Review Article

A Contemporary Literature Review on Advances in Biology of Orthodontic Tooth Movement

Tamanam Vinny Pushpanjali, Tarakesh Karri, Uday Kumar Digumarthi*, Neeraja Pitta, E. S. S. Hemanth, Sravya Ganta

Department of Orthodontics and Dentofacial Orthopedics, Anil Neerukonda Institute of Dental Sciences, Visakhapatnam, Andhra Pradesh, India.

Abstract

This review of literature describes the cellular and molecular events of biology of tooth movement, including phases, various theories, effect of chemical mediators, and various factors that are influencing biology of tooth movement. The better understanding of the tooth movement mechanism will inspire the orthodontists to design and implement effective appliances that will result in maximum benefits and minimum tissue damage to the patients. This review article also emphasizes the applied aspect of different medication and hormones, during orthodontic treatment, on the signaling molecules which produce bone remodeling.

Keywords: OTM, Pressure, Tension, Cytokines, Leukotrienes, PDL's, TNF.

Introduction

The evolution of clinical orthodontics is rooted in strong foundations, based on the scientific studies and mechanical principles.[1]

The orthodontic appliance is the clinician's primary tool for initiating and sustaining the biological processes that control tooth movement. The cascade of biological events that induce the orthodontic tooth movement (OTM) is initiated by mechanical stresses in the periodontium. Forces are transferred to the teeth by the orthodontist using appliances designed to displace teeth a prescribed amount in a desired direction. This sends signals to remodel tissues in a way that allows teeth to move. To interpret the biological responses to activation of any orthodontic appliance, each interface must be thoroughly understood.[2] Many studies observed a series of biological cell occurrences that turn biomechanical signals into chemical and electrical messages to which cells respond.[3] After 100 years, there is a good understanding of the sequence at both tissue and cellular levels and now, the current focus of research is at the molecular level.

The current evidence suggests that downstream from the initial event in the process of tooth movement which is the mechanotransduction at focal adhesions (which link the extracellular matrix to the cytoskeleton); mechanically induced remodeling is mediated by a complex feedback mechanism involving the synthesis of chemical messengers. These include cytokines such as interleukin-1 (IL-1), IL-6, and receptor activator of nuclear factor k B ligand by cells of the osteoblast and/or fibroblast lineages. These, in turn, act at the biomolecular level in an autocrine/paracrine fashion to regulate the expression of transcription factors, cytokines, prostaglandins (PGs), growth factors, enzymes, and structural molecules involved in the differentiation, proliferation, and function of mesenchymal and other cell types. Histochemical studies on animals and biochemical studies on humans support this conclusion.[4] A precondition for the remodeling activities and ultimately tooth displacement is the occurrence of an inflammatory process Growth of the sensory nerve fibers and their neuropeptides in control and development of inflammation, that is, their role in tooth movement has been established.[5]

OTM generally involves two interrelated processes: (1) Deflection or bending of the alveolar bone and (2) remodeling of the periodontal tissues. Bone modeling is a very important aspect of tooth movement and needs proper understanding. Bone modeling is a mechanically mediated

Access this article online

Website: www.jrad.co.in

DOI: https://doi.org/10.53064/jrad.2022.13.4.226

Address for correspondence: Dr. Uday Kumar Digumarthi, Department of Orthodontics and Dentofacial Orthopedics, Anil Neerukonda Institute of Dental Sciences, Visakhapatnam, Andhra Pradesh, India.
E-mail: drsaiuday@gmail.com

Received: Apr. 01, 2022; **Accepted:** May. 02, 2022; **Published:** Jun. 20, 2022

How to cite this article: Pushpanjali TV, Karri T, Digumarthi UK, Pitta N, Hemanth ESS, Ganta S. A Contemporary Literature Review on Advances in Biology of Orthodontic Tooth Movement. J Res Adv Dent 2022;13(4):179-184.

adaptive process which includes changing a bone's size, shape, or position. Orthodontic aspects of bone modeling are reviewed relative to morphology, biomechanics, neurology, molecular control mechanisms, and the periodontal adaptation to stress. The study of these phenomena and genetic influences may help to understand better the response to environmental factors such as orthodontic treatment.[6]

Phases of Tooth Movement

Burstone (1962) suggested three phases of tooth movement (Figure 1).

