

## An extensive review of literature: considering bone reaction to different agents in orthodontically induced root and alveolar resorption

Simran Kaur Pawar<sup>1,\*</sup>, Harsimran Jeet Singh Pawar<sup>2</sup>, Priya Ghangas<sup>3</sup>, Puneet Gupta<sup>4</sup>, Radhika Chawla<sup>5</sup>

<sup>1</sup>Intern, <sup>3</sup>PG Student, DAV Dental College, Yamunanagar, Haryana, <sup>2</sup>PG Student, UNT Health Sciences Centre, USA, <sup>4</sup>Associate Professor, MM College of Dental Sciences & Research, Haryana, <sup>5</sup>Intern, Subharti University, Meerut, Uttar Pradesh

**\*Corresponding Author:**

Email: simranpawar1992@gmail.com

### Abstract

**Objective:** Orthodontically induced root resorption is a common problem in day to day practice. If such root resorption could be prevented, it would be an important contribution toward reducing risk factors in orthodontic treatment. The aim of the review is to focus on different agents which can be therapeutically useful in orthodontic tooth movement.

**Methods and Materials:** The article reviews various agents inhibiting as well as promoting root and alveolar bone resorption to orthodontic tooth movement based on advanced PubMed Central (PMC), Cochrane database, Wiley online search of the English language literature from the year 1951 to present in order to help us select the most suitable among them fulfilling the desired criteria of being safe, having less adverse effects, minimal contraindications, rare cross reactions, economically viable, having a scope to be used for successful prognosis and possibly not requiring any special considerations to interpret the results.

**Results:** Forty-nine articles were included in the review, but their interpretation was hindered by the variability in experimental design, magnitude of force applied during tooth movement, and medication regimens. Corticosteroid hormones, parathyroid hormone, and thyroxin have all been shown to increase tooth movement. Bisphosphonates had a strong inhibitory effect.

**Conclusion:** By this review, we conclude that low laser therapy and arginylglycylaspartic acid (RGD) peptide emerges as the clear winner and can result in better prognosis in orthodontic treatment. These techniques are new and cannot replace the conventional agents as a whole.

**Keywords:** Root resorption; Integrins; Matrix metalloproteins; Echistatin; Low laser therapy; Doxycycline.

### Introduction

Orthodontic tooth movement is a biologic response towards a mechanical force. The movement is induced by the prolonged application of controlled mechanical forces, which create pressure and tension zones in the periodontal ligament and alveolar bone, causing remodeling of the tooth sockets.<sup>(1)</sup> But excessive forces results in orthodontically induced inflammatory root resorption. It has been considered a side-effect of the cellular activity associated with the removal of necrotic tissue in an over-compressed periodontal ligament (PDL).<sup>(2)</sup> Resorption appears to proceed by the intricate coordination of the processes of attachment to bone, polarized secretion of acid and proteases, and active motility of osteoclasts along the bone substrate.<sup>(3)</sup> Cells active in resorption are tightly apposed to the bone surface and form specialized structures at this interface consisting of a highly convoluted membrane called the "ruffled border," surrounded by an actin-rich region, called the "clear zone".<sup>(4)</sup> The molecular mechanisms by which osteoclasts attach to bone are not well understood. By analogy to other cells, members of the integrin superfamily of divalent cation-dependent adhesion molecules may mediate this interaction. Integrins are heterodimeric glycoproteins of a and b subunits that participate in both cell-substrate and cell-cell interactions.<sup>(5)</sup> The superfamily is subdivided into several families defined by the highly disulfide-linked b subunit. These are the VLA/fibronectin b1 receptors, the leukocyte Leu-CAM/ CD18 (b2) receptors, the b3

