Accelerated Orthodontics – Surgical, Mechanical And Pharmacological Methods

Darshan Mathew Yuhan¹, Siddarth Shetty², Supriya Nambiar³, Nidhin Philip⁴, Ashith M. V.⁵

^{1,2,3,4,5}Department of Orthodontics and Dentofacial Orthopaedics, Manipal College of Dental Sciences, Mangalore, India darshan.m.y@gmail.com

1. INTRODUCTION

Orthodontic treatment is a dental procedure which generally requires several months to years(1,2), with majority of treatment demanding around 2 years of treatment. This is of great concern as it carries the risk of (1,2)caries, external resorption(3) and decreased patient cooperation. Thus, any decrease in the treatment period by accelerating orthodontic tooth movement will be beneficial. It limits the risk of such undesirable effects and associated financial burden on the patient, in turn increasing patient contentment in the treatment(4,5). Efforts to speed-up tooth movement can be traced back to the 1890s(6). Several approaches have been advocated to accelerate orthodontic tooth movement. They can be broadly classified into surgical and non-surgical(7). The non-surgical approaches are more acceptable as to its non-invasive and less traumatic nature. This can further be looked at as device assisted method and pharmacological methods.

Biology of tooth movement

In orthodontic tooth movement a force is applied onto a tooth. Through the tooth it is transferred on to the periodontal ligament (PDL). This force creates compression of periodontal tissue on one side and compression on the other. There is altered perfusion in the PLD. As mechanical stress is induced, the cells in the PDL respond by inducing resorption and formation of the bone matrix by signaling for the osteoblast and osteoclast cells(8). An increase in the concentration of osteoclast is seen in the compressed side leading to more resorption on of the alveolar bone. (9,10). Osteoclastogenesis is regulated by cytokines of which the most important ones are the RANKL (receptor activator of nuclear factor kappa B ligand) and M-CSF (macrophage colony-stimulating factor(11). On the surface of the cells we can find the RANKL, which is a membrane bound protein, and it supports osteoclastogenesis. Cells belonging to the osteoclast lineage hold the RANK receptor (for RANKL)(12). Both RANK-L and osteoprotegerin (OPG) bind at the same RANK receptor. OPG can bind to the receptor and prevent the expression of RANK-L and a balance between the action of RANKL and OPG serve as a method of regulation of bone resorption(13).

2. SURGICAL APPROACH

A significant increase in bone turnover is seen after bone fracture and osteotomy. This is due to the induced regional accelerated phenomenon(14). As the bone turnover rate increases, it inadvertently increases the rate of alveolar bone remodeling. There is a reduction of density of bone, which, in turn will reduce the resistance to orthodontic tooth movement(15). This is the logic behind the surgical approach and is most commonly used in adult patients, in cases where the treatment is time bound.

The various surgical approach include

- 1. Interseptal alveolar surgery (distraction osteogenesis)
- 2. Osteotomy
- 3. Corticotomy
- 4. Piezocision
- 5. Micro osteoperforation

Inter septal alveolar surgery

Distraction osteogenesis was originally used for limb lengthening and for surgical treatment of craniofacial skeletal dysplasia.(16) The resultant increase in bone turnover rate in these surgical sites prompted its use in accelerating orthodontic tooth movement.

(17)In the rapid canine distraction technique, at the time of extraction of premolar, the bone distal to the canine is undermined surgically to a thickness of 1 to 1.5mm. The extraction socket is also deepened to the length of the canine using a round bur.

Corticotomy

In this surgical technique, the cortical bone is cut and the medullary bone is left undisturbed(18). The reasoning behind this is to reduce the resistance of the hard cortical bone, thus accelerating tooth movement. (19)It was first introduced in orthodontics by *Kole*

Decortication

The intention of doing decortication is not to create movable bone segment but to induce the RAP response. To achieve this we generally use a No.1 or No.2 round bur with a high-speed handpiece or dental implant drill. The decortications are made on the alveolar bone. A piezoelectric knife may also be used in its place. In the inter-radicular space, midway between the root prominences, a vertical groove is placed. This groove extends from a point 2 to 3 mm below the crest of the bone to a point 2 mm beyond the apices of the roots. These vertical corticotomies are then connected with a circular-shaped corticotomy. It is important not to extent the cortical cuts to areas with neurovascular structure.

Particulate Grafting

Corticotomies are usually followed by grafting. The direction and amount of tooth movement expected, the thickness of the alveolar bone prior to corticotomy, and the requirement for labial support by the alveolar bone determine the volume of the graft material to be used. Bovine bone, autogenous bone, decalcified freeze-dried bone allograft are the most commonly used graft material.

Closure Techniques

Excessive tension should be avoided when doing the primary closure of the gingival flaps. The sutures are maintained in place for 1 to 2 weeks.

