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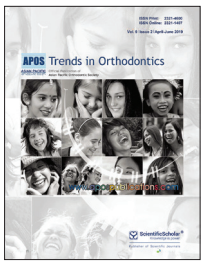

Experts Corner

Age-related osteogenesis on lateral force application to rat incisor – Part III: Periodontal and periosteal bone remodeling

Sung-Seo Mo[1], Jin-Wook Kim[2], Hyoung-Seon Baik[2], Hai-Van Giap[2], Kee-Joon Lee[2]

[1]Department of Orthodontics, Division of Dentistry, College of Medicine, The Catholic University, [2]Department of Orthodontics, College of Dentistry, Institute of Craniofacial Deformity, Seoul, Korea.

***Corresponding author:**
Kee-Joon Lee,
Department of Orthodontics, College of Dentistry, Institute of Craniofacial Deformity, Seoul, Korea.

orthojn@yuhs.ac

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ABSTRACT

Objectives: This study was aimed to compare the histological pattern of bone modeling on either periodontal or periosteal side induced by lateral orthodontic tooth movement in different age groups.

Material and Methods: A total of 50 male Sprague-Dawley rats (25 rats in the adult group – 52 weeks and 25 rats in the young group – 10 weeks) were utilized in this study. Each age group was classified into the control, 3 days, 7 days, 14 days, and 21 days groups (five rats in each) by the duration of experimental device application. A double-helical spring was produced using 0.014" stainless steel wire to provide 40 g lateral force to the left and right incisors. Hematoxylin-eosin staining, proliferating cell nuclear antigen (PCNA) immunohistochemical staining, fibroblast growth factor receptor 2 (FGFR2) immunohistochemical staining, and Masson trichrome staining were performed; and the slides were subject to histological examination.

Results: In 7 days, active bone modeling represented by the scalloped surface was observed on the periosteal side of the crestal and middle alveolus at the pressure side in the young group, while similar changes were observed only on the crestal area in the adult group. In the young group, the number of PCNA-positive cells increased significantly on the crestal area and middle alveolus on the 3, 7, and 14 day groups, with subsequent decrease at 21 days. In the adult group, PCNA-positive cells were localized on the crestal area throughout the period. In the young group, FGFR2-positive cells were observed mainly on the crestal and middle alveolus at 3, 7, and 14 days than the control group. In the adult group, these cells appeared on the crestal and middle alveolus in the 3 days group, but mainly on the crestal area at 14 days. In the young group, FGFR2-positive cells were observed on the crestal and middle alveolus on the 3, 7, and 14 days groups more than on the control group. In the adult group, these cells appeared on the crestal and middle alveolus in the 3 days group, but mainly on the crestal area in the 14 days group. In Masson trichrome stain, an increased number of type I collagen fibers were observed after helical spring activation in both age groups. Large resorption lacunae indicating undermining bone resorption were progressively present in both young and adult groups.

Conclusion: According to these results, orthodontic tooth movement may stimulate cell proliferation and differentiation primarily on the periosteal side according to progressive undermining bone resorption on the periodontal side. This response may lead to prominent bone modeling during tooth movement in the young group, compared to the relatively delayed response in the adult group.

Keywords: Age, Compensatory bone formation, Periodontal, Periosteal side

INTRODUCTION

It has been known that tooth movement is fundamentally induced by bone resorption of the pressure side (the alveolar bone side of the periodontal ligament directly contacted with

periodontal membrane), and bone formation of the tension side according to pressure-tension theory.[1] However, orthodontic tooth movement may accompany several side effects including root resorption, bone dehiscence, and bone fenestration associated with bone modeling in the periosteal side of alveolar bone.[2-4]

Lingual or buccolingual tooth movement requires substantial bone modeling not only in the alveolus but also in the periosteal side of alveolar bone, generally known as compensatory bone formation.[5-7] Although some studies observed positive results regarding compensatory bone formation even with severe buccolingual tooth movement,[5-8] controversies still exist.[9,10] In the studies performed by Steiner *et al.*[11] and Engelking and Zachrisson,[12] when upper and lower incisor was moved forward, alveolar bone loss was observed in monkeys, and a significant amount of labial bone tissues was regenerated when the incisor was moved backward again. In addition, Garib *et al.* identified an average of 7.1 mm of bone dehiscence when maxillary expansion was carried out in young patients utilizing rapid maxillary expansion.[13] Moreover, Sarikaya *et al.* observed a reduction in palatal bone thickness during the posterior retraction of incisors.[14] Dorfman,[15] Artun and Krogstad,[16] and Yared[17] also reported that bone dehiscence and gingival recession were induced in the anterior tipping of lower incisors. On the other hand, Ruf *et al.*[18] and Artun and Grobéty[19] illustrated that the anterior tipping of lower incisors did not cause bone dehiscence and gingival recession in young patients, implementing that age could attribute to the difference in the capacity of compensatory bone formation. Jäger exhibited lowered bone formation capacity and response against stimulation on aging[20] whereas Bridges *et al.* found that low bone mineral density and anatomical resistance of alveolar bone would be advantageous for tooth movement in the young group.[21]

To resolve the discrepancies, additional studies are needed to investigate the cellular behavior on the periodontal and periosteal side of alveolar bone on orthodontic force application. The objectives of this study were to investigate the differences of bone modeling around the alveolar bone depending on age and duration of lateral force application on the rat incisors through an immunohistochemical method.

MATERIAL AND METHODS

Experiment animals and device installation

This study was approved in advance by the Institutional Animal Care and Use Committee. A total of 50 male Sprague-Dawley rats included 25 rats in the adult group (52 weeks) and 25 rats in the young group (10 weeks) were involved in this study.

A double-helical spring used 0.014" stainless steel wire was applied to the left and right incisor with 40 g of lateral force. Then, five rats in each age group were allocated into the control, 3 days, 7 days, 14 days, and 21 days' groups regarding the duration of experimental device application.

