Accelerated orthodontics: A review on methods of accelerated orthodontic treatment**Pathak Mandar N¹, Tohid Mujawar²**

¹Senior Lecture, Dept. of Orthodontics, SDDC & Hospital, Parbhani, Maharashtra, ²Private Practitioner, Miraj, Maharashtra, India

***Corresponding Author: Pathak Mandar N**

Email: mandarpathak87@gmail.com

Abstract

Nowadays, every patient demanding for a shorter orthodontic treatment time. As long duration of Orthodontic treatment timing poses several disadvantages like high risk of caries, gingival recession & severe root resorption so there should be high demand of increased tooth movement with minimal disadvantages. The purpose of the study is to view different approaches to accelerate the tooth movement.

Keywords: Accelerated Orthodontics, Corticotomy; Piezocision, Low level laser.**Introduction**

Recent days, there is an increased tendency for researches to focus on accelerating methods for tooth movement due to the huge demand of adults for a shorter orthodontic treatment time. A major challenge in orthodontics is decreasing treatment time without compromising treatment outcome. Assuming that mechanotherapy and cooperation are optimized for any given patient, the rate limiting step in treatment time will be the patient's biological response to mechanotherapy. Thus, identifying and harnessing the cellular regulators of tooth movement are essential if we are to safely shorten orthodontic treatment time. High amount of research done on the biological method for tooth movement; Cytokine, PTH, vitamin D, and RANKL/RANK/OPG show promising results,^[1,2] on the other hand, relaxin does not accelerate tooth movement, but increases the tooth mobility.^[3]

Orthodontic tooth movement occurs in the presence of a mechanical stimuli sequenced by remodeling of the alveolar bone and periodontal ligament (PDL). Bone remodeling is a process of both bone resorption on the pressure site and bone formation on the tension site^[4] Orthodontic tooth movement can be controlled by the size of the applied force and the biological responses from the PDL^[5] The force applied on the teeth will cause changes in the microenvironment around the PDL due to alterations of blood flow, leading to the secretion of different inflammatory mediators such as cytokines, growth factors, neurotransmitters, colony-stimulating factors, and arachidonic acid metabolites. As a result of these secretions, remodeling of the bone occurs.^[6, 7]

Osteoclasts form on the compressed side of an orthodontically moving tooth and resorb the alveolar bone.^[8-10] Osteoclastogenesis is mainly regulated by two cytokines, receptor activator of nuclear factor kappa B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF).^[11] RANKL is a membrane-bound protein, expressed on the cell surface of the cells, which can support

osteoclastogenesis, such as osteoblasts and stromal cells.^[11] RANK, the receptor for RANKL, was identified and its expression was confirmed on the osteoclast lineage cells from precursors to mature osteoclasts.^[12] RANKL signaling is inhibited by osteoprotegerin (OPG),^[13] and a balance between RANKL and OPG contributes to the regulation of bone resorption.^[14] Oshiro *et al.*^[15] reported that RANKL induction was observed in the periodontal tissue of orthodontically moving tooth, and the RANK-RANKL regulation system was confirmed even in the site-specific bone remodeling that occurred during the orthodontic tooth movement.

Based on biological principles existing techniques are Categorized into two types

- a) Indirect technique
 - Micro – osteoperforations
 - Piezocision
 - Corticotomy
- b) Direct technique
 - Vibrations
 - Lasers
 - Ultrasound

In recent decades major attempts have been made to shorten the length of treatment. These techniques include rapid distraction of the canines^[16] and corticotomy-facilitated orthodontics.^[17]

In the late 1990s the Wilcko brothers added the alveolar augmentation to the corticotomies and developed the Accelerated Osteogenic Orthodontics (AOO) procedure and claimed that the orthodontic treatment time could be reduced by 75% in the majority of orthodontic cases ^[18]. An alternative approach has been introduced by Park *et al*^[19] consisting of incisions directly through the gingiva and bone using a combination of blades and a surgical mallet.

The initial response of cells to mechanical stress in vitro appears within 30 minutes.^[20-22] so to activate these initial responses at the cellular level by applying resonance vibrational stimulation to a tooth and its periodontal tissue. Moreover, the loading of resonance vibration that is equal to the natural frequency of the first molar and its periodontal tissue stimulates more effectively the periodontal tissue. Thus, the application of resonance vibration during orthodontic tooth movement should affect the acceleration of tooth movement by increasing the activity of the cells in the PDL.

