Chapter 7

Effect of Allergy on Root Resorption Induced by Orthodontic Tooth Movement

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/59972

1. Introduction

Orthodontic teeth movement results from the application of orthodontic forces to teeth through orthodontic appliances which transmit the forces to the surrounding tissues. However, an undesirable and unexpected result of orthodontic treatment is the orthodontically induced tooth resorption (Fig. 1). The development of excessive root resorption during orthodontic treatment is considered an adverse side effect of the orthodontic tooth movement. Many factors have been investigated to explain the orthodontically induced root resorption observed among orthodontic patients. However, there are still controversies over this issue.

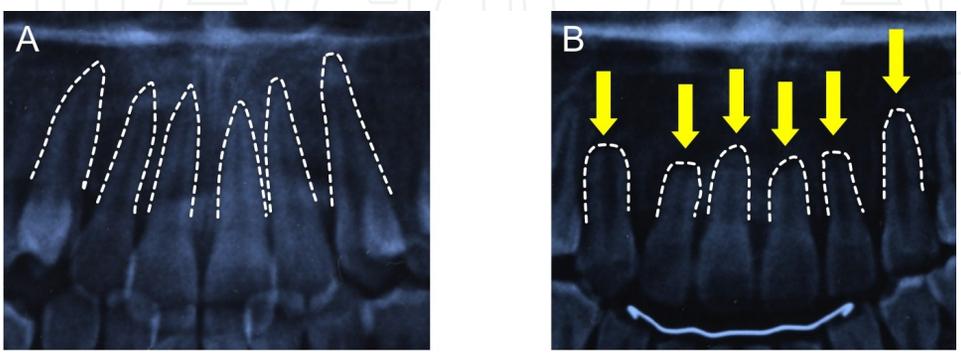

Figure 1. An undesirable and unexpected result of orthodontic treatment (A) Before treatment, (B) After treatment.

Davidovitch et al. [1] hypothesized that individuals who have a history of immune diseases including allergy, asthma, and systemic diseases may be at a high level of risk for developing excessive root resorption during the course of orthodontic treatment. To confirm the association between allergy and the orthodontically induced root resorption, we designed the epidemiological clinical study. Moreover, to extrapolate the direct effect of allergy on the orthodontically induced root resorption, which is difficult to prove in the clinical study design, we conducted experimental animal study using rats.

In this chapter, we refer at the beginning to the current knowledge of root resorption and then focus on the risk factors inherent in individuals to the external root resorption (ERR), especially allergic diseases as a possible risk factor of ERR.

2. Basic information

2.1. Prevalence

The presence of root resorption is common after orthodontic treatment [2]. Prevalence of root resorption following orthodontic treatment has been reported from 0% to 100% [3-5]. Thus, the prevalence varies widely due to differing methods of reporting root resorption, differing radiographic technique and interpretation, and individual susceptibility [2]. Close radiographic examination revealed that some loss of root length occurred in nearly every orthodontic patient. Moderate to severe apical root resorption (>2 mm, <1/3 of the root length) has been found in 10-17% of orthodontically treated patients [6,7] and excessive root resorption (>1/3 of the root length) in 1-5% [8,9]. Phillips [10] stated apical root resorption exceeding one-fourth of the original root length was shown in 1.5 % of maxillary central incisors and in 2.2 % of lateral incisors.

2.2. Site of root resorption

Regardless of patient-related or treatment-related factors, the maxillary incisors likely indicated more root resorption than the other teeth, followed by the mandibular incisors and first molars [11]. However, every tooth is capable of root resorption during orthodontic treatment.

2.3. Risk factors

2.3.1. Orthodontic treatment-related risk factors

Magnitude of force

Many studies have shown a distinct positive correlation between the applied orthodontic force and the amount of root resorption in both animal studies and clinical studies [12-16]. Owman-Mall et al. [17,18] reported that there were large individual variations in the amount of root resorption even when the same degree of orthodontic force was applied. They speculated that root resorption would not be very force-sensitive.

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Duration of force

Several investigations revealed that the duration of force was one of the risk factors of orthodontically induced root resorption [19,20]. Some claimed that the duration of force application was an even more critical factor than the degree of orthodontic force [21,22]. Interaction between magnitude and duration of force would play an important role for orthodontic treatment-related risk factors. Large individual variations still existed even in well-controlled research design [17,18].

2.3.2. Patient-related risk factors (individual susceptibility)

Besides orthodontic treatment-related factors, patient-related risk factors have also been discussed previously. This includes systemic diseases [23], nutrition [24,25], age [26], trauma [10,27], previous root resorption [28,29], gender [20,28], nail biting habits [30], root morphology [31], endodontically treated teeth [32], gingivitis [9], allergy [33-35], and medications [36]. Al-Qawasmi et al. [37] identified an interleukin (IL)-1β polymorphism in orthodontically treated individuals as having a role in the genetic influence on external apical root resorption.