They are:
1. Initial phase
2. Lag phase
3. Post-lag phase.

The initial phase of OTM is characterized by rapid movement of the tooth within 24–48 h after the first application of the force.[7] The movement is rapid due to the displacement of the tooth in periodontal space. The time frame of the initial phase usually occurs between 24 h and 2 days. The movement of the tooth occurs within the socket of bone. Due to the force applied on the tooth, there is a compression and stretching of periodontal ligament which, in turns, causes extravasation, chemoattraction of inflammatory cells, and recruitment of the osteoblast and the osteoclast progenitors. The tooth movement in this phase is between 0.4 and 0.9 mm and usually occurs within a week time.[7]

After the initial phase, there is a lag phase in which the movement is minimal or sometimes no movement at all. The reason for initial phase is the hyalinization of compressed periodontal ligament. The movement does not occur until the necrosed tissue is removed by the cells (Kashyap, 2016).

In the lag phase, the tooth movement stops for 20–30 days and during this time, all the necrotic tissue is removed along with the resorption of adjacent bone marrow. The necrotic tissue from the compressed bone and compressed periodontal ligament sites is removed by macrophages, foreign body giant cells, and osteoclast cells.[8] The third phase is the post-lag phase in which the movement of tooth gradually or suddenly increases and is usually seen after forty days after the initial application of force (Krishnan and Davidovitch, 2006). It has been hypothesized that during displacement of tooth, a continuous development and removal of necrotic tissue occur.[9]

Pilon *et al*. recently divided the curve of tooth movement into four phases.[10]

Theories of Tooth Movement

The control mechanisms by which biological response, that is, movement of a tooth to the orthodontic force can be explained on the basis of different contrasting theories. There are three widely accepted theories.

They are:
1. Pressure-tension Theory (Figures 2 and 3)
2. Bone-bending theory
3. Fluid Dynamic theory.

Pressure-tension theory

This classic theory of tooth movement relies on the chemical signals as the stimulus for cellular differentiation and ultimately tooth movement. According to this theory, an alteration in the blood flow within the periodontal ligament is produced by the sustained pressure that causes the tooth to shift in position within the periodontal ligament space compressing the ligament in some areas while stretching it in others. Blood flow is decreased where the periodontal ligament is compressed while it is maintained or increased where the periodontal ligament is under tension.[11,12]

Bone-bending theory

Farrar in 1888 suggested that alveolar bone bending plays a pivotal role in the OTM. This hypothesis was later confirmed with the experiments of Baumrind in rats and another scientist called Grimm in humans.[13] When a force is exerted on the teeth to be moved, two principal changes take place in the alveolar process. First, a bending of the process; second, absorption of the process in advance of the moving teeth and deposition of bone behind it. Experiments of Mühlemann and Zander (1954) with *Macaca mulatta* (rhesus) monkeys found that deformation of the alveolar bone started when the forces are >100 g applied to the teeth.[14]

Fluid dynamic theory

This theory was proposed by Bein. According to him, within the geometry and structures of the periodontium, fluid systems act in the transmission and damping of forces acting on a tooth. There are three distinct but interacting fluid systems that are involved in damping oscillation of the tooth in its socket; first, the vascular system enclosed within the blood vessel and lymph vessel walls; second, the system of the periodontal membrane comprised of cells and periodontal fibers; and third, the interstitial fluid continuum that permeates the spaces between the cells, fibers, blood vessels, tooth, and bone. The dynamic activities of the fluid systems operating in the periodontium exhibit separate but interrelated functional properties.[13] Experiments were conducted on rats which showed that the extracellular fluid system in the periodontium dissipates part of the force acting on a tooth in life during intrusion. The drag effect of the periodontium on teeth was exerted by the intracellular fluids confined within the cells and fibers whether there was extracellular fluid flow or not. The thickness of the periodontal membrane is extremely small relative to the tooth root and the alveolus. The interstitial fluid or ground substance is continuous throughout the periodontium. The behavior of the periodontium under a load is in accord with the behavior of the squeeze film.[13] The squeeze films investigated were lubricant films in a non-rotating journal bearing and also between plates. These films enabled the bearing or plates to sustain

loads resulting in pressures of many hundreds of thousands of grams per square centimeter, exceeding by 10-fold the pressures generated during mastication. The squeeze film effect is applicable to tooth-periodontium reaction to loads.[13]