Corticision technique

The corticision technique was put forward by *Park et al in 2006*(20), and *Kim et al in 2009*(21), as a minimally invasive alternative option to surgically injure the bone without flap elevation. They used a reinforced scalpel and mallet to go through the gingiva and cortical bone. (21)Corticision procedure was able to achieve bone resorption of the bundle bone with minimal hyalinization and faster removal of hyalinizes tissue, thanks to the cell mediated response stimulated via RAP phenomenon.

Piezocision

In the year 2007, *Vercelotti and Podesta*(22), introduced a technique for accelerated orthodontics which utilised piezo-surgery. Here a full periosteal flap was raised which led to a good amount of post-surgery discomfort. This compromised the acceptance of this technique. *Dibart et al* in 2009 came-up with the technique piezocision(23). His aim was to develop a technique that would achieve faster orthodontic tooth movement at the same time would not have the side-effects of extensively invasive surgical procedures.

Micro-Osteo Perforation

Micro-osteoperforation is the least invasive of all the surgical alternatives in accelerated orthodontics. It was first advices by *Teixeira et al*(15). This method utilises the natural inflammatory response of the body. Controlled micro-trauma in the form of micro-osteoperforation are applied in the desired area. These micro trauma can help preserve the integrity and architecture of the adjacent tissue. It will exaggerate the normal body reaction to orthodontic force(24).

Previous studies have clearly stated the heightened activity of chemokines and cytokines in response to orthodontic tooth movement(25–27). Chemokines increase osteoclast cells. Cytokines increase osteoclast cell through the prostaglandin E2 pathway and the RANK/RANKL pathway(28–30).

(24)In micro-osteoperforations there is less chance of root resorption because of two reasons

- 1. Osteoclast are more on the endosteal surface and not on the periodontal ligament tissue
- 2. The cell free zone is smaller since the density of bone is less. Smaller cell-free zone is resorbed faster

3.

3. PHYSICAL/MECHANICAL METHODS

All surgical methods are invasive in one way or the other and so have their related complications and side effects. Therefor device assisted approach, which is far less invasive has come into use to accelerate orthodontic tooth movement.

The technique available are

- 1. Direct electric currents
- 2. Pulsed electromagnetic field
- 3. Static magnetic field
- 4. Resonance vibration
- 5. Low level laser

Of all the above techniques, the low level laser technique has given the best results.

The above mentioned techniques are all based on the bone bending theory. Application of orthodontic force develops bone bending and a bioelectric potential. The concave side is negatively charged and the convex side will be positively charged attracting osteoblast and osteoclast respectively. This has been explained by Zengo(31) in his study conducted on dogs. It was found that application of discontinuous forces cause the bioelectrical potential to be created and so the idea of using cyclic forces and vibrations were considered.

Photo-stimulation: LED and low level laser

When light is emitted onto living tissue, it can get absorbed, reflected, scattered or transmitted to the tissue as energy(32). The effects can be photochemical, photo thermal or photoionizing. The nature and amount of interaction can depend on the wavelength and intensity of light. Photobiostimulation is the nonthermal effect on tissue when light is applied onto living tissue. In medicine, photobiostimulation has found its application in accelerating would healing, control inflammation, reduce pain and improve blood circulation(32).

Photo-bio-stimulation may be used therapeutically through lasers and light emitting diodes. Both uses near infrared wavelength of around 600 to 1000 nm. The ideal and recommended range is 730 to 850 nm which being relatively narrow allows more response from the tissue(33–36).

Photobiostimulation at the cellular and molecular level

Photostimulation has the ability to increase cellular metabolism. At the wavelength between 600 to 950nm, it stimulates the production of mitochondrial cytochrome c oxidase which in turn increases cell metabolism(34,37).

According to "single-oxygen hypotheses" molecules like porphyrins and flavoproteins can become activated and react with oxygen to give electronically excited oxygen molecules thus increasing to metabolism(37).

Another hypothesis explaining photostimulation is the "redox properties alteration hypothesis". Here the cell redox potential is altered for greater oxidation. This allows cells with lower resting intracellular state to have a better metabolic state(37).

Photobiostimulation is thought to have a direct positive effect on RNA and DNA synthesis and replication, protein synthesis and cell metabolism by increases in Na^+/K^+ pump activity and intracellular Ca^{2+} .(38).

Low level laser therapy(LLLT)

The biostimulatory effect of laser on bone tissue is being utilized in accelerating tooth movement. Application of laser onto the tissue stimulates the proliferation of osteoclast osteoblast and fibroblast, which in turn increases bone remodeling paving the way for accelerated movement of tooth. Tooth movement is accelerated by the production of ATP and activation of cytochrome-C.In 2004, *Cruz et al*(39) was the first to carry out a human study on the effect of low-intensity laser therapy on orthodontic tooth movement. They showed that

the irradiated canines were retracted at a rate 34% greater than the control canines over 60 days.

Orthodontic tooth movement is considered to increase by 30-60% and is supported by various studies. The variations amongst the studies seems to arise from variations in frequency of application of laser, intensity of laser, and method of force application on the tooth.