Different Methods to Accelerate Orthodontic Tooth Movement

Corticotomy

A corticotomy is defined as a surgical procedure whereby only the cortical bone is cut, perforated, or mechanically altered. The medullary bone is not changed. This is in contrast to an **osteotomy**, which is defined as a surgical cut through both the cortical and medullary bone.

Typical orthodontic treatment can take 18-36 months. The treatment time depends on the distances the teeth need to be moved, treatment goals, the type of technique involved and the cooperation of the patient. Rapid tooth movement followed by decortication, commonly known as 'WILCKODONTICS' 'OR' ACCELERATED OSTEOGENIC ORTHODONTICS"

Corticotomy –facilitated tooth movements was first described by L.C.Bryan in 1893. Surgical intervention to affect the alveolar housing and tooth movement have been described in various forms for over a hundred years. Corticotomy is relatively safe and considered as an effective intervention to accelerate orthodontic tooth movement.

Heinrich Köle's publication in 1959 was the first to describe modern-day corticotomy-facilitated orthodontics.^[23]

The RAP (regional acceleratory Phenomenon) is a normal localized reaction of soft and hard tissues to noxious stimuli (Fig. 1); it is associated with increased perfusion and bone turnover and decreased bone density.^[24]

Figure 1. The process by which corticotomies

Bring about faster tooth movements.

RAP was first described by **Frost** in 1983. RAP is simply an acceleration of existing biological processes; it does not illicit new processes. The processes associated with corticotomies are similar to the processes associated with normal fracture healing, which include a reactive phase, a reparative phase, and a remodeling phase (Fig. 2).

Figure 2: The 3 phases of the healing process.

Indications

1. Decreasing the duration of orthodontic treatment in patients who are undergoing conventional, nonsurgical orthodontic therapy.
2. Expanding the alveolar basis, therefore reducing the need for premolar extractions and strengthens the periodontium, lowering the risk for periodontal damage during and after treatment.
3. Selectively altering the differential anchorage among groups of teeth that have to be moved and diminishing the counter effect in the teeth that should not be moved.
4. As a tool in multidisciplinary treatment, including the managing of partial edentulism in adult and growing patients.
5. Modifying the lower third of face.
6. Adjunctive measure in facilitating treatment of impacted teeth.
7. Decreasing the duration of pre-operative orthodontic treatment in patients undergoing conventional, combined surgical orthodontic therapy.
8. Alternative to orthognathic surgery for combined surgical orthodontic management of select dentoskeletal malocclusions.
9. Salvage technique for the management of post-orthognathic, occlusion related complications.
10. Management of clinically refractory orthodontic dental conditions.

Contraindications

1. These are similar to those for any minor oral surgery or periodontal surgery procedures, especially when related to conditions affecting systemic health and illness (cardiac, endocrine, musculoskeletal etc.)
2. It is also contraindicated in certain local disease states, such as active periodontitis or systemic conditions (e.g., uncontrolled osteoporosis)
3. It may also have an increased complications rate in patients who have a history of use of certain medications (e.g., nonsteroidal anti-inflammatory drugs, immunosuppressive medications, steroids, bisphosphonates)

4. Radiation therapy to the maxillofacial region.

Surgical technique

Flap design

Objectives of the flap design are

1. Provide access to the alveolar bone wherein corticotomies are to be performed.
2. Provide for coverage of the particulate graft.
3. Maintain the height and volume of the interdental tissues.
4. Enhance the esthetic appearance of the gingival form where necessary.

The basic flap design is a combination of a full thickness flap in the most coronal aspect of the flap with a split-thickness dissection performed in the apical portions. The purpose of the split-thickness dissection is to provide mobility of the flap so that it may be sutured with minimal tension. After the split-thickness dissection is performed, the periosteal layer is carefully elevated from the alveolar bone, providing access to the alveolar bone surface and facilitating identification of critical neurovascular structures.