3. The role of allergy related to orthodontically induced root resorption

Teeth are relocated under the dynamic balance of bone metabolism. The role of bone cells, including osteocytes, osteoblasts, and osteoclasts, are to resorb alveolar bone in sites of mechanically compressed tissues, thus enabling dental roots in these locations to move in the direction of the applied orthodontic force [38]. In these sites of tissue compression, one finds infiltrations of inflammatory cells followed by multinucleated osteocalsts and odontoclasts engaged in resorbing the dental roots [39,40]. Osteoclasts and their mononucleated progenitors are derived from the monocyte/macrophage lineage [41]. Osteoclasts and odontoclasts have a similar histochemical appearance; we defined here the multinucleated cells faced to tooth root as odontoclasts.

Patients with asthma and rhinitis share common physiology including heightened bronchial hyperresponsiveness and heightened reactivity to a variety of stimuli. Immunopathology of allergic rhinitis is also similar with a predominance of T-helper type 2 inflammation and tissue eosinophilia [42]. Allergy and asthma trigger the various associated biological, cellular, and molecular events with inflammation, such as increased vascular permeability, vasodilatation, cellular migration, increased mucus secretion, bronchoconstriction, structural changes of airway architecture, decline in pulmonary functions, release of intracellular mediators, increased formation of reactive oxygen species, cartilage degradation, and loss of function [43].

During orthodontic tooth movement, inflammation appears to be the main mechanism whereby immune cells and blood plasma reach the periodontal ligament of mechanically loaded teeth [44]. Apparently, strained sensory nerve endings in close proximity to periodontal ligament small blood vessels and capillaries release signal molecules such as substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide [45]. Substance P stimulates

endothelial cells to adhere to circulating leukocytes and promote their migration to the extravascular space, where they secrete a variety of cytokines, such as interleukins and tumor necrosis factors (TNFs).

TNF-α and IL-1β play an important role in bone pathophysiology [46,47] and have been suggested to be involved in orthodontic tooth movement [48]. These inflammatory cytokines induce local expression of receptor activator of nuclear factor-κB ligand (RANKL), which is critical for the terminal differentiation of osteoclast precursor cells [49].

Furthermore, leukotrienes, which are metabolites of arachidonic acid, are potent lipid mediators that play an important role in a variety of allergic and inflammatory reactions and comprise several products of the 5-lipoxygenase (5-LOX) pathway [50–52]. Leukotrienes are produced by activated leukocytes in inflammatory diseases such as bronchial asthma and rheumatoid arthritis [53,54]. LTB_4 is known to play an important role in the allergic reactions induced by ovalbumin (OVA) in rodents [55] and has been suggested to modulate bone metabolism by increasing osteoclastic bone resorption [56].

In light of these facts, we hypothesize that patients with allergic diseases such as food allergy, allergic asthma, allergic rhinitis, and allergic conjunctivitis are susceptible to orthodontic root resorption. We show the scheme to explain the hypothesis of orthodontically induced root resorption due to the risk factor of allergy (Fig. 2).

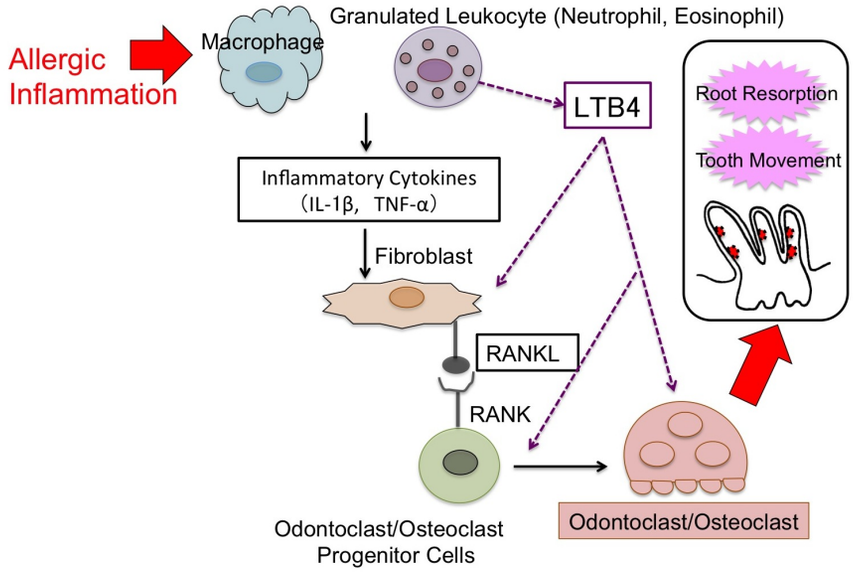

Figure 2. Scheme of possible explanation of the orthodontically induced root resorption due to the risk factor of allergy.