Vibration aided orthodontic tooth movement

According to the piezoelectricity theory of alveolar bone remodeling, osteogenic changes are induced by the electrical charges generated through the applied orthodontic force. Piezoelectric charges are generated when stress is applied and released(40). For this reason *Shapiro et al*(41) advices that orthodontic force aid in tooth movement should not be continuous. The intermittent force applied by the vibrational force help tooth movement in two ways. One by inducing piezoelectric charges with in the bone inducing bone remodeling. Secondly, by decreasing the frictional resistance to sliding between brackets and archwires(42,43). Pain preserved by the patient during the treatment is also seen to be less in patients when treated with vibrational devices(44–46).

(47)There are mainly two devices available in the market that utilizes this technology:- Acceledent and Tooth Masseuse. Tooth masseuse is no longer available in the market. Acceledent is manufactured by OrthoAccel Technologies(47).

Low Intensity Pulsed Ultra Sound(LIPUS)

Low Intensity Pulsed Ultra Sound abbreviated as LIPUS is a form of mechanical energy passed through the living tissue creating biochemical changes at the cellular and molecular level. It is transmitted as acoustic wave pressure(48). One of the outcomes of the biochemical changes is the soft tissue and hard tissue healing rate(49,50).

The bio-stimulatory effect of LIPUS is due to the mechanical stress and microstream signal given onto the tissue. These signals result in signal transduction and subsequent gene transcription through direct stimulation of the cell membrane, cytoskeleton and adhesion molecules(51).

Upon LIPUS stimulation, the tissue changes help in the faster orthodontic tooth movement(52).LIPUS also helps in prevention of root resorption. LIPUS is considered to inhibit the resorption of root or to induce periodontal regeneration after root resorption has occurred. *el-Bialy et al* suggested that anti-root resorptive action of LIPUS is due to the induced deposition of cementum and dentin which acts as a preventive layer against root resorption(53).

LIPUS is a safe non invasive technique to accelerate orthodontic tooth movement. Further studies are required to further explore the full potential of this technique.

Electric current and electromagnetic field

Ze'ev Davidovitch in 1980, published a study where he looked into the effect of D.C. electric current on the periodontal tissue, the difference it creates in the tissue turnover and on how it will effect the rate of orthodontic tooth movement(54). Application of electric current onto the alveolar bone supporting the tooth has a direct effect on the rate of tooth

movement. Both, an electric current and orthodontic force is applied onto the tooth to be moved orthodontically(55). This technique has the potential to increase the rate of tooth movement by one third and thus reduce the treatment duration. It can accelerate orthodontic tooth movement by 2.42mm/month. In case of canines, the current should be applied 5 hours a day.

In the study by *Kim et al*, there was a 30% increase in the amount of tooth movement in the experimental side when compared to the control side. The difference was statistically significant. In the four week period of the experiment, the first two weeks showed the maximum amount of difference in tooth movement when comparing the experimental and control side. The study concluded that, when exogenous current had the potential to significantly increase in rate of tooth movement. A one third increase in rate of movement was noted.

4. PHARMACEUTICAL METHODS

Drugs and nutrients ingested by the patient can interact and alter the normal response of tissue supporting teeth and involved in orthodontic tooth movement. The change can be inhibitory, additive or synergistic. Inflammatory mediators, neurotransmitters, growth factors and other cytokines are all involved in orthodontic tooth movement. Their synthesis and release can get affected by drugs consumed by the patient(56).

Prostaglandins and analogs

In orthodontic tooth movement, at the site of compression prostaglandins and leukotrienes are released from the paradental cells. On realising the effect of prostaglandins on tooth movement, researchers have considered the possibility of accelerated tooth movement by local injection of prostaglandins. *Yamasaki et al*(57,58) conducted a study where he observed a rise in number of osteoclast cells after local injection of PGE1. PGE2 stimulated differentiation of osteoblastic cells, thus leading to bone deposition coupled with bone resorption in an invitro environment.(59). Studies on the relation of rate of tooth movement to prostacyclin and thromboxane A2 showed an increase in the concentration of bone resorptive cells and improvement in the resorption of alveolar bone.(60).

Hyperalgesia and associated discomfort and uncooperative nature from the patient is seen with local injection of prostaglandins.(61) as a solution to this, research is being done to use this technique along with local anesthetics to minimize the pain(62).

Relaxin

Relaxin was discovered in 1926 as a naturally occurring hormone in the body(63). Relaxin belongs to the insulin/relaxin family of structurally related hormones. (64). An increase in relaxin levels is seen in pregnancy. The role of relaxin in physiologic processes like collagen turnover, angiogenesis, and antifibrosis in both males and females is well documented. These effects of relaxin point out that it can create alterations of the periodontal ligament (PDL) which in turn can directly affect orthodontic tooth movement(65).