Anesthetics (0.05 ml of Rompun; Rompun, Bayer, Korea; and 0.45 ml of Zoletil; Zoletil 50, Virbac Lab, Carros, France) were intraperitoneally administered to the experimental groups for installation and activation of helical spring according to part I and II of this serial study,[22,23] using a high speed 1/4 round bur [Figure 1a]. After the experimental period, the elasticity of the spring was confirmed.

Production and staining of tissue specimens

Hematoxylin-Eosin (H-E) staining

The control group and the experimental group were sacrificed at each time point by a strong dose of ether then the upper pre-maxilla was dissected. Isolated tissues were fixed with 4% paraformaldehyde for 4 days followed by clearing with Calci-Clear Rapid™ solution (National Diagnostics, Atlanta, USA) for 24 h. After the clearing, the tissues were cut in the direction described in [Figure 1b] to examine the periosteal side of alveolar bone, then were subjected to paraffin embedding in 5 μm thicknesses. After the tissue sections on the slides were deparaffinized using xylene, they were hydrated by a sequentially low concentration of alcohol. H-E staining was performed based on general rules and histological examination was carried out on the areas of interest [Figures 1c, 2, and 3].

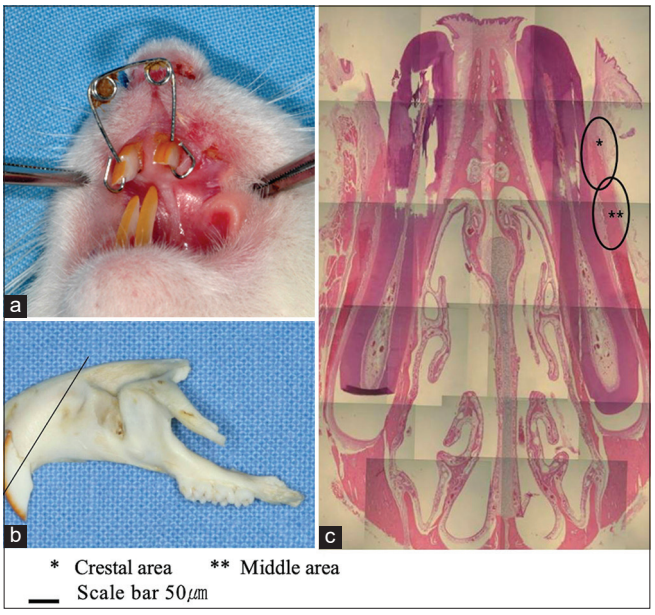

Figure 1: (a) Spring activated on rat incisor, (b) tissue section direction, (c) region of interest (×40).

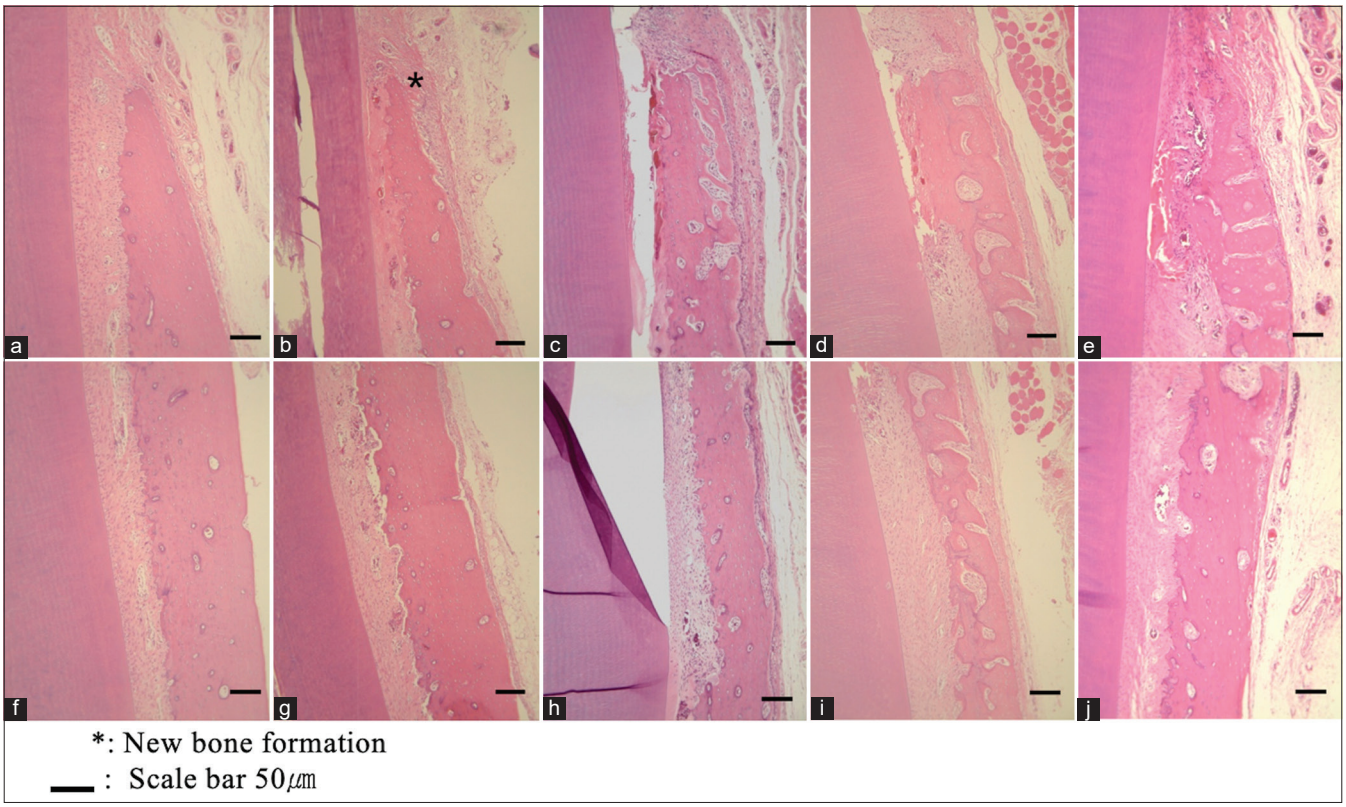

Figure 2: Hematoxylin-eosin stain in the young group in the crestal (i) and middle (ii) areas on the control (a and f), 3 days (b and g), 7 days (c and h), 14 days (d and i), 21 days (e and j) groups, respectively (×100).