At first, we report the possible association between excessive root resorption during the orthodontic tooth movement and allergy using clinical study design. Next, we extrapolate the effect of allergy on orthodontically induced root resorption using animal models.

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3.1. Epidemiological study

3.1.1. Sample

The records of 3500 patients were obtained from the Section of Orthodontics, Kyushu University Hospital, Fukuoka, Japan. All these patients have completed their course of orthodontic treatment. In this sample, 100 individuals were found to have developed excessive resorption of dental roots. In the root resorption group, 29 subjects were males and 71 were females (Table 1). A control group was selected from the remaining patients of this sample who did not display any significant radiographic evidence for dental root resorption in the light of root morphology at the end of their orthodontic treatment. Each individual in the control group was pair-matched with one in the root resorption group based on age, gender, treatment period, and the type of malocclusion (Table 1).

	Number	Age (y)	Treatment Period (y)
Root resorption group			
Male	29	18.9 ± 5.4	2.9 ± 0.8
Female	71	17.3 ± 6.5	3.1 ± 1.1
Total	100	17.8 ± 6.2	3.1 ± 1.1
Control group			
Male	29	17.9 ± 6.1	2.8 ± 0.8
Female	71	18.2 ± 4.8	2.9 ± 0.8
Total	100	18.1 ± 5.2	2.9 ± 0.8

Table 1. Comparison of Means and Standard Deviations of Age and Treatment Period in the Root Resorption and Control Groups

3.1.2. Methods

Determination of root resorption

Determination of the root resorption status of each patient was established by comparing the dental panoramic radiographs that had been taken before and after treatment. All teeth were measured along the tooth's longitudinal axis for root length (defined as cement-enamel junction to apex of root). This method was similar to that used by Linge & Linge [7]. Individuals were assigned to the root resorption group when it was disclosed that one or more of their dental roots had been shortened by more than 25% of the original root length in the time that had elapsed between the two radiographs. The root shape was recorded subjectively as normal or abnormal (shortened, blunt, eroded, pointed, bent, bottle shaped) (Fig. 3) by examining dental panoramic radiographs that had been taken before the onset of treatment.

Questionnaire

The questionnaire sought information on the following subjects: personal details, medical history, dental history, and oral habits. Information on medical history included local or systemic diseases, details on medication uptake, hospitalizations, allergies, health during

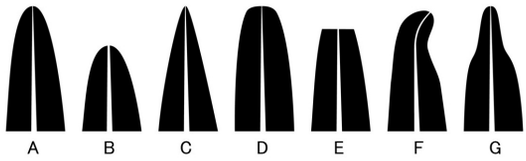


Figure 3. Morphology classification of the root (A) Normal, (B) Shortened, (C) Pointed, (D) Blunt, (E) Eroded, (F) Bent, (G) Bottle shaped.

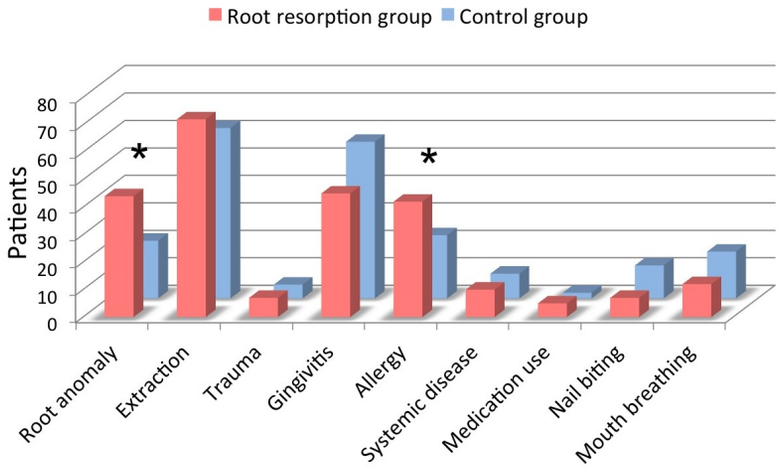
gestation and first year of life, childhood diseases, other conditions, and developmental events in infancy and childhood. Dental history questions referred to details on previous dental treatment and information about past oral injuries. Habits listed in the questionnaire were nail biting, tongue thrusting, and mouth breathing.

Statistical analysis

The validity of our hypothesis was tested by the logistic regression analysis using the Stat View 5.0 pro- gram (SAS Institute Inc, Cary, NC). Logistic regression produces odds ratios associated with each predictor variables (root anomaly, extraction, trauma, gingivitis, allergy, asthma, systemic disease, medication use, thumb sucking, nail biting, tongue thrusting, mouth breathing).