Mesial and distal extension of the flap beyond the corticotomy areas is suggested to reduce the need for vertical releasing incisions. The initial incision is carried out on both surfaces of the alveolus. Preservation of the interdental gingival tissues is critical for a successful esthetic outcome. Numerous different papillae preservation techniques are frequently used. If possible, the papillae between the maxillary central incisors should not be elevated. Access to the labial alveolar bone in this area is achieved by “tunneling” from the distal aspect (Fig 3).

Fig. 3: A, in esthetically sensitive areas such as the papillae between the central incisors, the initial incision is not carried through the papillae. Access to the interproximal bone is achieved by tunneling under the flap. B, Healing at 7 days after use of microsurgical closure techniques. C, Completed tooth movement at 6 months. (Orthodontic therapy was performed by Dr Nancy Ward, Baltimore, MD).

In almost all cases the papilla is not reflected from the palatal aspect between the central incisors. Retention of a palatal or lingual gingival collar of tissue, not reflected from the underlying alveolar bone, is frequently used to provide a collateral blood supply to the papillary tissue (Fig 4).

Fig. 4: Typical palatal incision leaving collar of gingival tissue, decreasing likelihood of sloughing of interproximal tissue. Murphy et al. Periodontal Accelerated Osteogenic Orthodontics.

Laser assisted flapless corticotomy

Lasers in general consist of an active medium and a pumping source enclosed in an optical cavity.

The pumping source pumps the active medium from its ground state to an excited state. Very intense flashes of lights or electrical discharges pumps the lasing medium and creates a large collection of atoms in excited state for the laser to work efficiently.

Based on the active lasing medium it can be a container of gas or a solid crystal rod.

The gas active medium lasers available in dentistry today are Argon and CO₂ laser.

In solid state lasers a garnet crystal made from Yttrium and aluminium is commonly used and these are known as YAG LASERS.

Advantages

1. Creates clear, dry field with no bleeding.
2. Decreasing the possibility of infection
3. Creates less trauma to the area
4. Decreases chances of post-operative swelling
5. Minimal post-operative pain

Nd: YAG LASERS are the most commonly used lasers in soft tissue application.

Among all lasers Er:YAG possesses characteristics suitable for oral treatment due to its dual ability to ablate soft and hard tissues with minimal damage.

Also its bacterial effect with elimination of lipopolysaccharide, ability to remove plaque and calculus, irradiation effect limited to an ultra thin layer of tissue, even or faster bone repair after irradiation than conventional bur

drilling and effective ability for implant maintainance, make it a promising tool for periodontal treatment.

In another study, Pourzandian et al demonstrated that the initial bone healing following Er:YAG laser irradiation occurred faster than that after mechanical bur drilling and CO2 laser irradiation.

Periodontal tissue activation by vibration

Accelerating the speed of orthodontic tooth movement should contribute to the shortening of the treatment period. This would be beneficial because long treatment times are a negative aspect of orthodontic treatment.

The application of resonance vibration might accelerate orthodontic tooth movement via enhanced RANKL expression in the periodontal ligament without additional damage to periodontal tissues such as root resorption. Orthodontic tooth movement is generated by the coupling of bone resorption on the compressed side of the periodontal ligament (PDL) and by bone formation on the stretched side of the PDL as a consequence of therapeutic mechanical stress. Since orthodontic treatment usually takes place over a long period of time, the problems of caries, periodontal disease, and prolonged treatment period are burdensome for the patient. Furthermore, it has been reported that total treatment duration proves to be highly correlated

With root resorption.^[25] In this respect, it is important to accelerate alveolar bone remodeling during orthodontic treatment, to shorten the time required for successful therapy. To date, to accelerate tooth movement, physical approaches with low-energy laser irradiation^[26] and magnetic fields,^[27,28] as well as pharmacological approaches with the injection of prostaglandin E2 (PGE2)^[29-31] and 1,25-(OH)2D3^[32-34] during tooth movement, have been investigated. However, many side effects, such as local pain, severe root resorption,^[35] and drug-induced side effects^[36] have been reported. The initial response of cells to mechanical stress in vitro appears within 30 minutes.^[37-39] vibrational stimulation to a tooth and its periodontal tissue is used to activate initial responses of cellular level. Moreover, the loading of resonance vibration that is equal to the natural frequency of the first molar and its periodontal tissue stimulates more effectively the periodontal tissue.^[40]

Thus, the application of resonance vibration during orthodontic tooth movement should affect the acceleration of tooth movement by increasing the activity of the cells in the PDL.