On application of orthodontic tooth movement, both the soft and hard tissue responds to it, of which soft tissue is the first to respond. The tooth is not in direct contact with the soft tissue, but through the periodontal ligament. Because of relaxin's ability to remodel soft tissues, its use in orthodontic tooth movement is being studied. With tooth movement, the gingival response is to increase collagen formation to resist movement. The gingival "memory" also plays a role in relapse after treatment.(66)

Vitamin D3

Once orthodontic tooth moving force is applied, bone remodeling occurs, which includes a bone resorptive and formative phases occurring within the alveolar bone.(67). A clear correlation has been shown to exist between vitamin D receptor polymorphisms and periodontitis and bone metabolism(68).

Collins and Sinclair(69) did a study exploring the use of vitamin D to increase the rate of tooth movement. They were able to show that vitamin D metabolites when applied locally through intra-ligamentary injection can lead to an increase in the number of osteoclasts in the area, which would complement the rate of bone resorption, leading to an increase in the rate of tooth movement during canine retraction. In 2004, *Kale et al*(70) studies how the administration of prostaglandin (PG) and 1,25-dihydroxy cholecalciferol (1,25 DHCC) can change the rate of orthodontic tooth movement. Both PG and 1,25 DHCC were found to have a significant positive effect on tooth movement when compared to controls. They were able to find a higher number of Howship lacunae and capillaries with both the experiment groups on their pressure side. The number of osteoblasts were also seen to have increased on the surface of alveolar bone in the experimental group where 1,25 DHCC was given when compared to the group where PG was administered. The authors conclude that 1,25 DHCC has an impact on the amount of bone deposition and resorption thus changing the rate of tooth movement.

Other investigators have also suggested other merits to the use of Vit.D. Some suggest that apart from increased rate of tooth movement, local administration of Vit.D also improves the tooth position post-treatment stability. Experiments have been conducted by Kawakami and Takano- Yamamoto(67) on rats to explore the effect of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) on alveolar bone formation. The stability of orthodontic treatment relies a lot on the supportive tissue. The study was bases on calcitriol's effect on its improvement in bone and periodontal tissue remodelling through improved local cellar activity. With local injection of 1,25-dihydroxyvitamin D3, an increase in mineral appositional rate was noted on the tension side of the orthodontically moved teeth. The authors were able to learn that there is a better reestablishment of tooth supporting tissue post orthodontic treatment with 1,25-dihydroxyvitamin injections. Relatable findings can also be seen in experiments by Boyce and Weisbrode, (71). They say that in the first two days there is a temporary rise in the rate of bone resorption which is followed by a rise in bone formation after 14 days of calcitriol administration.

Osteocalcin

Osteocalcin, or BGP (Bone Gla Protein) is a non-collagenous protein commonly seen in the periodontium. It amounts to 3% of total bone protein. The protein consist of 49 amino-acids with three gammacarboxyglutamic acid residues. Gammacarboxyglutamic acid is an amino acid that binds to calcium and in the protein it form the calcium binding site. BGP is secreted in the sites of mineralisation by osteoblast cells, cementoblast cells and periodontal ligament fibroblast subpopulations.(72,73).

Presence of BGP in alveolar bone, dentin and root cement have been confirmed through immune-histochemistry studies. Its role in the biomineralization process has been partially determined. It was noted that in animal studies where warfarin, a Vit.K antagonist, was given to the animals, they showed bone hyper-mineralization(74–76).

The local application of osteocalcin accelerated the rate of tooth movement (mm/day) in the early experimental period and increased the total amount of tooth movement. On histological observation it was revealed that the acceleration of tooth movement was due to enhanced recruitment of osteoclastic cells(77).

Parathormone

Parathyroid glands secrete parathyroid hormone which serves the function of increasing calcium level in blood through stimulation of bone resorption. It is an 84 amino acid molecule, but the active segment contains only amino acids from 1 to 34(78).

If an increases PTH level is maintained over time it can lead to bone loss but an intermittent short increase in the hormone level can have an anabolic effect on bone tissue(79). Several studies and research data has shown that a daily application of PTH hormone for a short duration can lead to an improvement in skeletal tissue strength, density, and mass(80). Teriparatide is used in the treatment of osteoporosis. It contains the active segment of PTH (amino acid 1 to 34). Daily injections of teriparatide stimulate new bone formation, leading to increased bone mineral density(78).

Soma et al., 1999(81) did a in-vivo study on rats to find out the effect of infusion of PTH on the rate of orthodontic tooth movement. They reported that a continuous infusion of PTH created a 2 to 3 fold increase in the number of osteoclast cells in the region of compressed periodontium. This means that there is an increased resorptive activity in the side with compression which is in favour of accelerating the orthodontic tooth movement. No significant increase in bone loss was noted in the other areas of the periodontal tissue. With intermittent injection of PTH at the same dose, no significant increase in the rate of tooth movement was noted. Based on these findings, it can be concluded that, with a continuous administration of PTH an acceleration of tooth movement can be achieved. The study by Takano Yamamoto and Rodan, 1990(82) showed that direct injection of PTH into the bone marrow of long bones can induce an increase in the number of osteoclast. This suggest a positive effect of PTH on the bone resorptive activity in the injected area. Based on the above research data it can be inferred that a local and continuous long-term administration of PTH into the periodontal tissue can have a desirable effect leading to an increased rate of orthodontic tooth movement especially when the concentration of PTH in the area is kept at an increased level.

