure と Figure Legend の訂正箇所

Fig.1. →訂正箇所なし

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Fig.4. →訂正あり

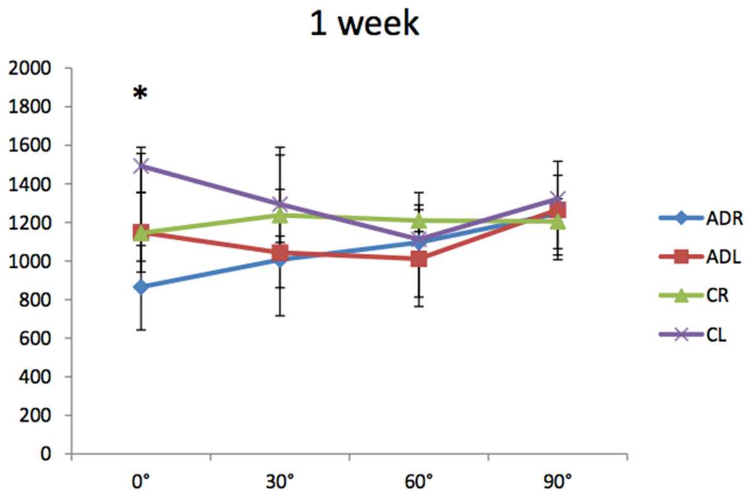

Fig. 4. Computed tomographic results after 1 week. Median and error bars (maximum and minimum values) are shown. *At the 0° site of the condylar surface, values in the ADR group were significantly lowest among all the groups after 1 week (P = 0.0325).

Fig.5. →訂正あり

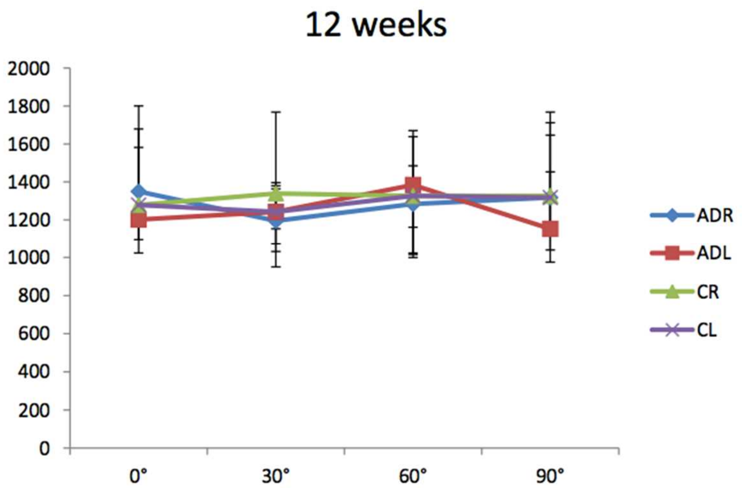

Fig. 5. Computed tomographic results after 12 weeks. Median and error bars (maximum and minimum values) are shown.

Fig.6. →訂正あり

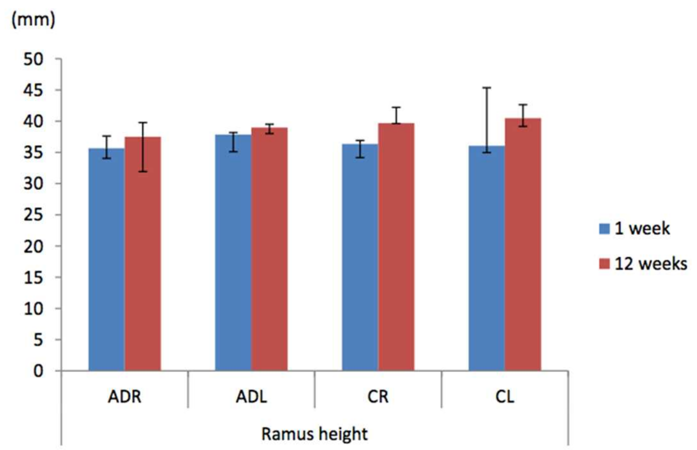

Fig. 6. Ramus height. Median and error bars (maximum and minimum values) are shown.

Fig.7. →訂正あり

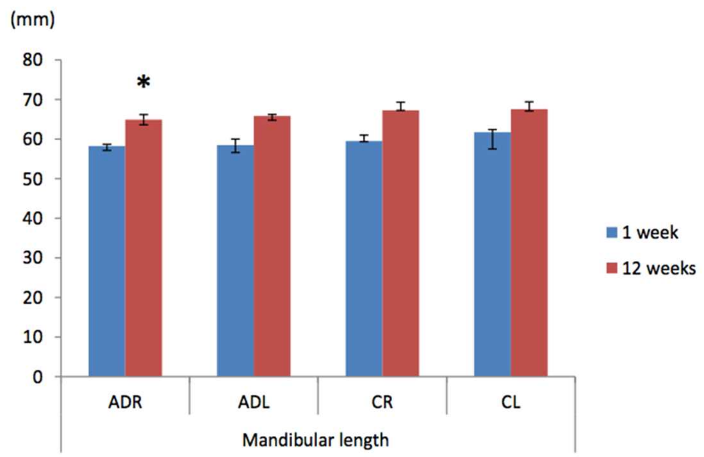

Fig. 7. Mandibular length. Median and error bars (maximum and minimum values) are shown. *The ADR group values were significantly lowest among all groups after 12 weeks (P = 0.0079).