Effect of Local Drug on Orthodontic tooth movement Analgesics

Analgesic is a drug that selectively relieves pain by acting on the CNS or peripheral pain mechanisms, without significantly altering consciousness. Nonsteroid anti-inflammatory drugs (NSAIDs) do not affect the tenderness induced by direct application of PGs, but block the pain-sensitizing mechanism induced by bradykinins, tumor necrosis factors (TNFs), interleukins (ILs), etc. The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG mediated sensitization of nerve

endings. NSAIDs are a relatively weak inhibitor of PG synthesis and anti-inflammatory action may be exerted by reduced generation of superoxide by neutrophils, and TNF release, free radical scavenging, and inhibition of metalloprotease activity in cartilage.

Effect of NSAIDs on tooth movement

Most commonly used medications in orthodontics are for control of pain following mechanical force application to tooth. Inhibition of the inflammatory reaction produced by PGs slows the tooth movement. Recent research demonstrated the molecular mechanisms behind the inhibition of tooth movement by NSAIDs. The levels of matrix metalloproteinases (MMP9 and MMP2) were found to be increased, along with elevated collagenase activity, followed by a reduction in procollagen synthesis which is essential for bone and periodontal remodeling. The whole process is controlled by inhibition of cyclooxygenase (COX) activity, leading to altered vascular and extravascular matrix remodeling, causing a reduction in the pace of the tooth movement.

Vitamin D

Vitamin D and its active metabolite, 1, 25, 2(OH) D3, together with parathyroid hormone (PTH) and calcitonin, regulate the amount of calcium and phosphorus levels. Vitamin D receptors have been demonstrated not only in osteoblasts but also in osteoclast precursors and in active osteoclasts. In 1988, Collins and Sinclair demonstrated that intraligamentary injections of vitamin D metabolite, 1, 25-dihydroxy cholecalciferol, caused increase in the number of osteoclasts and amount of tooth movement during canine retraction with light forces.^[41] In 2004, Kale and colleagues observed that local applications of vitamins enhanced the rate of tooth movement in rats due to the wellbalanced bone turnover induced by vitamin D.^[42]

Stimulatory action of vitamin D on osteoblasts can help stabilize orthodontic tooth movement. In 1976, Bran and colleagues reported that rats treated with vitamin D showed increased bone formation on the pressure side of the periodontal ligament after application of orthodontic forces. In 2004, Kawakami observed an increase in the mineral appositional rate on alveolar bone after orthodontic force application; they suggested that local application of vitamin D could intensify the re-establishment of supporting alveolar bone, after orthodontic treatment.^[43]

Hormones

Estrogens

Estrogen is considered to be the most important hormone affecting the bone metabolism in women. It inhibits the production of various cytokines which are involved in bone resorption by stimulating osteoclast formation and osteoclast bone resorption. It also inhibits osteoblasts' responsiveness to PTH. Estrogens do not have any anabolic effects on bone tissue; they directly stimulate the bone forming activity of osteoblasts. Studies have shown that estrogens decrease the velocity of tooth movement.^[44] Oral contraceptives, taken for

long periods of time, can influence the rate of tooth movement. Androgens also inhibit bone resorption, modulate the growth of the muscular system, and may affect the length and results of the orthodontic treatment.

Thyroid hormones

Thyroid hormones are recommended for the treatment of hypothyroidism and used after thyroidectomy in substitutive therapy. Thyroxin administration lead to increased bone remodeling, increased bone resorptive activity and reduced bone density. Effects on bone tissue may be related to the augmentation of interleukin-1 (IL-1B) production induced by thyroid hormones at low concentrations, cytokine stimulated osteoclast formation and osteoclastic bone resorption. The thyroid hormone increases the speed of orthodontic tooth movement in patients undergoing such medication.^[45] Low dosage and short-term thyroxine administration are reported to lower the frequency of “force-induced” root resorption. Decrease in resorption may be correlated to a change in bone remodelling process and a reinforcement of the protection of the cementum and dentin to “force-induced” osteoclastic resorption.