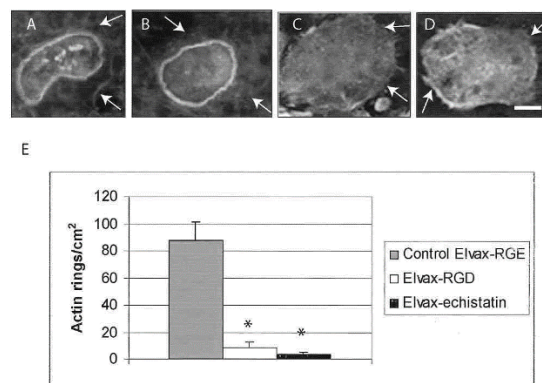
receptors, and the epithelial cell b4 receptor. The b3 family, also called cytohesin, include the platelet GP IIb IIIa complex that is essential for platelet aggregation and a vitronectin receptor (avb3). Antibodies recognizing this integrin inhibit bone resorption, and so it may function to anchor resorbing cells to bone.<sup>(6,7)</sup> The etiology of root resorption is most likely a multifactorial problem involving genetic predisposition, environmental factors related to the morphology of the roots, and orthodontic treatment-related issues.<sup>(8-10)</sup> It has been shown that orthodontic tooth movement can be influenced by general and local pharmacological modulation.<sup>(11)</sup> In this review, we will describe the effects of various agents in promoting and inhibiting orthodontically induced root resorption.

### Various Techniques

#### A. Resorption Inhibiting Agent:

- a. **Echistatin, an RGD-containing peptide:** The integrins are a family of cell surface glycoproteins that act as receptors for extracellular matrix (ECM) proteins, or for membrane-bound counter-receptors on other cells.<sup>(12)</sup> Integrins can bind adhesive ligands and upon this binding results in conformational changes.<sup>(13)</sup> Over 20 known integrins recognize the Arg-Gly-Asp (RGD) sequence in their adhesion protein ligands.<sup>(14)</sup> The effect of RGD peptides on bone formation and resorption was described in a study, in the mineralizing organ

culture system derived from growing rat parietal bones. 0.1–50  $\mu\text{M}$  GRGDSPK added to bones cultured for four days.<sup>(15)</sup> The inhibition of bone formation and resorption by an RGD-containing peptide in a mineralizing organ culture system suggests that integrins have an important role in osteoblast and osteoclast-mediated bone remodeling. A 49 amino acid protein, disintegrin(echistatin) is a snake venom protein and is one of the smallest natural adhesive ligands with integrin type receptors through Arg-Gly-Asp(RGD) sequence capable of binding to integrins and interfering with integrin function.<sup>(16)</sup> The structure of echistatin consists of a core, from this core, an irregular hairpin and the C-terminus protrude these are further stabilized by hydrogen bonds. The role of the  $\alpha\text{v}\beta\text{3}$  integrin in bone resorption during orthodontic tooth movement is unknown. However, a study examined the expression of the  $\alpha\text{v}\beta\text{3}$  integrin during experimental tooth movement. The expression of  $\alpha\text{v}\beta\text{3}$  integrin was examined with two primary antibodies: a polyclonal anti- $\alpha$  integrin subunit antibody and a polyclonal anti- $\beta\text{3}$  integrin subunit antibody. Negative controls were similarly processed but without incubation with primary antibodies. The  $\alpha\text{v}\beta\text{3}$  integrin was expressed both by osteoclasts associated with alveolar bone resorption and by odontoclasts associated with root resorption during experimental tooth movement.<sup>(17)</sup> It appears that  $\alpha\text{v}\beta\text{3}$ ,  $\alpha\text{v}\beta\text{5}$ , and  $\alpha\text{mb}\beta\text{3}$  are the integrins most reported to be involved in bone function and RGD sequence binding.<sup>(18)</sup> Another study tested echistatin RGD peptide effectiveness by local administration ethylene-vinyl acetate (ELVAX), a non-biodegradable, sustained-release polymer adjacent to maxillary molars in rats and shows the feasibility of using ELVAX to deliver integrin inhibitors adjacent to teeth to limit local tooth movement in response to orthodontic forces(**Fig. 1**).<sup>(19)</sup> Echistatin may interfere with subtle aspects of integrin-mediated signal transduction<sup>(11)</sup> important for osteoclastic activity or migration. Regardless of the mechanism, direct evidence for echistatin inhibition of bone resorption *in vivo* makes integrin ligands attractive candidates for the treatment of diseases associated with increased bone resorption.