Proliferating cell nuclear antigen (PCNA) immunohistochemical staining

The tissue sections on the slides were deparaffinized using xylene, then hydrated by sequentially low concentration of alcohol followed by antigen retrieval through 0.5% Triton X-100 solution at room temperature for 10 min. To inactivate endogenous peroxidase, the tissue sections were incubated in 0.3% H_2O_2 for 5 min and the reaction was blocked by 5% bovine serum albumin for 30 min.

For PCNA staining, FL-261(Santa Cruz Co., USA) was diluted in 1:100 with a primary antibody and was subjected to incubation at room temperature for 1 h followed by overnight incubation at 4°C. Envision kit (DAKO Co., Denmark) was utilized as 2nd antibody-conjugated polymer. After DAB development for 2–3 min, contrast staining was performed using Gill's hematoxylin, and dehydration was done with a gradual increase of alcohol concentration followed by mounting. Prepared slides were subjected to histological examination [Figures 4 and 5].

Fibroblast growth factor receptor 2 (FGFR2) immunohistochemical staining

The tissue sections on the slides were deparaffinized utilizing xylene and then hydrated by a sequentially low concentration of alcohol. Antigen retrieval was carried out using proteinase K at 36°C for 10 min. Endogenous peroxidase inactivation was performed by incubating the sections in 0.3% H_2O_2 for 5 min and the reaction was blocked by 5% bovine serum albumin for 30 min. To implement FGFR2 immunohistochemical staining, Beksc-122 (Santa Cruz Co., USA) was diluted in 1:100 with a primary antibody and then incubated at room temperature for 1 h followed by overnight incubation at 4°C. Envision kit (DAKO) was employed as 2nd antibody-conjugated polymer. DAB development was performed for 2–3 min and then was subjected to contrast staining using Gill's hematoxylin. The sections were then dehydrated with a gradual increase of alcohol concentration followed by mounting [Figures 6 and 7].

Masson trichrome staining

The tissue sections on the slides were subjected to deparaffinization using xylene followed by hydration utilizing a sequentially low concentration of alcohol. The nuclear stain was done by Weigert's iron hematoxylin for 10 min and rinsed. The sections were distained by 1% HCl-alcohol solution and then rinsed. Ponceau-acid fuchsin solution was applied for background staining for 10 min and then rinsed with 0.2% acetic acid solution. Mordant staining was performed using phosphomolybdic acid-orange G