Parathyroid hormone

PTH affects osteoblasts' cellular metabolic activity, gene transcriptional activity, and multiple protease secretion. Its effects on osteoclasts occur through the production of RANK-L Receptor activator of nuclear factor kappa -B ligand), a protein playing a crucial role in osteoclasts' formation and activity. In 1970s, animal studies demonstrated that PTH could induce an increase in bone turnover that would accelerate orthodontic tooth movement. More recently, an increased rate of tooth movements has been observed in rats treated with PTH, whether administered systemically or locally.^[46] These results indicate that orthodontists should take note of patients being treated with PTH, as for example, in cases of severe osteoporosis.

Relaxin

Relaxin has been known as a pregnancy hormone. It is released just before child birth to loosen the public symphysis, so that the relaxed suture will allow widening of the birth canal for parturition. In 2005, Liu and colleagues showed that the administration of relaxin might accelerate the early stages of orthodontic tooth movements in rats.^[47] Stewart and colleagues used gingival injections of Relaxin to relieve rotational memory in the connective tissues of maxillary lateral incisors that had been orthodontically rotated. In 2000, Nicozis and colleagues suggested that Relaxin might be used as an adjuvant to orthodontic therapy, during or after tooth movement, for promotion of stability, for rapid remodeling of gingival tissue during extraction space closure, for orthopedic expansion in non – growing patients, by reducing the tension of the stretched soft tissue envelope, particularly the expanded palatal mucosa, after orthognathic surgery.

Calcitonin

Calcitonin inhibits bone resorption by direct action on osteoclasts, decreasing their ruffled surface which forms contact with resorptive pit. It also stimulates the activity of osteoblasts. Because of its physiological role, it is considered to inhibit the tooth movement; consequently, delay in orthodontic treatment can be expected.

Corticosteroids

Evidence indicates that the main effect of corticosteroid on bone tissue is direct inhibition of osteoblastic function and thus decreases total bone formation. Decrease in bone formation is due to elevated PTH levels caused by inhibition of intestinal calcium absorption which is induced by corticosteroids. Corticosteroids increase the rate of tooth movement, and since new bone formation can be difficult in a treated patient, they decrease the stability of tooth movement and stability of orthodontic treatment in general.^[48] When they are used for longer periods of time, the main side effect is osteoporosis. It has been demonstrated in animal models with this type of osteoporosis that the rate of active tooth movement is greater, but tooth movement is less stable since little bone is present and there is no indication of bone formation. A more extensive retention may be required.

Conclusion

Now a day's every patient wants to reduce the orthodontic treatment timing So as we have discussed earlier there are various methods to accelerate the orthodontic tooth movement. Depending upon the Regional Acceleratory Phenomenon micro perforations, piezosisions, lasers and mechanical vibrations reduces the invasive nature of prior procedures.

Funding

None.

Conflict of Interest

None.

References

1. Collins MK, Sinclair PM. The local use of vitamin D to increase the rate of orthodontic tooth movement. *Am J Orthod Dentofacial Orthop.* 1988; 94(4):278–84.
2. Soma S, Iwamoto M, Higuchi Y, Kurisu K. Effects of continuous infusion of PTH on experimental tooth movement in rats. *J Bone Miner Res.* 1999;14(4):546–54.
3. Madan M S, Liu ZJ, Gu GM, Gregory J. King Effect of human relaxin on orthodontic tooth movement and periodontal ligament in rats. *Am J Orthod Dentofacial Orthop.* 2007;131(1);8.e1-8.e10.
4. Davidovitch Z. Tooth movement. *Crit Rev Oral Biol Med.* 1991;2(4):411-50
5. Meikle MC. The tissue, cellular, and molecular regulation of orthodontic tooth movement: 100 years after Carl Sandstedt. *Eur J Orthod.* 2006;28(3):221-40.