3.1.3. Results

The prevalence of excessive root resorption was 7.8%. The distribution of each risk factor in the root resorption and the control groups is shown in Figure 4. The logistic regression analysis is shown in Table 2. The incidence of allergy and asthma was significantly higher in the root resorption group (P = 0.005), with a mean odds ratio of 2.54 and 95% confidence interval of 1.34–4.92. The incidence of root anomaly was significantly higher in the root resorption group (P = 0.001), with a mean odds ratio of 2.95 and 95% confidence interval of 1.53–5.83.



*: $P < 0.05$.

Figure 4. Prevalence of each risk factor in the root resorption and control groups.

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Risk Factors	*P Value*	Odds Ratio	95% Confidence Interval
Root anomaly	0.001	2.95	1.53-5.83
Extraction	0.168	1.56	0.83-2.98
Trauma	0.473	1.59	0.45-5.97
Gingivitis	0.120	0.62	0.34-1.13
Allergy	0.005	2.54	1.34-4.92
Systemic disease	0.900	0.93	0.32-2.70
Medication use	0.344	2.31	0.45-17.2
Nail biting	0.311	1.57	0.66-3.84
Mouth breathing	0.539	0.76	0.31-1.81

Table 2. Logistic Regression Analysis of Each Risk Factor

3.1.4. Discussion

This clinical study showed that allergy might be an aetiological factor in increased root resorption. The same association was found in earlier studies [1,57]. However, those studies were primarily performed on Caucasian subjects. Our finding, derived from an examination of the clinical records of Japanese subjects, supports the hypothesis that allergy is a high risk factor for the development of excessive root resorption during orthodontic treatment.

Our results also indicate that abnormal root shape is probably associated with excessive root resorption (p=0.056). This finding is in agreement with the results of the previous study [23,58-60]. If the same orthodontic force is applied to the dental crown, the root apex is exposed to increasing stress as the root becomes shorter. Additionally, when the same orthodontic force is applied to the root apex, the distribution of the stress is different according to the types of root anatomy, and the dental root with pointed or bent shape may be exposed to larger stress than roots with normal morphological features. These increased stresses may traumatize the apical periodontal ligament, followed by an inflammatory/repair process, which includes resorption of the root apex.

Patients with periodontal disease have circulating primed monocytes, and sera of patients with periodontal disease contain high levels of proinflammatory cytokines [8]. In this study, however, gingivitis did not have a significant association to orthodontic root resorption. This is most likely due to the sample selection of young patients; mean age of 17.8 ± 6.2 years, and the method used to detect the status of periodontal health; examination of intra-oral photographs.

In cases requiring tooth extraction, the remaining teeth are usually moved relatively great distance, particularly when maxillary incisors are retracted in order to reduce large overjet [58,59,61]. Additionally, biologically, tooth extraction and the ensuing wound healing attract vast numbers of immune cells to the extraction site. These inflammatory cells may directly spread from the wound site to tissues surrounding adjacent teeth or, indirectly, produce large

amounts of cytokines that enter the circulation and exit into the extravascular space in the periodontal ligament of neighboring mechanically stressed teeth, which regulate remodeling activities not only at extraction site but also in tissues surrounding adjacent teeth. However, in this study, we have not found a significant association between extraction of permanent teeth and orthodontic root resorption. Therefore, we conclude that healing of extraction sites is primarily a local event which does not promote the resorption of adjacent teeth.

One limitation of this study was using the panoramic radiographs in order to evaluate the amount of root resorption. Although this method of examination makes it possible to view the whole dentition, its main drawback is distortion of the tooth image, predominantly in the incisor region. Periapical radiographs would be preferable to determine the size and shape of dental roots, but these radiographs were not available to us this time.

3.2. Animal model study

In the experimental animal study, we used Brown–Norway (BN) rats, which are known to produce high levels of IgE after sensitization with OVA. BN rats have been used extensively as animal models of allergic asthma [62–64], atopic dermatitis [65], and food allergies [66,67].

This study aimed to determine whether systemic allergic inflammation had adverse effects on orthodontic tooth movement and bone and root resorption and, if so, to investigate the possible mechanisms of the acceleration. Furthermore, we examined the ability of aspirin, which has been reported to improve bone mineral density (BMD) in human epidemiological studies [68,69], to reverse tooth root resorption.

3.2.1. Allergen sensitization for rats and OF

Six-week-old male BN rats (weighing 110–140 g) were sensitized by a subcutaneous injection of saline (1 mL) containing 1 mg of OVA (grade V; Sigma-Aldrich, St. Louis, MO, USA) and 200 mg of aluminum hydroxide. A *Bordetella pertussis* vaccine containing 1×10^{10} heat-killed bacilli (Wako, Osaka, Japan) was given intraperitoneally as an adjuvant. After 7 days, OVA was injected for a booster effect. The serum IgE levels were measured using an IgE ELISA Kit (Shibayagi, Gunma, Japan). At 7 days after the second sensitization, an orthodontic appliance consisting of an Ni-Ti closed-coil spring (Sentalloy®, Ultra Light; Tomy International Inc., Tokyo, Japan) was inserted between the upper right first molar (M1) and the incisors. The orthodontic force (OF) level of the spring was set at approximately 0.1N (Fig. 5).