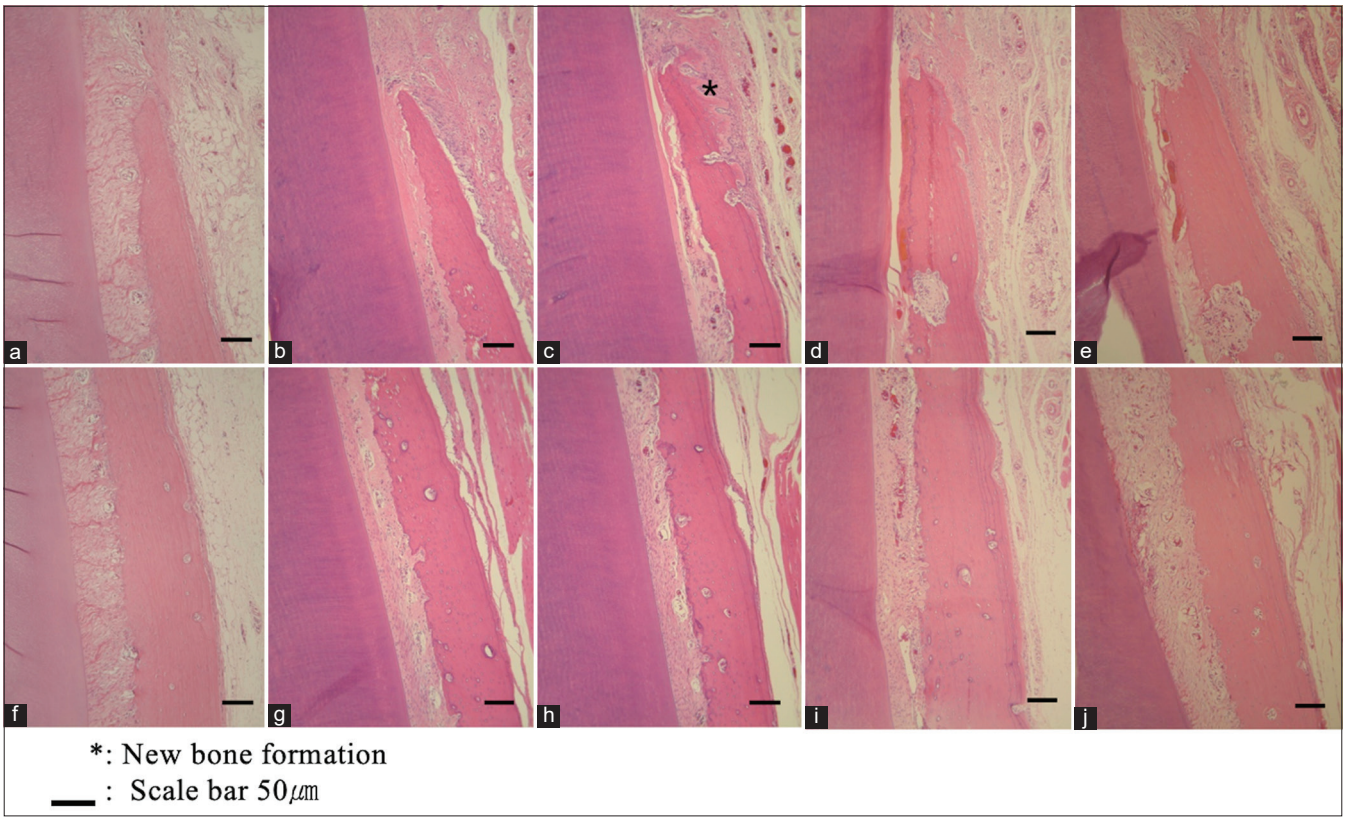

Figure 3: Hematoxylin-eosin stain in the adult group in the crestal (i) and middle (ii) areas on the control (a and f), 3 days (b and g), 7 days (c and h), 14 days (d and i), 21 days (e and j) groups, respectively (×100).

solution for 5 min followed by rinsing with 0.2% acetic acid. Collagen was stained using a light green staining solution and then unbound light green was washed out by 0.2% acetic acid. The slides were dried and then subjected to histological examination [Figure 8].

RESULTS

The areas of interest were selected on the stained slides and then examined [Figure 1c].

Examination of Hematoxylin-Eosin staining tissues

In the control group, normal periodontal ligament space was shown in the young and adult groups and was extended towards the crestal area [Figures 2 and 3a, f]. At day 3, both age groups showed a reduction of periodontal ligament space in the crestal area and decrease in the number of cells with hyalinization. In the periosteal side of alveolar bone, thicker cell layers were found around the periosteum in the crestal area, especially in the young group [Figures 2 and 3b, g].

At day 7, in the periodontal side of alveolar bone, undermining and direct bone resorption were identified, respectively, in the crestal and middle areas in both age groups. Meanwhile, in the periosteal side of alveolar bone, the surface increased irregularity in the crestal area with a thicker alveolar bone [Figures 2 and 3c, h].

At day 14, extensive resorption lacunae indicating undermining bone resorption increased in the alveolar bone side of the periodontal ligament in both age groups. In the periosteal side of the alveolar bone, the surface irregularity was increased at the middle area in the young group [Figures 2 and 3d, i].

At day 21, in both age groups, the irregularity in the periosteal side of alveolar bone was notably reduced in the crestal and middle areas [Figures 2 and 3e, j].

Examination of PCNA immunohistochemical staining

Before the activation of the orthodontic device, PCNA-positive cells were identified in the periosteal side of alveolar bone and periodontal ligament space (data not shown) in both young and adult groups. However, PCNA-positive cells were hardly exhibited in the middle area of the periosteal side in both age groups [Figures 4 and 5a, f].

At day 3, both age groups showed a remarkable increase of PCNA-positive cells in the upper part of the crestal area of the periosteal side of alveolar bone, especially in the young group. Whereas, no PCNA-positive cells were observed in