GENE THERAPY

In the study by *Kanzaki et al*(83), it was hypothesized that if RANKL gene was transferred into the periodontal tissue it may accelerate orthodontic tooth movement. Kanzaki et al did the study on 6-week-old male Wistar rats, where the upper first molars were moved palatally using orthodontic force. Periodic injection of hemagglutinating-virus of Japan(HVJ) envelope vector containing RANKL expression plasmid was given into the periodontal tissue on the palatal aspect of maxillary molar. It was noted that local injection of RANKL gene significantly improved its expression and osteoclastogenesis with any significant systemic effect. An improvement was noted with the rate of tooth movement on the side with RANKL gene transfer. The study concluded that activation of osteoclastogenesis and an increased rate of tooth movement was seen after the transfer of RANKL gene to the periodontal tissue. It is also suggested that local RANKL gene transfer can also be used in the treatment of ankylosed teeth.

5. CONCLUSION

One of the main drawbacks of orthodontic treatment is its long duration. From the patient's point of view, it makes the treatment looks tedious and time consuming. Accelerated orthodontics address this issue. Attempts to fasten the progress of orthodontic treatment can be dated back to 1890s. These attempts have definitely taken the field of orthodontics to newer heights. It started with surgeries that were highly invasive which moved onto minimally invasive techniques like micro-osteoperforations, to treatment modalities that are negligibly invasive or completely non-invasive. All these developments provide us with a wide array of techniques that can cater the different demands that are being put forward by treatment needs of patients.

Further possibilities are still being explored by enthusiasts from within and outside the orthodontic fraternity. These efforts will help us get better and faster results expanding the reach and possibilities of orthodontic treatment.

6. REFERENCES

- Fisher MA, Wenger RM, Hans MG. Pretreatment characteristics associated with orthodontic treatment duration. Am J Orthod Dentofac Orthop [Internet]. 2010;137(2):178–86. Available from: http://dx.doi.org/10.1016/j.ajodo.2008.09.028
- [2] Fink DF, Smith RJ. The duration of orthodontic treatment. Am J Orthod Dentofac Orthop. 1992;102(1):45–51.
- [3] Pandis N, Nasika M, Polychronopoulou A, Eliades T. External apical root resorption in patients treated with conventional and self-ligating brackets. Am J Orthod Dentofac Orthop. 2008;134(5):646–51.
- [4] Riedmann T, Georg T, Berg R. Adult patients' view of orthodontic treatment outcome compared to professional assessments. J Orofac Orthop. 1999;60(5):308–20.
- [5] Segal GR, Schiffman PH, Tuncay OC. Meta analysis of the treatment-related factors of external apical root resorption. Orthod Craniofacial Res. 2004;7(2):71–8.

- [6] Fitzpatrick BN. Corticotomy. 1980;25(5):2–5.
- [7] El-Angbawi A, Mcintyre GT, Bearn DR, Fleming PS. Non-surgical adjunctive interventions for accelerating tooth movement in patients undergoing fixed orthodontic treatment. Cochrane Database Syst Rev. 2013;2013(12).
- [8] Lekic P. Periodontal Ligament Cell Populations: The Central Role of Fibroblasts in Creating a Unique Tissue. 1996;341:327–41.
- [9] Davidovitch Z, Nicolay OF, Ngan PW SJ. Neurotransmitters, cytokines, and the control of alveolar bone remodeling in orthodontics. Dent Clin North Am. 32: 411–43.
- [10] Storey E. The nature of tooth movement. Am J Orthod. 1973;63(3):292–314.
- [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(5):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. 1999;25(1):109–13.
- [13] 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. 2000;15(1):2–12.
- [14] Wilcko W, Wilcko M, ... JB-... of P and, 2001 U. The nature of orthodontic tooth.
 PdfsSemanticscholarOrg [Internet]. 2001;21(1):1–11. Available from: https://pdfs.semanticscholar.org/cfa0/62aa82b5ec4fa52a264660ce28ce5f09bba0.pdf
- [15] Teixeira CC, Khoo E, Tran J, Chartres I, Liu Y, Thant LM, et al. Cytokine expression and accelerated tooth movement. J Dent Res. 2010;89(10):1135–41.
- [16] GA I. The possibilities offered by our method for lengthening various segments in upper and lower limbs. Basic Life Sci. 1988;48:323–4.
- [17] Liou EJ, Huang CS. Rapid canine retraction through distraction of the periodontal ligament. Am J Orthod Dentofacial Orthop. 1998;114(4):372–82.
- [18] Murphy KG, Wilcko MT, Wilcko WM FD. Periodontal Accelerated Osteogenic Orthodontics: A description of the Surgical Technique. J Oral Maxillofac Surg. 2009;67:2160 21.
- [19] Köle H. Surgical operations on the alveolar ridge to correct occlusal abnormalities. Oral Surgery, Oral Med Oral Pathol. 1959;12(5):515–29.
- [20] YG Park, SG Kang, SJ Kim, YG PARK SK. Accelerated tooth movement by corticision as an osseous orthodontic paradigm. Kinki Tokai Kyosei Shika Gakkai Gakujyutsu Taikai, Sokai. 2006;
- [21] Kim SJ, Park YG, Kang SG. Effects of corticision on paradental remodeling in orthodontic tooth movement. Angle Orthod. 2008;79(2):284–91.
- [22] Vercellotti T, Podesta A. Orthodontic microsurgery: a new surgically guided technique for dental movement. Int J Periodontics Restorative Dent [Internet]. 2007;27(4):325–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17726988
- [23] Serge Dibart, DMD;1 Jean David Sebaoun, DDS, MS;2 and Jerome Surmenian, DDS M. Piezocision: A Minimally Invasive, Periodontally Accelerated Orthodontic Tooth Movement Procedure. Compendium. Volume 30,.