The animals were divided into four groups: OVA with OF group, OVA alone group (no OF), OF alone group (no OVA), and control group (no OVA or OF).

After 7 or 14 days of OF (at days 7 and 14, respectively), the animals were perfused transcardially. The two halves of the maxilla were decalcified in 10% ethylenediamine-tetraacetic acid and cut into 8-μm-thick parasagittal sections. The sections were stained for tartrate-resistant acid phosphatase (TRAP) (Sigma-Aldrich) and counterstained with toluidine blue.

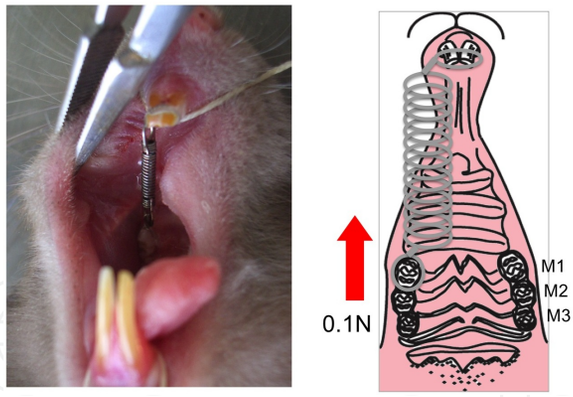

Figure 5. Maxillary first molar (M1) was moved medially with Ni-Ti Coil spring (0.1N) (Murata et al., 2013).

3.2.2. Measurements and analyses

We measured the area of ERR as well as the number of odontoclasts and osteoclasts within a defined area according to the method of Mavragani et al. [70]. TRAP-positive cells in resorption lacunae that faced the tooth roots were counted as odontoclasts, and other TRAP-positive cells (containing more than two nuclei) were counted as osteoclasts.

Proinflammatory cytokines were measured in the periodontal tissues, including the bone surrounding M1, after 24 hours of OF. The levels of TNF-α, IL-1β, and IL-6 were evaluated using a TNF-αELISA Kit (Shibayagi), IL-1β ELISA Kit, and IL-6 ELISA Kit (Biosource, Camarillo, CA, USA), respectively, according to the manufacturers' protocols.

The lipid components were extracted in 100% methanol at –30°C overnight.

The periodontal tissues around M1 after 24 hours of OF were rapidly frozen in liquid nitrogen and homogenized. After mRNA isolation, quantitative real-time PCR or conventional RT-PCR was performed with gene-specific primer sets as described previously [71].

Micro-CT images were acquired at a resolution of 9 μm using a SkyScan 1076 (SkyScan, Antwerp, Belgium) to assess the degree of OF. At day 14 (10 weeks of age), the hemi-maxilla samples were excised. The hemi-maxilla samples were directed parallel to the occlusal plane and scanned for 2.70 mm. The distance from the distal surface of M1 to the mesial surface of the second molar (M2) was measured using DataViewer software (ver. 1.4.3; SkyScan).

Aspirin dissolved in feed water (250 μg/kg/day) was administered orally to OVA-sensitized rats with orthodontic force application. For histologic experiments, aspirin was administered from the initiation of OF. For ELISA and RT-PCR analyses, aspirin was administered from 24 hours before OF.

3.2.3. Statistical analysis

The total serum IgE was compared using Student's *t*-test. The means of multiple groups were compared by one-way ANOVA. Other values were compared by ANOVA followed by Tukey's multiple comparison test. Values of $P < 0.05$ were considered to indicate statistical significance.

3.2.4. Results

OVA sensitization, OF, and root and bone resorption

At day 14, the degree of tooth movement in the OVA with OF group was significantly larger than that in the OF alone group. Without orthodontic force application, no osteoclasts and/or odontoclasts were observed on the medial surface of the alveolar bone in any of the groups (Fig. 6A, 6B). On day 7, marked ERR was observed on the pressured side in the OF alone group, especially in the OVA with OF group (Figs. 7A, 7B). On day 14, these tendencies became further significant in both the OF alone and the OVA with OF groups (Figs. 8A, 8B). The OVA with OF group exhibited significantly broader and deeper TRAP-stained areas compared to the OF alone group on days 7 as well as 14 (Fig. 9A). The number of odontoclasts and osteoclasts was significantly greater in the OVA with OF group than in the OF alone group on day 7 (Figs. 9B, 9C). The number of osteoclasts peaked on day 7 in the OVA with OF group and then decreased by day 14. While the area of ERR increased from day 7 to day 14, the number of odontoclasts was maintained through days 7 to 14 (Figs. 9A, 9C). The alveolar bone resorption and osteoclast number were significantly greater in the OVA with OF group than in the OF alone group on days 7 and 14 (Figs. 9D, 9E).