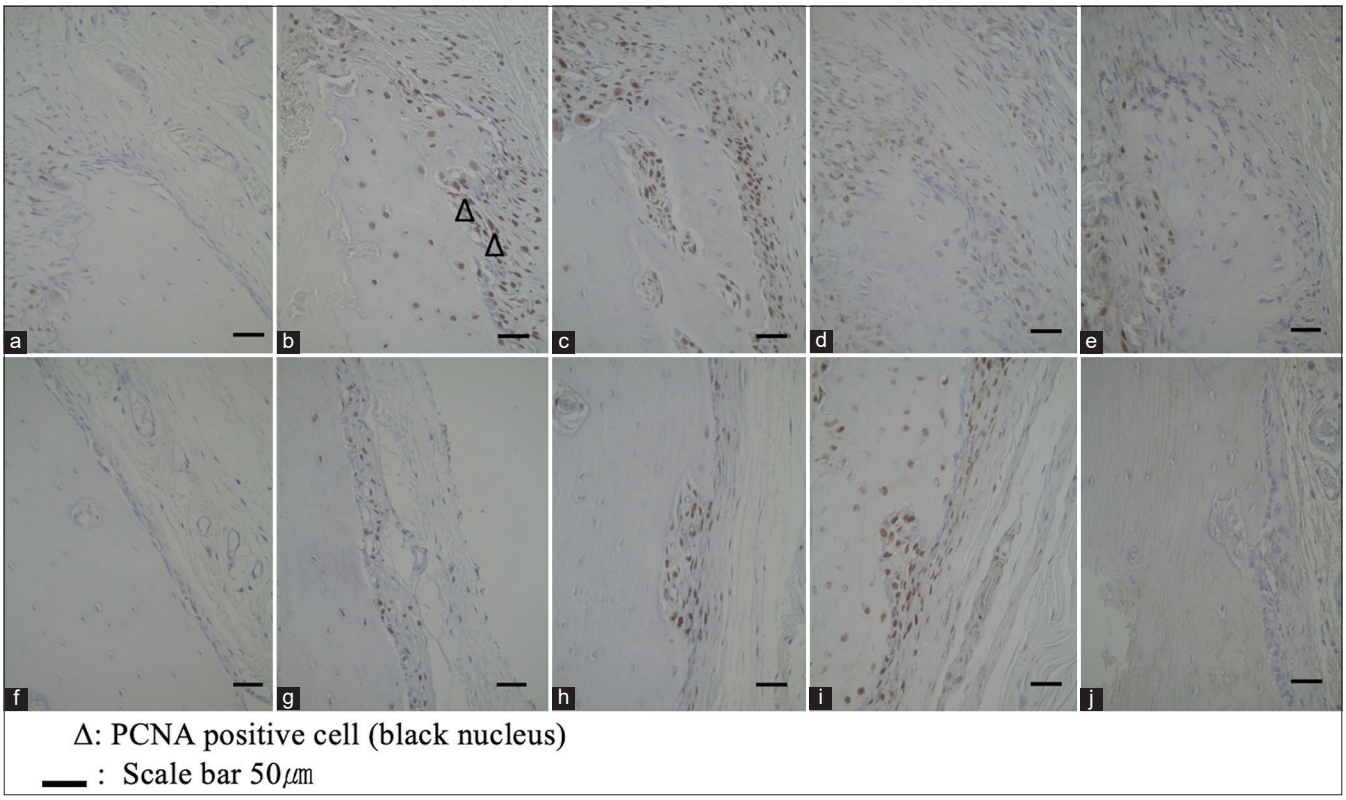

Figure 4: PCNA immunohistochemistry stain in the young group in the crestal (i) and middle (ii) areas on the control (a and f), 3 days (b and g), 7 days (c and h), 14 days (d and i), 21 days (e and j) groups, respectively (×400). PCNA: Proliferating cell nuclear antigen.

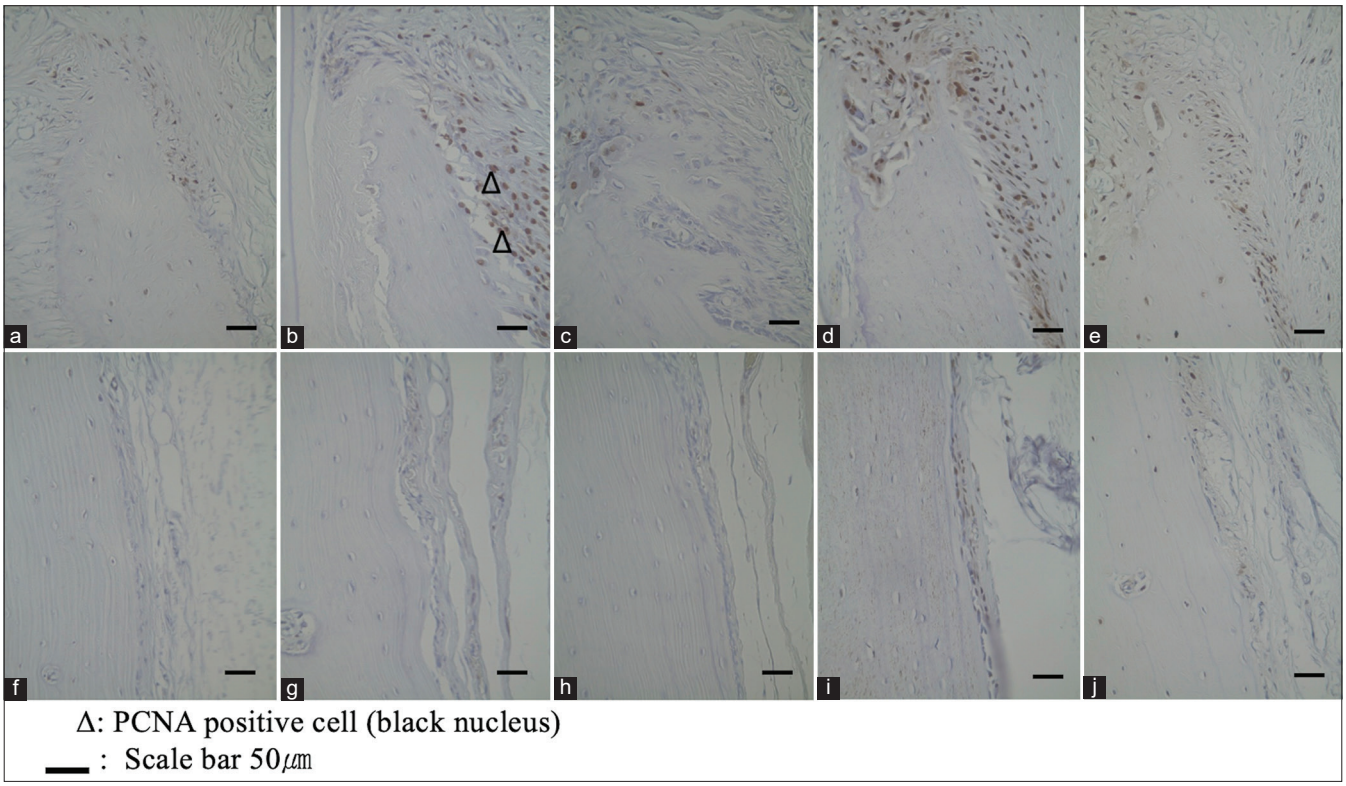

Figure 5: PCNA immunohistochemistry stain in the adult group in the crestal (i) and middle (ii) areas on the control (a and f), 3 days (b and g), 7 days (c and h), 14 days (d and i), 21 days (e and j) groups, respectively (×400). PCNA: Proliferating cell nuclear antigen.