**Fig. 1:** (A), treated with ELVAX alone (B), or with ELVAX loaded with echistatin (C) or RGD peptide (D). After 90 min, the cells were fixed with 2% formaldehyde in PBS, permeabilized with 0.5% Triton X-100 in PBS, and stained with fluorescein-tagged phalloidin

- b. **Low Laser Therapy:** Numerous studies have shown the effect of LLLT at different wavelengths.(**Fig. 2**) When LLLT(continuous wave at 830nm)was applied for different set of days such as 9days for 2.15 min total 54j/cm<sup>2</sup> or 7days mid-palatal expansion or 12 days for 3 min total 35.3 w/cm<sup>2</sup> concluded that the acceleration of tooth movement was linked to the stimulatory effect on the process of alveolar bone remodeling in LLLT group, indicated by the significant increases in the amount of bone formation, blood vessels dilatation, and periodontal cell proliferation in the tension side of the dental root as well as the increase in the number and activity of osteoclasts in the opposite pressure side.<sup>(21)</sup> LLLT(continuous wave GaAlAs at 810 nm) in stimulating alveolar bone resorption at the pressure side of the dental root during orthodontic treatment by regulating the activities of osteoclasts through the 84OPG/RANKL/ RANK system.<sup>(22,23)</sup> LLLT(continuous wave GaAlAs at 780nm and 809 nm) causes a significant acceleration of the teeth movement, and patients experience a significantly lower degree of pain level in teeth that received LLLT during the orthodontic treatment.<sup>(24,25)</sup> Two studies of LLLT (continuous wave GaAlAs at 808nm at 0.71J/cm<sup>2</sup> and 4.98 J/cm<sup>2</sup> respectively) significantly increases the remodeling and the turnover rate of the connective tissues surrounding the root during tooth movement in rats.<sup>(21,26)</sup> These results indicate that LLLT application at the range of 830 nm wavelength is an effective modality in stimulating the remodeling activity and the regenerative capability of the connective tissues around the dental root.<sup>(27)</sup> Similar results were concluded with light-emitting diode-mediated-

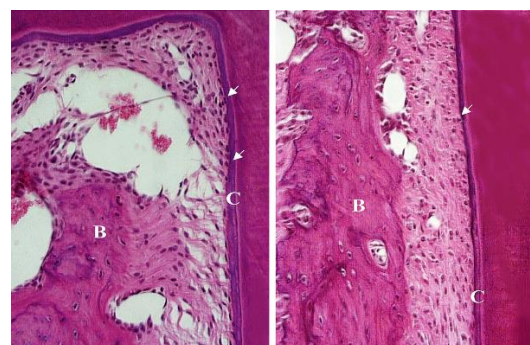
photobiomodulation therapy (LPT), on the rate of orthodontic tooth movement (TM) and orthodontically induced root resorption, in rats. Wistar rats were separated into two groups (control and LPT), and 50 CN of force was applied. The surface area of root resorption lacunae was measured histomorphometrically using digital photomicrographs. Statistical analysis showed significant differences between two groups after treatment/observation period ( $p=0.017$ ). Statistically significant inhibition of root resorption with LPT was determined ( $p<0.001$ ) on the TM side showing that LPT method has the potential of accelerating orthodontic tooth movement and inhibitory effects on orthodontically induced resorptive activity.<sup>(28)</sup>