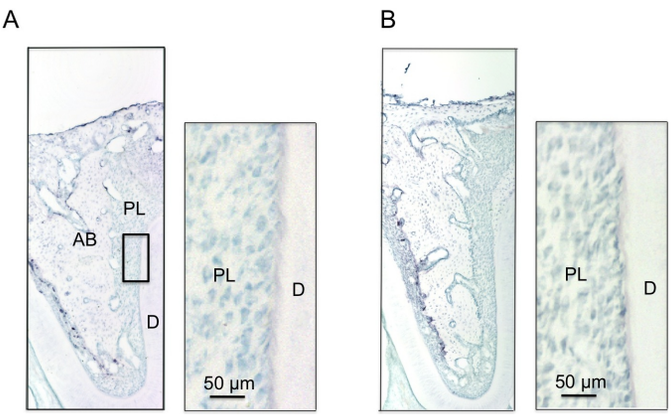

Figure 6. Histologic sections of periodontal tissues around the distopalatal root of the first molar stained for TRAP. (A) Control group (no treatment), (B) OVA-alone group (Murata et al., 2013).

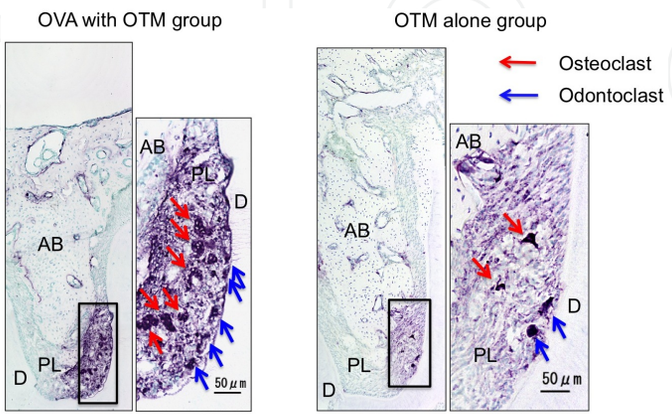

Figure 7. Histologic sections of periodontal tissues around the distopalatal root of the first molar stained for TRAP on day 7. (A) OVA with OTM group, (B) OTM-alone group (Murata et al., 2013).

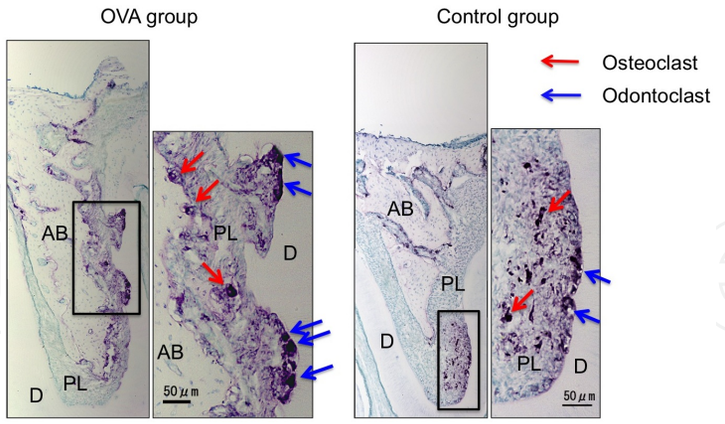

Figure 8. Histologic sections of periodontal tissues around the distopalatal root of the first molar stained for TRAP on day 14. (A) OVA with OTM group, (B) OTM-alone group (Murata et al., 2013).