- [24] Alikhani M, Alansari S, Sangsuwon C, Alikhani M, Chou MY, Alyami B, et al. Micro-osteoperforations: Minimally invasive accelerated tooth movement. Semin Orthod [Internet]. 2015;21(3):162–9. Available from: http://dx.doi.org/10.1053/j.sodo.2015.06.002
- [25] Taddei SRDA, Andrade I, Queiroz-Junior CM, Garlet TP, Garlet GP, Cunha FDQ, et al. Role of CCR2 in orthodontic tooth movement. Am J Orthod Dentofac Orthop. 2012;141(2):153-160.e1.
- [26] Garlet GP, Garlet TP, Teixeira AL. CCR5 Down-regulates Osteoclast Movement. 2015;1–5.
- [27] Bletsa A, Berggreen E, Interleukin- BP. Interleukin-1 a and tumor necrosis factor- a expression during the early phases of orthodontic tooth movement in rats. 2006;(3):423–9.
- [28] Fuller K, Kirstein B, Chambers TJ. Murine Osteoclast Formation and Function: Differential Regulation by Humoral Agents. 2015;147(October):1979–85.
- [29] Brien CAO, Gubrij I, Lin S, Saylors RL, Manolagas SC. STAT3 Activation in Stromal / Osteoblastic Cells Is Required for Induction of the Receptor Activator of NF- Ligand and Stimulation of Osteoclastogenesis by gp130-utilizing Cytokines or Interleukin-1 but Not 1, 25-Dihydroxyvitamin D 3 or Parathyroid H. 1999;274(27):19301–8.
- [30] Suzawa T, Miyaura C, Inada M, Maruyama T, Te D, Ta S. The Role of Prostaglandin E Receptor Subtypes (EP1, EP2, EP3, and EP4) in Bone Resorption: An Analysis Using Specific Agonists for the Respective EPs. 2015;141(4):1554–9.
- [31] Zengo AN, Bassett CAL, Pawluk RJ, Prountzos G. In vivo bioelectric potentials in the dentoalveolar complex. Am J Orthod. 1974;66(2):130–9.
- [32] Cernavin I, Pugatschew A, de Boer N, Tyas MJ. Laser applications in dentistry: A review of the literature. Aust Dent J. 1994;39(1):28–32.
- [33] Karu TI, Pyatibrat L V., Afanasyeva NI. Cellular effects of low power laser therapy can be mediated by nitric oxide. Lasers Surg Med. 2005;36(4):307–14.
- [34] Desmet KD, Paz DA, Corry JJ, Eells JT, Wong-Riley MTT, Henry MM, et al. Clinical and experimental applications of NIR-LED photobiomodulation. Photomed Laser Surg. 2006;24(2):121–8.
- [35] Yoshida T, Yamaguchi M, Utsunomiya T, Kato M, Arai Y, Kaneda T, et al. Low-energy laser irradiation accelerates the velocity of tooth movement via stimulation of the alveolar bone remodeling. Orthod Craniofacial Res. 2009;12(4):289–98.
- [36] Carvalho-Lobato P, Garcia VJ, Kasem K, Ustrell-Torrent JM, Tall??n-Walton V, Manzanares-C??spedes MC. Tooth movement in orthodontic treatment with low-level laser therapy: A systematic review of human and animal studies. Photomed Laser Surg. 2014;32(5):302–9.
- [37] Hamblin MR, Demidova TN. Mechanisms of low level light therapy. Mech Low-Light Ther. 2006;6140:614001.
- [38] Chung S, Milligan M, Gong SG. Photobiostimulation as a modality to accelerate orthodontic tooth movement. Semin Orthod [Internet]. 2015;21(3):195–202. Available from: http://dx.doi.org/10.1053/j.sodo.2015.06.006
- [39] Cruz DR, Kohara EK, Ribeiro MS, Wetter NU. Effects of low-intensity laser therapy on

the orthodontic movement velocity of human teeth: A preliminary study. Lasers Surg Med. 2004;35(2):117–20.