**Fig. 2: Intraoral application of LLLT**

- c. **Doxycycline and L-thyroxine:** A series of studies has been published describing anti-inflammatory properties of tetracyclines unrelated to their antimicrobial effect.<sup>(29-31)</sup> Among the tetracyclines, doxycycline (DC) has been shown to reduce the total number of osteoclasts and prevent root resorption and alveolar bone loss in rats.<sup>(32,33)</sup> In an experimental study, Various factors were compared between DC-treated and non-DC-treated animals. The results revealed a significant reduction in root resorption, the number of odontoclasts, osteoclasts, mononuclear cells on the root surface, and TRAP-positive cells on the root and bone for the DC-administered group.**(Fig. 3)** The absolute alveolar bone area was greater, whereas the distance between the first and second molars did not differ between groups.<sup>(34)</sup> Tetracyclines, as anti-resorptive drugs, may act similarly to bisphosphonates and primarily affect osteoclast function.<sup>(36)</sup> Another study was done to histologically evaluate and compare the effects of the systemic administration of L-thyroxine (TX) and doxycycline (DC) on orthodontically induced root resorption. Histomorphometric analysis of

root resorption expressed as a percentage, showed that the average relative root resorption affecting the maxillary molars on the TM side was less in the DC groups as compared to control.<sup>(37)</sup> However, it was demonstrated in a study that although the level of parathyroid hormone in serum plays an important role in the regulation of the resorptive activity in bone, a change in serum calcium level is a determining factor for root resorption.<sup>(38)</sup> In addition to parathyroid hormone, bone resorptive activity is also regulated by L-thyroxine.<sup>(39,40)</sup> Thyroid hormone plays a crucial role in normal growth and development of vertebrate bones.<sup>(41)</sup> The administration of high doses of TX has been shown to increase bone resorption.<sup>(42)</sup> Another study<sup>(43)</sup> reported that thyroid hormones increase osteoclastic bone resorption by stimulation of prostaglandin, especially prostacyclin synthesis. The effects of TX on root resorption are still controversial.



**Fig. 3: (a) Untreated control specimen. Arrows indicate the area of cementum resorption by mononuclear cells (bar = 100  $\mu$ m). (b) Doxy-control specimen. The cementum surface appears intact with only a few mononuclear resorbing cells (arrow) (bar = 100  $\mu$ m). B, inter-radicular bone; C, cementum**

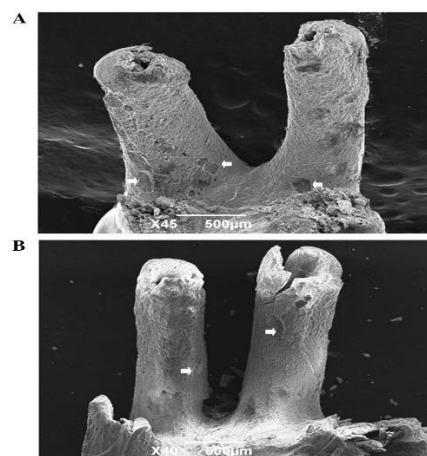
- d. **Odanacatib:** Odanacatib (Pinn; codenamed MK-0822) is an investigational treatment for osteoporosis and bone metastasis.<sup>(44)</sup> It is an inhibitor of cathepsin K<sup>(45)</sup> an enzyme involved in bone resorption. A study was done to investigate the effect of local administration of odanacatib (ODN) on orthodontic root resorption and the status of alveolar bone metabolism in rat molars. The total volume of the root resorption craters of the 60 g-NS (normal saline) group was higher than in the 60 g-ODN group and the control group. The results of tartrate-resistant acid phosphatase-positive (TRAP+) numbers showed that there was no difference between the 60 g-NS group and the 60 g-ODN group. The expression of cathepsin K was decreased significantly in the 60 g-ODN group. These

results indicate that ODN reduces orthodontics-induced external root resorption and increases alveolar bone metabolism. This may be because ODN inhibits the activity of odontoclasts, but maintains the quantity of odontoclasts and enhances bone formation. ODN promotes local alveolar bone metabolism but does not affect systemic bone metabolism.<sup>(46)</sup>