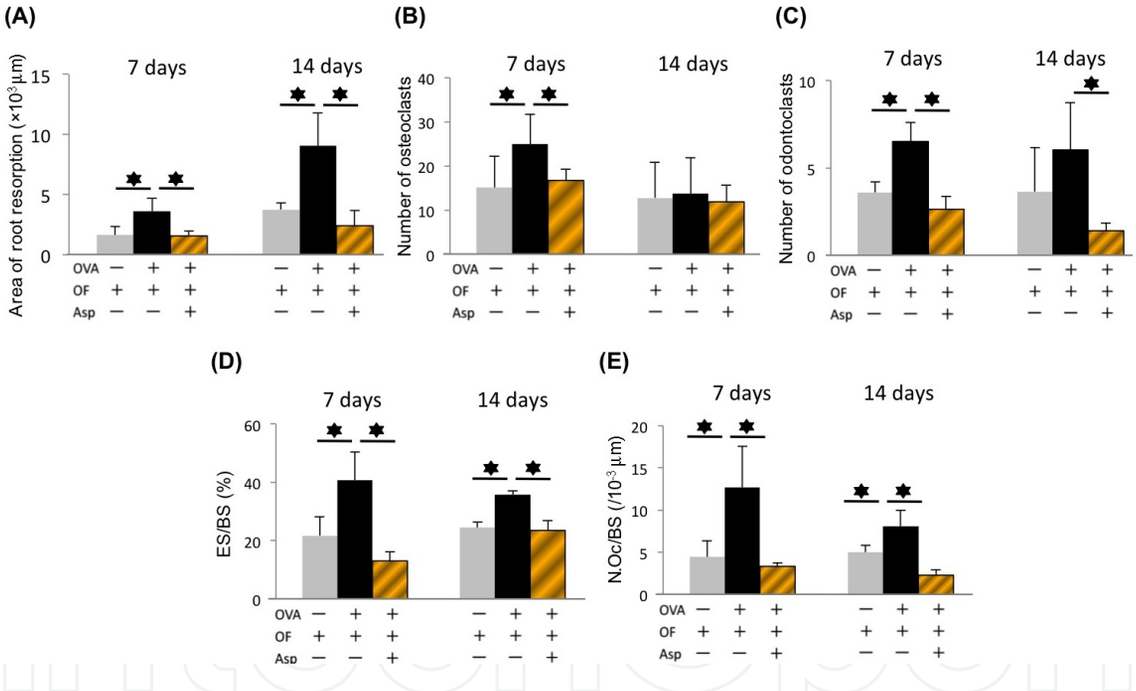

Figure 9. The numbers of osteoclasts/odontoclasts and amounts of root/bone resorption on the pressured side after tooth movement. (A) Area of root resorption (×103 μm2), (B) Number of osteoclasts, (C) Number of odontoclasts, (D) Eroded surface per alveolar bone surface (ES/ BS), (E) Number of osteoclasts per alveolar bone surface (N.Oc/BS). *: $P < 0.05$. (Murata et al., 2013).

Pro-inflammatory cytokines

The expression levels of RANKL, TNF-α, and IL-1β were significantly higher in the OVA with OF group than in the other groups after 24 hours of OF (Figs. 10A–10C), while the difference in IL-6 was not significant (Fig. 10D). Although no significant differences were observed, the OF alone group showed tendencies toward higher levels of TNF-α and IL-1β (Figs. 10B, 10C).

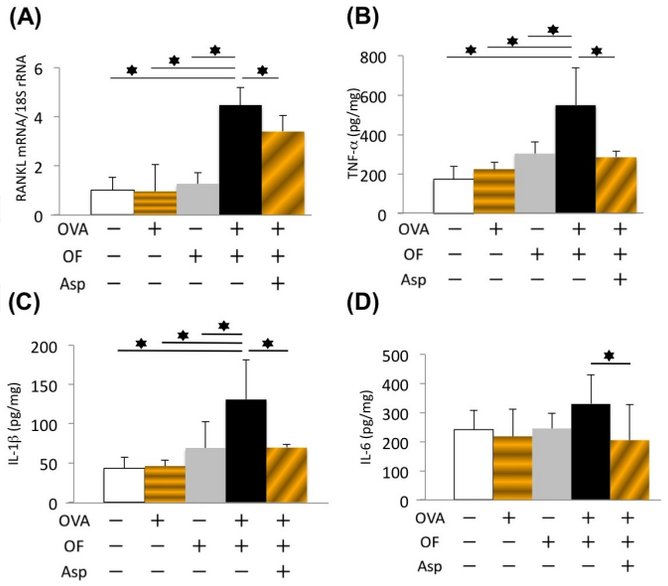

Figure 10. Concentrations of RANKL and inflammatory cytokines in rat periodontal tissues with or without OVA sensitization, after 24 h of orthodontic force application, and after aspirin administration. (A) RANKL, (B) TNF-α, (C) IL-1β, (D) IL-6. *: $P < 0.05$. (Murata et al., 2013).

Leukotrienes

The LTB_4 level and mRNA levels of the leukotriene synthases LTA4h were significantly increased in the OVA with orthodontic force group after 24 hours of orthodontic force compared with the other groups (Figs. 11A, 11B).

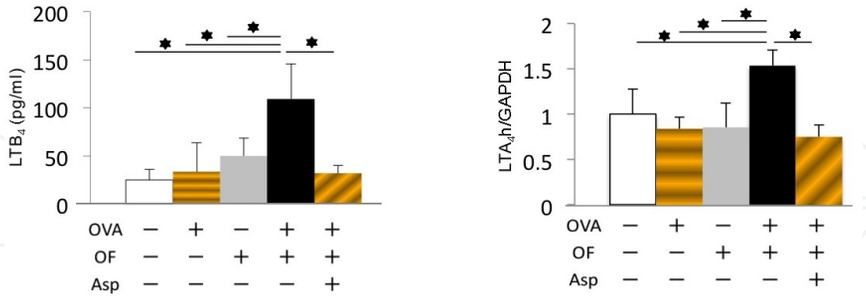

Figure 11. Effects of OVA sensitization, OF application for 24 h, and aspirin administration on the leukotriene synthases. (A) LTB_4, (B) LTA_4h. *: $P < 0.05$. (Murata et al., 2013).