- [40] Grimm FM. Bone bending, a feature of orthodontic tooth movement. Am J Orthod. 1972;62(4):384–93.
- [41] Shapiro E, Roeber FW, Klempner LS. Orthodontic movement using pulsating forceinduced piezoelectricity. Am J Orthod. 1979;76(1):59–66.
- [42] Olson JE, Liu Y, Nickel JC, Walker MP, Iwasaki LR. Archwire vibration and stick-slip behavior at the bracket-archwire interface. Am J Orthod Dentofac Orthop [Internet]. 2012;142(3):314–22. Available from: http://dx.doi.org/10.1016/j.ajodo.2012.03.032
- [43] Seo YJ, Lim BS, Park YG, Yang IH, Ahn SJ, Kim TW, et al. Effect of self-ligating bracket type and vibration on frictional force and stick-slip phenomenon in diverse tooth displacement conditions: An in vitro mechanical analysis. Eur J Orthod. 2015;37(5):474–80.
- [44] Lundeberg T, Nordemar R, Ottoson D. Pain alleviation by vibratory stimulation. Pain. 1984;20(1):25–44.
- [45] Staud R, Robinson ME, Goldman CT, Price DD. Attenuation of experimental pain by vibro-tactile stimulation in patients with chronic local or widespread musculoskeletal pain. Eur J Pain. 2011;15(8):836–42.
- [46] Ottoson D, Ekblom A, Hansson P. Vibratory stimulation for the relief of pain of dental origin. Pain. 1981;10(1):37–45.
- [47] Aljabaa A, Almoammar K, Aldrees A, Huang G. Effects of vibrational devices on orthodontic tooth movement: A systematic review. Am J Orthod Dentofac Orthop [Internet]. 2018;154(6):768–79. Available from: https://doi.org/10.1016/j.ajodo.2018.07.012
- [48] Buckley MJ, Banes AJ, Levin LG et al. Osteoblasts increase their rate of division and align in response to cyclic, mechanical tension in vitro. Bone Min.
- [49] Claes L, Willie B. The enhancement of bone regeneration by ultrasound. Prog Biophys Mol Biol. 2007;93(1–3):384–98.
- [50] Romano CL, Romano D, Logoluso N. Low-Intensity Pulsed Ultrasound for the Treatment of Bone Delayed Union or Nonunion: A Review. Ultrasound Med Biol. 2009;35(4):529–36.
- [51] Khan Y, Laurencin CT. Fracture repair with ultrasound: Clinical and cell-based evaluation. J Bone Jt Surg Ser A. 2008;90(SUPPL. 1):138–44.
- [52] Xue H, Zheng J, Cui Z, Bai X, Li G, Zhang C, et al. Low-Intensity Pulsed Ultrasound Accelerates Tooth Movement via Activation of the BMP-2 Signaling Pathway. PLoS One. 2013;8(7):1–10.
- [53] 5El-Bialy T, Lam B, Aldaghreer S, Sloan AJ. The effect of low intensity pulsed ultrasound in a 3D ex vivo orthodontic model. J Dent [Internet]. 2011;39(10):693–9. Available from: http://dx.doi.org/10.1016/j.jdent.2011.08.001
- [54] Zeev Davidovitch, D.M.D., Mathew D. Finkelson, B.S., Shulamit Steigman, D.M.D., Joseph L. Shanfeld, Ph.D., Paul C. Montgomery, Ph.D., and Edward Korostoff PD. Electric currents, bone remodeling, and orthodontic tooth movement. II. Increase in rate of tooth movement and periodontal cyclic nucleotide levels by combined force and electric current. Am J Orthod. 1980;