- e. **Histamine receptor blocker:** Although histamine was shown to be involved in bone remodeling, a study was done to determine the effects of cetirizine, an H(1) receptor antagonist, on bone modeling processes during orthodontic tooth movement. Results showed Cetirizine decreased the amount of tooth movement from day 28 onward ( $P < 0.01$ ), and it also decreased osteoclast volume density ( $P < 0.001$ ). An increase in alveolar bone volume density was observed in the cetirizine group ( $P < 0.01$ ) compared with the appliance-only group. Concluded Cetirizine influences bone modeling, mainly by inhibiting bone resorption. Therefore, H(1) receptor antagonists could interfere with orthodontic treatment.<sup>(47)</sup> Another study made a comparison between three possible osteoporotic treatments in the prevention of glucocorticoid-induced alveolar bone loss. Result present Histopathologically the glucocorticoid group showed wide medullary cavities with wide osteocytic lacunae. The DEXA revealed a significant reduction in the bone mineral density in all experimental groups compared to the control group. Concluded, the administration of H1 or H2 receptor antagonists separately could minimize the alveolar bone loss caused by the administration of glucocorticoids while concomitant administration of both H1 and H2 receptor antagonists deteriorated the bone condition.<sup>(48)</sup>

- f. **Lithium Chloride:** Studies have demonstrated the ability of Lithium Chloride(LiCl) to enhance bone formation via the canonical Wnt/ $\beta$ -catenin signaling pathway. LiCl has been used for decades for the treatment of bipolar disorder by increasing  $\beta$ -catenin signaling through the inhibition of GSK-3 $\beta$ .<sup>(49,50)</sup> The canonical Wnt/ $\beta$ -catenin pathway increases bone mass in several ways, including the renewal of stem cells, stimulation of preosteoblast replication, induction of osteogenesis and inhibition of osteoblast and osteocyte apoptosis.<sup>(51)</sup> Since orthodontic tooth movement involves the repeated process of alveolar bone remodeling,<sup>(52,53)</sup> LiCl has the potential to affect tooth movement during orthodontic treatment by affecting the process of bone formation. Osteoclasts are involved in resorbing the alveolar bone at pressure areas, which appear in the

direction of the applied force, while osteoblasts are involved in new bone formation at tension areas, on the opposite side.<sup>(52,54)</sup> Studies have shown high levels of  $\beta$ -catenin in osteoblasts form excessive bone substances with limited osteoclasts.<sup>(55,56)</sup> In a study, lithium chloride (LiCl), a Wnt signaling activator, was examined to determine its effect on root resorption, rats were randomly allocated into the experimental group (EG) and control group (CG). A 50g force was applied. The outcomes were analyzed using ANOVA. The average distance measured in the CG was slightly higher than in the EG. Root resorption craters were observed in the groups following the experiment. The mean root resorption area ratio of CG was significantly greater than EG ( $P < 0.05$ ). Results of the present study indicate that LiCl can attenuate orthodontically induce root resorption during orthodontic tooth movement. (Fig. 4) The effect of LiCl on tooth movement is insignificant.<sup>(57)</sup>



**Fig. 4: Scanning electron microscope images of tooth surface in the (A) control and (B) experimental groups. The resorption area is indicated by a white arrow**

- g. **Bisphosphonates:** Bisphosphonates(BSP) bind strongly to the bone mineral hydroxyapatite<sup>(58)</sup> and inhibit bone resorption. They target calcified tissues, in which they are internalized selectively by bone-resorbing osteoclasts.<sup>(59,60)</sup> Once internalized, BSP inhibits the ability of osteoclasts to resorb bone by mechanisms that interfere with cytoskeletal organization and formation of the ruffled border, and this leads to cell death by apoptosis.<sup>(61,62)</sup> A study was conducted to investigate the effect of BSP on orthodontic tooth movement and root resorption in mice. A force of 10 g was delivered BSP (2 microg/20 micro L) was injected daily into a local site adjacent to the upper molar. After 12