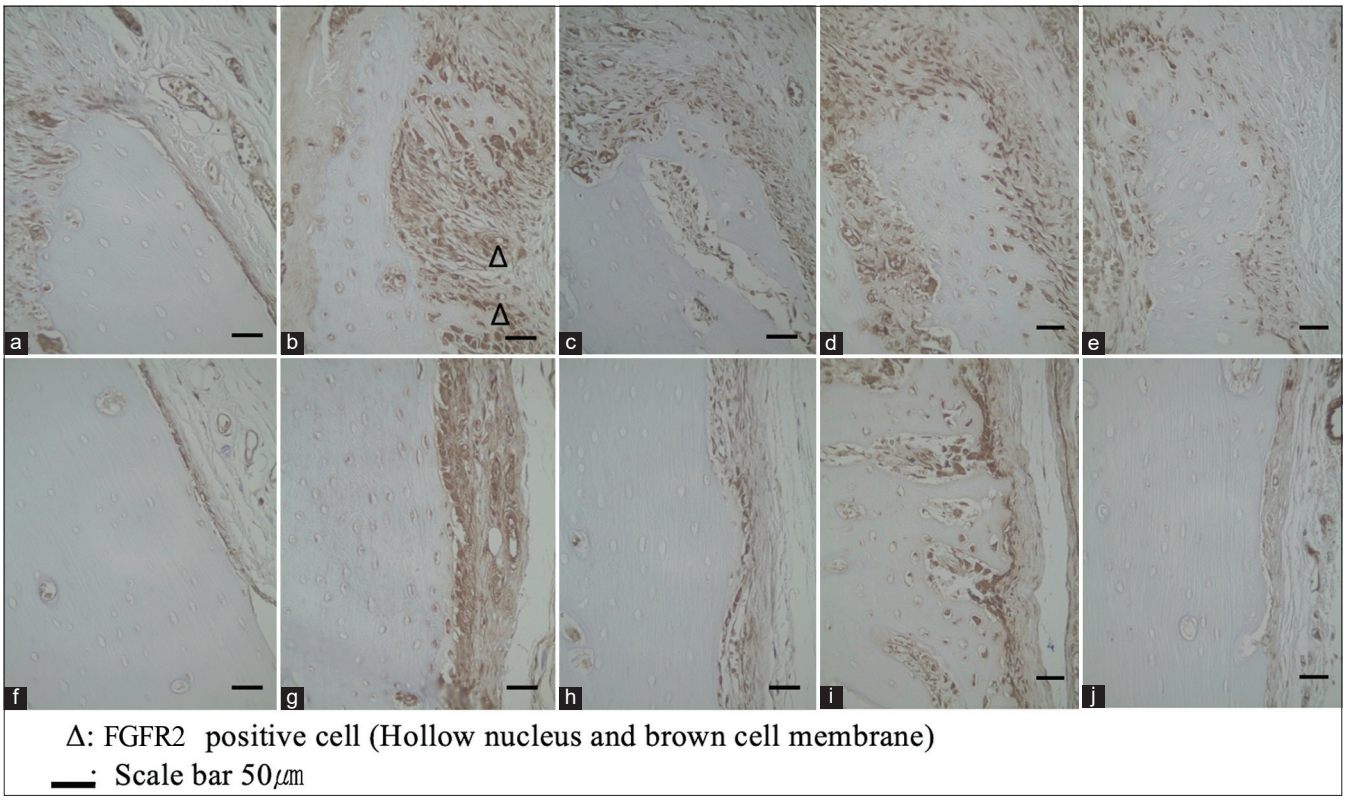

Figure 6: FGFR2 immunohistochemistry stain in the young group in the crestal (i) and middle (ii) areas on the control (a and f), 3 days (b and g), 7 days (c and h), 14 days (d and i), 21 days (e and j) groups, respectively (×400). FGFR2: Fibroblast growth factor receptor 2.