Aspirin effects

Aspirin administration reversed the degree of tooth movement in the OVA with OF group to a similar level of the OF alone group on day 14. Histologic examinations revealed that the area of ERR and the numbers of odontoclasts and osteoclasts were decreased to the levels observed in the OF alone group (Figs. 9A–9E). The expression levels of RANKL mRNA and TNF-α,

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IL-1β, and IL-6 proteins were also suppressed in the levels detected in the OF alone group (Figs. 10A–10D). Furthermore, the expression levels of LTB_4 and LTA_4h were suppressed by aspirin treatment (Fig. 11).

3.2.5. Discussion

We demonstrated that allergies affect ERR during orthodontic treatment using an animal model. It is notable that the degree of OF in the present study was greater in the OVA-sensitized animals, suggesting that allergies can affect OF. In the histological observations, we found that the OVA-sensitized rats showed increased numbers of odontoclasts and osteoclasts on the pressured side during OF. The present findings suggested that allergies enhanced both odontoclastogenesis and osteoclastogenesis under the condition of orthodontic force.

TNF-α, IL-1β, and IL-6, which are well-known proinflammatory cytokines, were detected at high levels in the periodontal tissues from the OVA with OF group. Recently, Polzer et al. [72] suggested that IL-1β contributes to TNF-mediated inflammatory osteopenia, reporting that TNF-α transgenic IL-1β-deleted mice were protected against bone loss. The elevated expression levels of TNF-α and IL-1β, together with RANKL as an essential cytokine for osteoclastogenesis, suggested boosts in the rates and magnitudes of ERR as well as orthodontic tooth movement due to the differentiation of osteoclasts and odontoclasts.

Lipid mediators derived from arachidonic acid through the lipoxygenase and cyclooxygenase pathways are known to act as important modulators of inflammation. Increased levels of leukotrienes are found in inflammatory diseases such as asthma, arthritis, and periodontal disease [73-75]. LTB4 has been reported to stimulate osteoclast formation and bone resorption in the mouse calvaria [55] and to inhibit osteogenesis [76]. In our model, the expression levels of the leukotriene synthases LTB_4 and LTA4h were increased in the periodontal tissues in OVA-sensitized rats with OF. The fact that mechanical loading with OVA sensitization elevated the expression of leukotriene synthases reveals a potential role for leukotrienes in bone and root resorption. Interestingly, these effects of mechanical OF suggest the involvement of the lipoxygenase pathway in response to mechanical loading. We assume that the present findings are compatible with our previous epidemiologic observations [33,34].

We further found that oral administration of aspirin was able to reverse the increases in ERR and degree of OF in the allergic model. The dose of aspirin in the present study, 250 μg/kg/day, was much lower than that for general use as a painkiller. A recent study showed that low-dose aspirin inhibited ovariectomy-induced osteoporosis by inhibiting T cell activation [77]. Our findings raise the possibility that low-dose aspirin administration inhibits osteoclastogenesis under inflammatory conditions.

Through the epidemiological and animal model studies, we have demonstrated that allergies would be possible risk factors of ERR in the course of orthodontic treatments. In the clinical study, the evidence would be strengthened using a prospective study involving a much larger sample, such as the randomized controlled test. Moreover, we need to investigate the unsolved

mechanism of ERR, and the elucidation of the pharmacological targets for ERR during orthodontic tooth movement would be warranted.

4. Conclusions

In the clinical study, we found that allergy and root morphology abnormalities may be considered high-risk factors for the development of excessive root resorption during the course of orthodontic treatment.

We have proposed a model for studying the effects of allergen-induced inflammation and/or mechanical stress on ERR during OTM. This process was affected by pro-inflammatory cytokines, together with lipid mediators. Furthermore, our findings suggest that pro-inflammatory cytokines and leukotrienes, together with low-dose aspirin, may represent pharmacological targets for ERR during orthodontic treatment with allergic conditions.

Acknowledgements

This work was supported by grants-in-aid for Scientific Research (C) (no. 18592238 to H.I), Scientific Research (C) (no. 21592600 to H.I), and Scientific Research (C) (no. 24593095 to H.I) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We would like to express our sincere gratitude to Professor Ze'ev Davidovitch and Professor Amy L. Counts for continuing support to our research.

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http://dx.doi.org/10.5772/59972

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