days, the results suggested that BSPs might have an inhibiting effect on root resorption during orthodontic tooth movement in humans and that they may interrupt tooth movement in orthodontic patients undergoing treatment, thus altering the outcome of treatment.<sup>(63)</sup> Another study was done to examine the effect of the local administration of clodronate on orthodontic tooth movement. The number of osteoclasts on the clodronate-injected side was significantly less ( $P < 0.01$ ) than on the control side. The results suggested that localized use of clodronate could be a useful therapeutic adjunct in orthodontic treatment.<sup>(64)</sup> One more study was done to examine the effect of topical administration of a BSP (risedronate). The topical administration of risedronate caused a significant and dose-dependent reduction of tooth movement after the orthodontic force was applied. In the second experiment, the spring was then removed, and administration of risedronate was begun. The topical administration of risedronate inhibited relapse of the tooth in a dose-dependent manner. The results suggested that topical application of risedronate may be helpful in anchoring and retaining teeth under orthodontic treatment.<sup>(65)</sup> To investigate the effects of systemically administered alendronate, one of the most potent BSPs, on alveolar bone resorption and angiogenesis in rats was subjected to experimental periapical lesions over two time periods with pulp chambers opened. The experimental group received daily subcutaneous injections of alendronate at a dose of 0.25 mg kg<sup>-1</sup>, whereas the control group received only the saline vehicle. After 2 or 4 weeks, the result showed Overall, periapical bone loss area and the number of TRAP-positive cells (osteoclasts) were significantly decreased at 2 and four weeks, respectively, after daily subcutaneous injection of alendronate compared with the control group ( $P < 0.05$ ). Concluded administration of alendronate to rats might inhibit alveolar bone resorption associated with periapical disease, which might not lead to impairment of angiogenesis.<sup>(66)</sup>

#### B. Resorption Promoting Agent:

- a. **Cyclosporine:** The effect of CsA on the human bone is still not clearly defined. Some studies in transplant patients suggested that CsA causes bone loss; however, it is difficult to be certain because these patients are usually treated with a combination of drugs, other than CsA, including glucocorticoids, which also could stimulate bone resorption.<sup>(67)</sup> On the other hand, the ability of CsA to inhibit the production of inflammatory cytokines associated with the T-cells activation could provide a direct protective effect against

bone resorption. This protective effect was demonstrated in vivo, as CsA prevented bone loss that usually occurs in association with arthritis in rats. Moreover, CsA can directly inhibit in-Vitro bone resorption induced by the application of active mediators such as interleukin-1 (IL-1), prostaglandin E2 (PGE2), 1,25-dihydroxy-vitamin D3, and parathyroid hormone.<sup>(68)</sup> The variation in the effect of CsA in the bone density could be related to the drug dose level. A study found that only a high oral dose of CsA, around 30 mg/kg, would decrease the bone volume in both growing and adult rats.<sup>(69)</sup> Moreover, gender-related differences in the effect of CsA on the bone tissues were also suggested. It has been reported that CsA stimulates bone formation in female rats while it increases bone resorption in male rats, even though, neither sex hormones nor gonadectomy was found to modulate the CsA effect on osseous tissues.<sup>(70)</sup> Therefore, it could be postulated that the decrease in male rats' mandibular bone mass following CsA therapy, as reported in the literature,<sup>(71)</sup> is related to the 46 animal gender. Accordingly, the effect of CsA on the alveolar bone is controversial. CsA therapy could have a suppression effect on alveolar bone mass, specifically on osteoid formation around the molar regions.<sup>(72)</sup> However, others found that use of immunosuppressive levels of CsA has no effect on alveolar bone homeostasis in rats' healthy periodontium tissues.<sup>(73)</sup> A study was done where two groups, were fed with 8 mg/kg CsA (experiment) or mineral oil (control) daily. Results showed significantly larger changes in intermolar distances after orthodontic force application in the CsA group at days 3 and 12 when compared with the control group. The inter-radicular dental alveolus of CSA-fed rats was osteopenic. Significantly increased TRAP-5b serum level was noted in the CsA group when compared with the control group. Suggested that CsA enhanced the rate of orthodontic tooth movement. The osteopenia and the increased osteoclastic activity could be the underlying factors.<sup>(74)</sup>