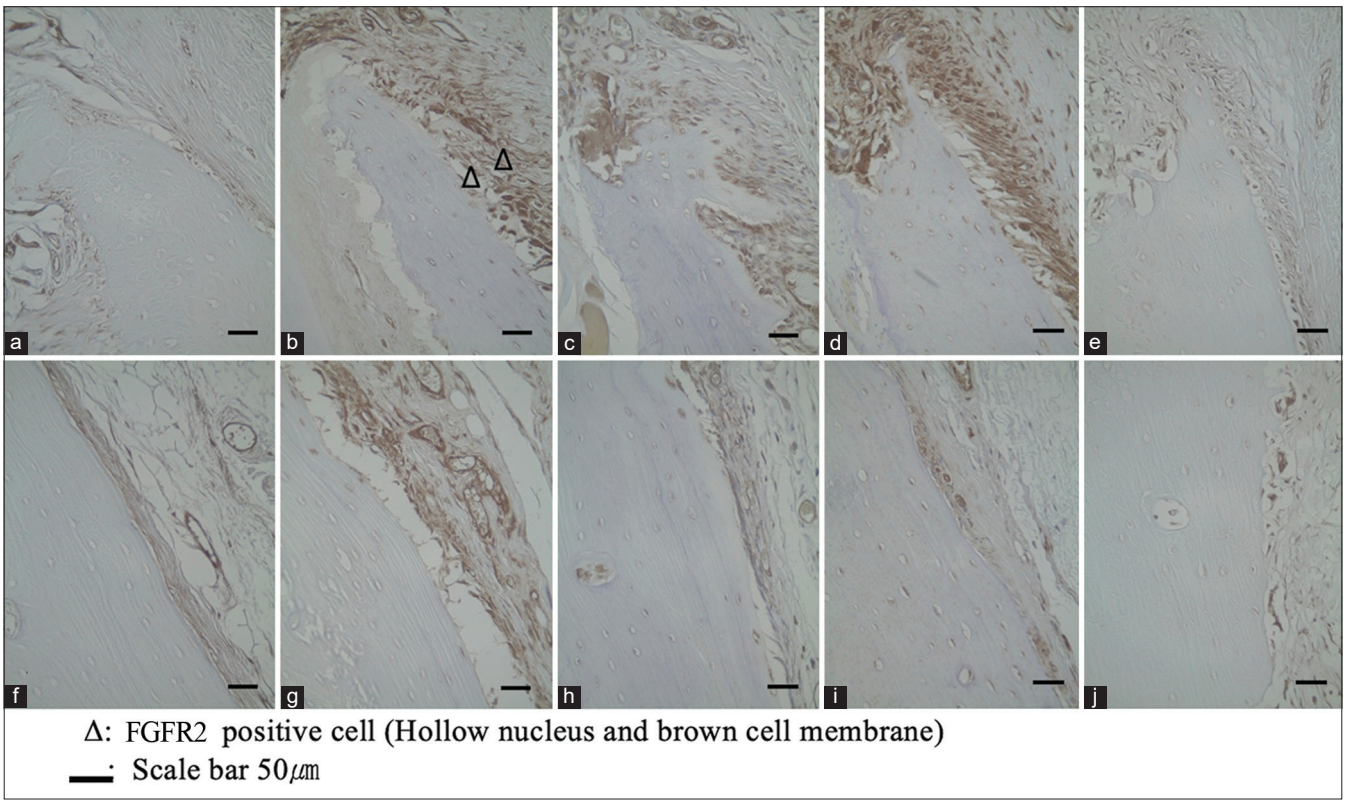

Figure 7: FGFR2 immunohistochemistry stain in the adult group in the crestal (i) and middle (ii) areas on the control (a and f), 3 days (b and g), 7 days (c and h), 14 days (d and i), 21 days (e and j) groups, respectively (×400). FGFR2: Fibroblast growth factor receptor 2.

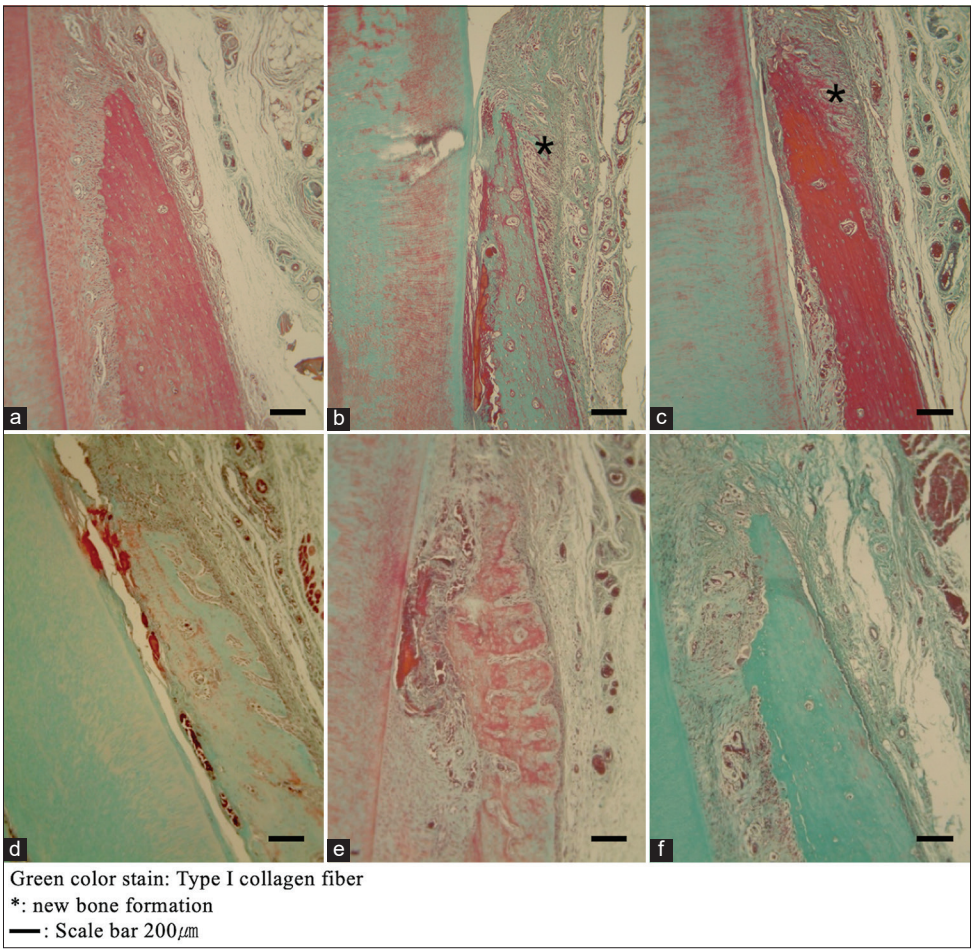

Figure 8: Masson trichrome stain in (a) the control group, (b) at the day 3 in the young group, (c) at the day 7 in the adult group, (d) at the day 14 in the young group, (e) at the day 21 in the young group, (f) at the day 21 in the adult group (×100).

the collapsed periodontal ligament side [Figures 4 and 5b, g]. In the middle area, PCNA-positive cells were found in both periosteal side of alveolar bone and periodontal ligament space in the young group.

At day 7, in the young group, PCNA-positive cells tended to decrease in the crestal area and increase in the middle area of the periosteal side of alveolar bone. Considerable reduction in the PCNA-positive cells was observed for adult group in the crestal and middle area of the periosteal side of alveolar bone compared to that of the 3 days group [Figures 4 and 5c, h].

At day 14, the young group showed a decrease of PCNA-positive cells in the crestal and middle area of the periosteal side of alveolar bone. In the adult group, on the other hand, both the crestal and middle areas of the periosteal side showed slight increase in PCNA-positive cells [Figures 4 and 5d, i].

At day 21, PCNA-positive cells decreased to the control group in the crestal and the middle area of the periosteal side of alveolar bone in the young group. In the adult group, PCNA-positive cells were observed in the crestal and middle areas of the periosteal side but remarkably decreased compared to that of the day 14 [Figures 4 and 5e, j].

FGFR2 immunohistochemical staining examination

Before the application of orthodontic force, a weak FGFR2-positive reaction was identified in the periosteal side of alveolar bone and osteocytes in the young and adult groups [Figures 6 and 7a, f]. At day 3, both age groups showed a strong FGFR2-positive reaction in the crestal and middle areas of the periosteal side of alveolar bone [Figures 6 and 7b, g].