- [55] Kim D-H, Park Y-G, Kang S-G. The effects of electrical current from a micro-electrical device on tooth movement. Korean J Orthod. 2008;38(5):337.
- [56] Krishnan V, Davidovitch Z. Cellular, molecular, and tissue-level reactions to orthodontic force. Am J Orthod Dentofac Orthop. 2006;129(4):469.e1-469.e32.
- [57] 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(10):1635–42.
- [58] Yamasaki K, Shibata Y, Fukuhara T. The effect of prostaglandins on experimental tooth movement in monkeys (Macaca fuscata). J Dent Res. 1982;61(12):1444–6.
- [59] Gustafson T, Eckerdal O, Leever DL, Shanfeld JL, Montgomery P DZ. Prostaglandin E2 (PGE2) levels in alveolar bone of orthodontically treated cats. J Dent Res. 1977;
- [60] Gurton AU, Akin E, Sagdic D, Olmez H. Effects of PGI2 and TxA2 analogs and inhibitors in orthodontic tooth movement. Angle Orthod. 2004;74(4):526–32.
- [61] Yamaguchi M, Kasai K. Inflammation in periodontal tissues in response to mechanical forces. Arch Immunol Ther Exp (Warsz). 2005;53(5):388–98.
- [62] Krishnan V, Davidovitch Z. The effect of drugs on orthodontic tooth movement. Orthod Craniofacial Res. 2006;2006/163–1.
- [63] FL H. Experimental relaxation of the pubic ligament of the guinea pig. Proc Soc Exp Biol Med. 1926;23:661-3:661-3.
- [64] Yan Y, Cai J, Fu P, Layfield S, Ferraro T, Kumagai J, et al. Studies on soluble ectodomain proteins of relaxin (LGR7) and insulin 3 (LGR8) receptors. Ann N Y Acad Sci. 2005;1041:35–9.
- [65] Madan MS, Liu ZJ, Gu GM, King GJ. Effects of human relaxin on orthodontic tooth movement and periodontal ligaments in rats. Am J Orthod Dentofac Orthop. 2007;131(1):8.e1-8.e10.
- [66] Stewart DR, Sherick P, Kramer S, Breining P. Use of relaxin in orthodontics. Ann N Y Acad Sci. 2005;1041:379–87.
- [67] Kawakami M, Takano-Yamamoto T. Local injection of 1,25-dihydroxyvitamin D3 enhanced bone formation for tooth stabilization after experimental tooth movement in rats. J Bone Miner Metab. 2004;22(6):541–6.
- [68] Martelli FS, Martelli FS. Vitamin D : relevance in dental practice izi o In te rn a zio na li Ed izi o In te VDR polymorphisms and periodontal disease : a na. 3:15–9.
- [69] Collins MK, Sinclair PM. The local use of vitamin D to increase the rate of orthodontic tooth movement. Am J Orthod Dentofac Orthop. 1988;94(4):278–84.
- [70] Kale S, Kocadereli I, Atilla P, Aşan E. Comparison of the effects of 1,25 dihydroxycholecalciferol and prostaglandin E2 on orthodontic tooth movement. Am J Orthod Dentofac Orthop. 2004;125(5):607–14.
- [71] Boyce RW, Weisbrode SE. Histogenesis of hyperosteoidosis in 1,25(OH)2D3-treated rats fed high levels of dietary calcium. Bone. 1985;6(2):105–12.
- [72] Hauschka P V., Lian JB, Cole DE, Gundberg CM. Osteocalcin and matrix Gla protein: Vitamin K-dependent proteins in bone. Physiol Rev. 1989;69(3):990–1047.
- [73] Alcaín FJ, Burón MI. Ascorbate on cell growth and differentiation. J Bioenerg Biomembr. 1994;26(4):393–8.
- [74] Glowacki J, Rey C, Cox K, Lian J. Effects of bone matrix components on osteoclast differentiation. Connect Tissue Res. 1989;20(1–4):121–9.

- [75] Ducy P, Desbois C, Boyce B, Pinero G, Story B, Dunstan C, et al. Increased bone formation in osteocalcin-deficient mice. Nature. 1996;382(6590):448–52.
- [76] Factor OT, Runx C, Xiao G, Jiang D, Franceschi RT. GENES: STRUCTURE AND REGULATION: Fibroblast Growth Factor 2 Induction of the Osteocalcin Gene Requires MAPK Activity and Phosphorylation of the Fibroblast Growth Factor 2 Induction of the Osteocalcin Gene Requires MAPK Activity and Phosphorylation of th. 2002;
- [77] Hashimoto F, Kobayashi Y, Mataki S, Kobayashi K, Kato Y, Sakai H. Administration of osteocalcin accelerates orthodontic tooth movement induced by a closed coil spring in rats. Eur J Orthod. 2001;23(5):535–45.
- [78] Bartzela T, Türp JC, Motschall E, Maltha JC. Medication effects on the rate of orthodontic tooth movement: A systematic literature review. Am J Orthod Dentofac Orthop [Internet]. 2009;135(1):16–26. Available from: http://dx.doi.org/10.1016/j.ajodo.2008.08.016
- [79] Potts JT, Gardella TJ. Progress , Paradox , and Potential over Five Decades. 2007;208:196–208.
- [80] Rodan GA MT. Therapeutic approaches to bone diseases. Science (80-). 289:1508-1.
- [81] Soma S, Iwamoto M, Higuchi Y, Kurisu K. Effects of Continuous Infusion of PTH on Experimental Tooth Movement in Rats. 1999;14(4):546–54.
- [82] Takano-Yamamoto T, Rodan GA. A model for investigating the local action of boneacting agents In vivo: Effects of hPTH(1-34) on the secondary spongiosa in the rat. Calcif Tissue Int. 1990;47(3):158–63.
- [83] Kanzaki H, Chiba M, Arai K, Takahashi I, Haruyama N, Nishimura M, et al. Local RANKL gene transfer to the periodontal tissue accelerates orthodontic tooth movement. Gene Ther. 2006;13(8):678–85.