6. Davidovitch Z, Nicolay OF, Ngan PW, Shanfeld JL. Neurotransmitters, cytokines, and the control of alveolar bone remodeling in orthodontics. *Dent Clin North Am.* 1988.
7. Krishnan V, Davidovitch Z. Cellular, molecular, and tissue-level reactions to orthodontic force. *Am J Orthod Dentofac Orthop.* 2006; 129(4):469. e461-432
8. Storey E. The nature of tooth movement. *Am J Orthod.* 1973;63(3):292-314.
9. Davidovitch Z, Nicolay OF, Ngan PW, Shanfeld JL. Neurotransmitters, cytokines, and the control of alveolar bone remodeling in orthodontics. *Dent Clin North Am.* 1988;32:411-35.
10. Brudvik P, Rygh P. Multi-nucleated cells remove the main hyalinized tissue and start resorption of adjacent root surfaces. *Eur J Orthod.* 1994;16 (4):265-73.
11. Udagawa N, Takahashi N, Jimi E, Matsuzaki K, Tsurukai T, Itoh K *et al.* Osteoblasts/stromal cells stimulate osteoclast activation through expression of osteoclast differentiation factor/RANKL but not macrophage colony-stimulating factor. *Bone* 1999;25:517-23.
12. Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Goto M *et al.* A novel molecular mechanism modulating osteoclast differentiation and function. *Bone* 1999;25:109-13.
13. Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, Luthy R *et al.* Osteoprotegerin: A novel secreted protein involved in the regulation of bone density. *Cell* 1997;89:309-19.
14. Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Boyle WJ, Riggs BL. The roles of osteoprotegerin and osteoprotegerin ligand in the paracrine regulation of bone resorption. *J Bone Miner Res.* 2000;15(1):2-12.
15. Oshiro T, Shiotani A, Shibasaki Y, Sasaki T. Osteoclast Induction in Periodontal Tissue During Experimental Movement of Incisors in Osteoprotegerin-Deficient Mice. *Anat Rec.* 2002;266:218-25.
16. Liou EJ., Huang CS. Rapid canine retraction through distraction of the periodontal ligament. *Am J Orthod Dentofacial Orthop.* 1998;114(4):372-82.
17. Anholm JM, Crites DA, Hoff R, Rathbun WE. Corticotomyfacilitated orthodontics. *Calif Dent Assoc J.* 1986;14(12):7-11.
18. Wilcko WM, Wilcko T, Bouquot JE, Ferguson DJ. Rapid orthodontics with alveolar reshaping: two case reports of decrowding. *Int J Periodontics Restorative Dent.* 2001;21(1):9-19.
19. Park YG, Kang SG, Kim SJ. Accelerated tooth movement by Corticision as an osseous orthodontic paradigm. *Kinki Tokai Kyosei Shika Gakkai Gakujyutsu Taikai, Sokai.* 2006;48:6.
20. Yamaguchi N, Chiba M, Mitani H. The induction of c-fos mRNA Expression by mechanical stress in human periodontal ligament cells. *Arch Oral Biol.* 2002;47:465-71.
21. Matsuda N, Morita N, Matsuda K, Watanabe M. Proliferation and differentiation of human osteoblastic cells associated with differential activation of MAP kinases in response to epidermal growth factor, hypoxia, and mechanical stress in vitro. *Biochem Biophys Res Commun.* 1998;249:350-4.
22. Kikuri T, Hasegawa T, Yoshimura Y, Shirakawa T, Oguchi H. Cyclic tension force activates nitric oxide production in cultured human periodontal ligament cells. *J Periodontol.* 2000;71:533-9.
23. Köle H: Surgical operations of the alveolar ridge to correct occlusal abnormalities. *Oral Surg Oral Med Oral Pathol.* 1959;12:515.
24. Generson RM, Porter JM, Zell A: Combined surgical and orthodontic management of anterior open bite using corticotomy. *J Oral Surg.* 1978;34:216.
25. Segal GR, Schiffman PH, Tuncay OC. Meta analysis of the treatment-related factors of external apical root resorption. *Orthod Craniofac Res.* 2004;7:71-8.
26. Kawasaki K, Shimizu N. Effects of low-energy laser irradiation on bone remodelling during experimental tooth movement in rats. *Lasers Surg Med.* 2000;26:282-91.
27. Tengku BS, Joseph BK, Harbrow D, Taverne AA, Symons AL. Effect of a static magnetic field on orthodontic tooth movement in the rat. *Eur J Orthod.* 2000;22:475-87.
28. Stark TM, Sinclair PM. Effect of pulsed electromagnetic fields on orthodontic tooth movement. *Am J Orthod Dentofacial Orthop.* 1987;91:91-104.
29. Yamasaki K, Miura F, Suda T. Prostaglandin as a mediator of bone resorption induced by experimental tooth movement in rats. *J Dent Res.* 1980;59:1635-42.
30. Yamasaki K, Shibata Y, Imai S, Tani Y, Shibasaki Y, Fukuhara T. Clinical application of prostaglandin E1 (PGE1) upon orthodontic tooth movement. *Am J Orthod.* 1984; 85:508-18.
31. Leiker BJ, Nanda RS, Currier GF, Howes RI, Sinha PK. The effects of exogenous prostaglandins on orthodontic tooth movement in rats. *Am J Orthod Dentofacial Orthop.* 1995;108:380-8.
32. Collins MK, Sinclair PM. The local use of vitamin D to increase the rate of orthodontic tooth movement. *Am J Orthod Dentofacial Orthop.* 1988;94:278-84.
33. Takano-Yamamoto T, Kawakami M, Yamashiro T. Effect of age on the rate of tooth movement in combination with local use of 1,25(OH)2D3 and mechanical force in the rat. *J Dent Res.* 1992;71:1487-92.
34. Takano-Yamamoto T, Kawakami M, Kobayashi Y, Yamashiro T, Sakuda M. The effect of local application of 1, 25-dihydroxycholecalciferol on osteoclast numbers in orthodontically treated rats. *J Dent Res.* 1992;71:53-9.
35. Brudvik P, Rygh P. Root resorption after local injection of prostaglandin E2 during experimental tooth movement. *Eur J Orthod.* 1991;13:255-63.
36. Ochiai H. Histological investigations on the effect of prostaglandin E2 (PGE2) applied to experimental tooth