At day 7, the positive reaction was notably reduced in both age groups [Figures 6 and 7c, h]. At day 14, a relatively elevated positive reaction was shown in the crestal and middle areas in both age groups compared to that of day 7, especially around the crestal area in the adult group [Figures 6 and 7d, i].

At day 21, the reaction was decreased to the control group in the crestal and the middle areas in both age groups [Figures 6 and 7e, j].

Masson trichrome staining examination

In general, type I collagen fiber turns green in Masson trichrome staining. In this study, both the age groups showed an increase of osteoid, new bone formation, and reformation of alveolar bone tissues in the periosteal side of alveolar bone by orthodontic force applied.[24] The active reaction of bone tissues was reduced in the 21 days group in the young group, while the bone reaction was delayed in the adult group [Figure 8].

DISCUSSION

Tooth movement beyond the alveolar bone necessitates bone modeling in the periosteal side of alveolar bone.[2-4] However, there have been few studies on compensatory bone formation related to orthodontic tooth movement. This study aimed to compare the pattern of bone modeling histologically in different age groups and duration of force application when orthodontic force (40 g) was applied to the incisor of young (12 weeks) and adult (48–52 weeks) rats using double-helical spring.

Regarding the compensatory bone formation in tooth movement, Shimpo *et al.*[5] demonstrated significant bone formation in lingual cortical bone regardless of age groups when rat molar was tipped to the lingual side, and Wingard[8] found considerable reformation of buccolingual cortical bone in monkeys. However, many clinical studies have reported the loss of alveolar bone in the buccolingual movement.[13-16] In the present study, compensatory bone formation has been observed in the crestal area of the periosteal side of alveolar bone on day 3 in the young group and day 7 in the adult group [Figures 2, 3 and 8]. Frost suggested a Mechanostat theory favoring the bone formation in the direction of bone tissue bending as bone tissues adapt to the external force.[25] Mechanostat theory demonstrates compensatory bone formation in tooth movement sufficiently and it is in agreement with the histological results in this study. In the young group, following the lateral tooth movement, the alveolar bone surface of the periodontal ligament side was hyalinized in the crestal area and may have resulted in external bending of alveolar bone as an orthodontic force was transferred to the alveolar bone.[6,7] This may explain the early bone formation in the crestal area in both groups. However, the indirect bone resorption of the hyalinized tissues on the crestal area progressed up to 21 days, therefore, the orthodontic force was not transferred to the alveolar bone, and the periodontal ligament space was increased due to direct bone resorption at the middle area. Therefore, there was no bone resorption progressed and bone modeling in the periosteal side of alveolar bone was reduced and became uniform. By the same mechanism, the compensatory bone formation was exhibited in the adult group of the 7 days group but bone modeling was not actively in the middle area due to the reduction of bone tissue turn-over by age-related tissue activity and bone mineral density.[21,26,27]

In this study, the irregularity on the surface of cortical bone was observed in the periosteal side of alveolar bone induced by orthodontic force [Figures 2 and 3]. This phenomenon had been reported in the study of Storey,[7] in which the different shapes of irregularity were explained based on the strength of force applied. In addition, Petrtýl *et al.* reported that the bone formation toward the external force was a general bone remodeling aspect occurring in the cortical bone when external force was applied.[28] They also explained the remodeling of internal cortical bone based on the bone tissue formation as osteoclasts absorb the surface of cortical bone in depth toward the external force followed by a tremendous number of osteoblasts.

In this study, PCNA and FGFR2 immunohistochemical staining were performed to investigate the reaction of bone tissues by orthodontic force. PCNA shows a positive reaction of the cells differentiating in a non-specific manner so that greater the positive reaction indicates more active tissue reaction against stimulation. FGFR2 immunohistochemical staining has specificity for osteoblast differentiating osteoprogenitor cells.[29,30] In this study, most of the PCNA positives were matched with the FGFR2 positives, indicating that bone modeling occurred actively in the periosteal side of alveolar bone in the reaction to orthodontic force [Figures 4-7]. Regarding the response in the periosteal side of alveolar bone against external force, Skerry *et al.*,[31] Klein-Nulend *et al.*,[32] and Cowin *et al.*[33] addressed that osteocytes presented in the bone tissues play a role as mechanosensors that transduced the force through the bone. This can explain the osteoblastic activity in the middle portion of the alveolar bone, especially in the young group [Figures 2, 4, and 8]. Considering the age-related changes in cell compositions of bone tissues, Roholl reported that the number of osteoblasts increased with an increase of age while the number of osteoclasts was not influenced.[34] In this study, the initial positive reaction period was not different between the young and adult groups. However, differences were observed in the age-related tissue activity such as the lower level of expression and relatively slower maximum positive reaction period in the adult group. A decrease of PCNA and FGFR2 reaction in the adult group represents a decrease of bone formation capacity according to an increase of age [Figures 5 and 7]. It would play a significant role in the homeostasis of alveolar bone along with an increase of bone mineral density in alveolar bone on aging,[21,26,27] reduction of periodontal ligament space, and a decrease of tooth movement speed in the adult group due to changes in the physical properties of periodontal ligament.[35]

To the best of our knowledge, this is the first report on the histologic mechanism of compensatory bone formation

by the lateral force. Interestingly summary, we observed osteoblastic activity on the periosteal side preceded the bone resorption and tooth displacement within the "pressure side" of periodontal ligament, especially in the crestal and middle areas. However, further studies are needed regard to biological reactions on aging under different sizes and durations of orthodontic force with long-term observation.

CONCLUSION

Taken together, we confirmed that orthodontic tooth movement facilitated cell proliferation, osteocyte differentiation, and bone formation on the surface of the periosteal side of alveolar bone, especially in the young group. The reduced bone modeling reaction in the adult group is considered a factor that restricts excessive tooth movement toward the buccolingual side of the alveolar bone during orthodontic treatment.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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