- C. **Glucocorticosteroids:** Corticosteroids are commonly used to treat many different diseases because of their anti-inflammatory effect.<sup>(75)</sup> A study was done to investigate the effect of different courses of glucocorticosteroid treatment on orthodontically induced root resorption. Rats were divided into three groups: control, acute and chronic. Acute and chronic groups received corticosteroid treatment (5 mg/kg/day of methylprednisolone) for 3 and seven weeks, respectively, while no pharmacological treatment was performed in the control group. A



histopathological based assessment method for the percentage of root resorption was performed. The results revealed that the percentage of root resorption is increased significantly in steroid-treated groups compared to control group, therefore; steroid administration will influence the occurrence of root resorption(Fig. 5).<sup>(76)</sup>



**Fig. 5: Microphotograph view for cross section to 1st molar rat tooth in the acute group (appliance side) showing highly obvious root resorption in the Mesial root (MR) at Compression site (C) compared to Tension site (T), H & E  $\times 100$**

### Discussion

Root resorption is a common feature during orthodontic tooth movement. Osteoclasts and odontoclasts are implicated in the root resorption process.<sup>(77)</sup> A variety of drugs that have been reported to limit the inflammation process induced by orthodontic biomechanics tend to suppress root resorption, thus interfering with tooth movement. In many experimental TM studies, non-standardized or unclearly explained springs or elastics had been used for application of force. According to Ren Y et al.<sup>(78)</sup> standardized closed coil springs were preferred to produce a constant and continuous force over the experimental period. In previous research, testing materials or pharmacological agents have been administered systemically through the drinking water of the experimental animals.<sup>(79)</sup> The implantation of mini-osmotic pumps offers a controlled way of continuous drug administration.<sup>(80)</sup> Therefore, pump implantation should, optimally, precede orthodontic appliance insertion by at least one day to establish a steady DC and TX serum level by the time of force application. The measurement of root resorption craters was adopted from Talic N f et al.<sup>(81)</sup> who used percentages instead of total resorption area in square micrometers. Thus, the percentage of resorption areas to root was considered to be appropriate for assessment of root resorption instead of total resorption area. According to Yu Wang et al. LiCl attenuates orthodontically induced root resorption during orthodontic tooth movement. The topical application of bisphosphonates, which are potent bone resorption inhibitors has been reported to suppress orthodontic tooth movement.<sup>(82-86)</sup> Kehoe MJ

et al. suggested, LLLT group in the first experiment was attributed to the change in tissue absorption of the laser energy caused by the angle at which the laser beam struck the root surfaces. Decreased reflection of laser light and subsequently increased available energy for tissue absorption are expected when the root surface is exposed to a perpendicular laser beam.<sup>(87)</sup> Moreover, the possible diminution of laser energy absorption at deeper aspects of the root surface may also explain the different tissue responses between the root surfaces in the LLLT group, because the energy of the laser beam decreases as the laser light passes through the tissue.<sup>(88)</sup> The osteopenia and the increased osteoclastic activity could be the underlying factors. In steroid study, Acute corticosteroid ingestion reduces bone turnover. Therefore, orthodontic treatment might best be postponed until a time the patient is free of the drug.

### Conclusion

By our review we can conclude that in low laser therapy more is the energy absorption of the laser treatment by the target tissue, more is the cementum forms over the root surface before applying the orthodontic force, and ultimately, the less OITRR occurs on that surface as compared to doxycycline and bisphosphonates. Whereas, echistatin mechanism can also bring success to the orthodontic treatment by interfering with subtle aspects of integrin-mediated signal transduction important for osteoclastic activity or migration. Glucocorticoids and lithium are bone-resorbing agents resulting failure of TM. Researches and further clinical trials are still needed to be done to evaluate the most valuable and successful agent in the stream of orthodontic tooth movement.

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