- movement. *Nippon Kyosei Shika Gakkai Zasshi*. 1987;46:500-16.
37. Yamaguchi N, Chiba M, Mitani H. The induction of c-fos mRNA expression by mechanical stress in human periodontal ligament cells. *Arch Oral Biol*. 2002;47:465-71.
38. Matsuda N, Morita N, Matsuda K, Watanabe M. Proliferation and differentiation of human osteoblastic cells associated with differential activation of MAP kinases in response to epidermal growth factor, hypoxia, and mechanical stress in vitro. *Biochem Biophys Res Commun*. 1998; 249:350-4.
39. Kikuri T, Hasegawa T, Yoshimura Y, Shirakawa T, Oguchi H. Cyclic tension force activates nitric oxide production in cultured human periodontal ligament cells. *J Periodontol*. 2000;71:533-9.
40. Emata T. The mechanical response of the periodontal structure in the maxillary lateral incisor of the macaca fuscata yakui, loading by a vibrating force. *J Oral Biol Sci*. 1979; 21:571-85.
41. Collins MK, Sinclair PM. The local use of vitamin D to increase the rate of orthodontic tooth movement. *Am J Orthod*. 1988;94:278-84.
42. Kale S, Kocadereli I, Atila P, Asan E. Comparison of the effects of 1,25 -dehydroxycholecalciferol and prostaglandin E2 on orthodontic tooth movement. *Am J Orthod*. 2004;125:607-14.
43. Kawakami M, Takamo-Yamamoto T. Local injection of 1,25-dihydroxyvitamin D3 enhanced bone formation for tooth stabilization after experimental tooth movements in rats. *J Bone Mineral Metabolism*. 2004;22:541-6.
44. Tyrovola JB, Spyropoulos MN. Effects of drugs and systemic factors on orthodontic treatment. *Quintessence Int*. 2001;32:365-71.
45. Shirazi M, Dehpour AR, Jafari F. The effect of thyroid hormone on orthodontic tooth movement in rats. *J Clin Pediatr Dent*. 1999;23:259-64.
46. Soma S, Iwamoto M, Higuchi Y, Kurisu K. Effects of continuous infusion of PTH on experimental tooth movement in rats. *J Bone Miner Res*. 1999;14:546-54.
47. Madan MS, Liu ZJ, Gu GM, King GJ. Effects of human relaxin on orthodontic tooth movement and periodontal ligaments in rats. *Am J Orthod*. 2007;131:8.e1-8.10.
48. Kalia S, Melsen B, Verna C. Tissue reaction to orthodontic tooth movement in acute and chronic corticosteroid treatment. *Orthod Craniofac Res*. 2004; 7:26-34.