Fig.8. →訂正あり

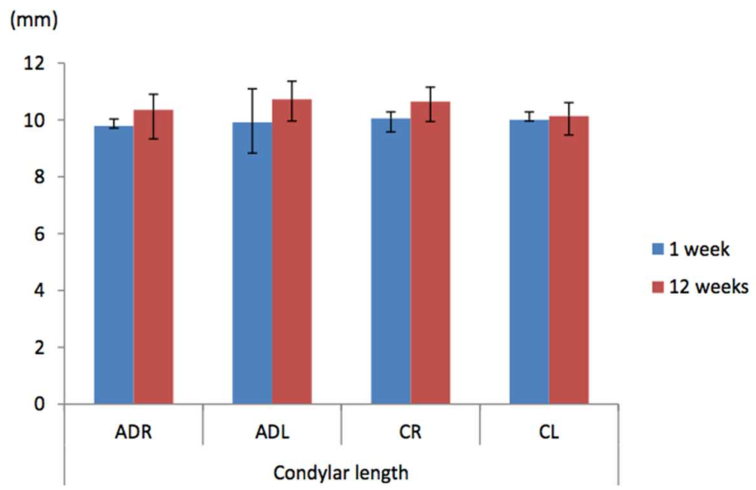

Fig. 8. Condylar length. Median and error bars (maximum and minimum values) are shown.

Fig.9. →訂正あり

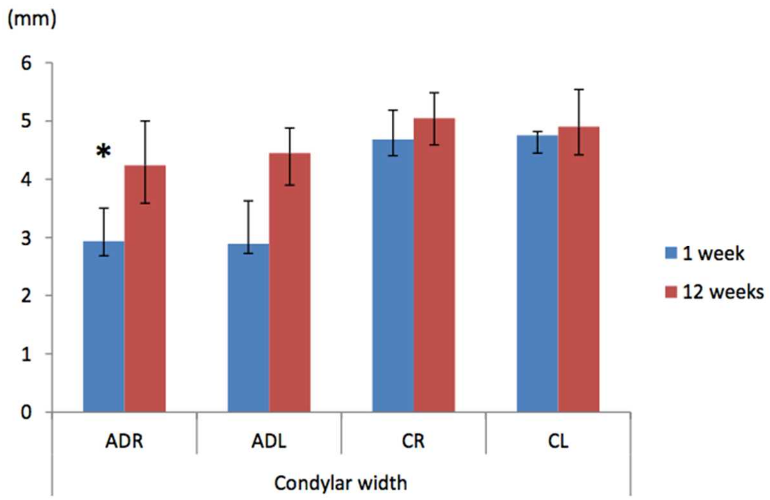

Fig. 9. Condylar width. Median and error bars (maximum and minimum values) are shown. *ADR group values were significantly lowest among all groups after 1 week ($P = 0.0097$).

Fig.10. →訂正あり

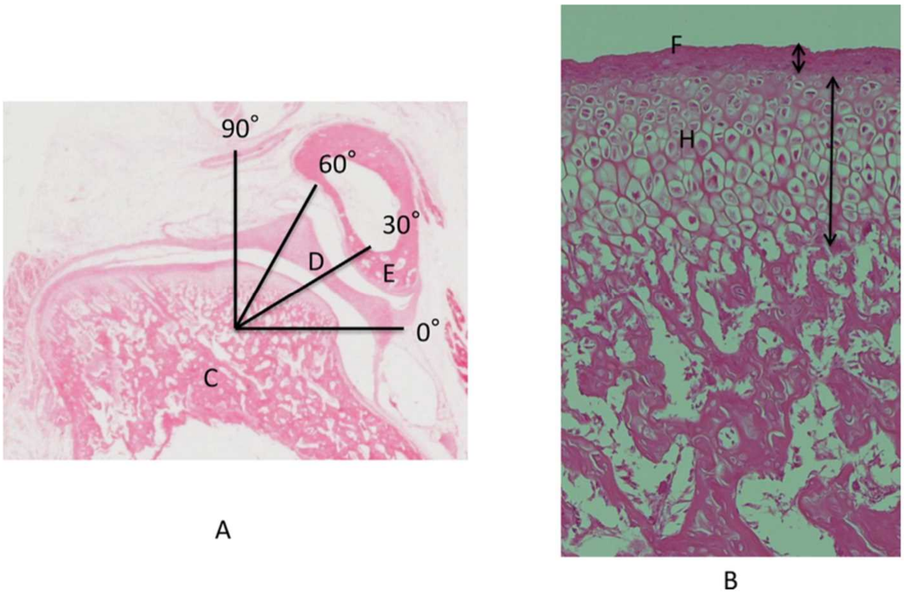

Fig. 10. Photomicrographs of the control group after 1 week. (A) Hematoxylin-eosin staining, original magnification × 10. The thickness was measured at the 0, 30, 60, and 90° sites. (B) Hematoxylin-eosin staining, original magnification × 100. Abbreviations: E = articular eminence, D = disc, C = condyle, F = fibrous articular zone, H = cell-rich proliferation and the hypertrophic chondrocyte zone.

Fig.11. →訂正箇所なし

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◆ P321 右側, パラグラフ 1, 11 行目

In the sham surgery of the control animals, the condyle and disc were ～

→In the sham surgery of the control animals, the condyle and disc were exposed after an incision was made, rh bFGF 0.1μg/μL solution in distilled water was injected into the left connective tissue close to the disc (CL group) and saline was injected into the right of the same site (CR group) , but disc reposition was not performed in the bilateral TMJ.

◆ P325 右側, パラグラフ 4, 4 行目

～hypertrophic chondrocyte zone was thinner in the surgical induced～

→～hypertrophic chondrocyte zone was thicker in the surgical induced～