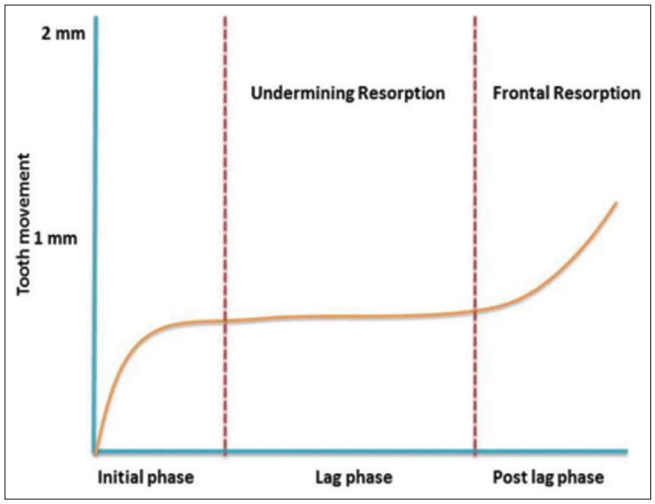

Figure 1: Phases of tooth movement

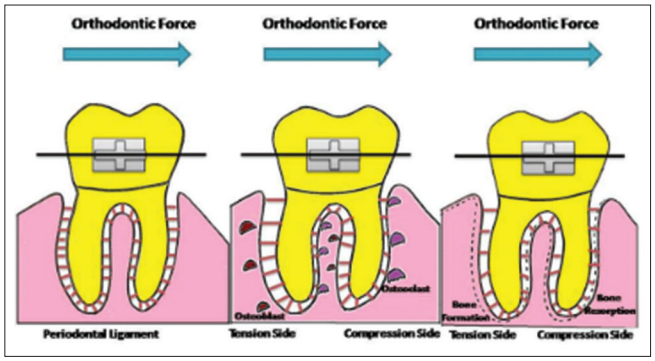

Figure 2: Pressure tension theory

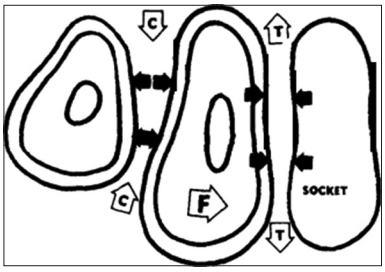

Figure 3: Direction of force on tooth[15]

Role of Chemical Mediators in Tooth Movement

Leukotrienes (LTs)

LTs are compounds, closely related to PGs that are produced by the conversion of arachidonic acid through the lipoxygenase pathway. They were originally demonstrated in leukocytes and they are trienes by structure which means the backbone of the molecule has three double bonds and, hence, they came to be known as LTs. Many studies have shown that challenges to tissues by various stimuli will cause the release of both the cyclooxygenase and lipoxygenase products. There is an interaction between the cyclooxygenase and lipoxygenase pathways and modulation of one pathway will usually be reflected in the modulation of the other. LTs in addition to PGs might have future clinical applications that could result in increased tooth movement (Table 1). Moreover clinical use of LT inhibitors for the control of allergic and inflammatory conditions should be a factor considered by the orthodontist in evaluating the success of the tooth movement protocol.[16]

Cytokines

Cytokines are low-molecular weight proteins (mw <25 kDa) produced by cells that regulate or modify the action of other cells in an autocrine (acting on the cell of origin) or paracrine (acting on adjacent cells) manner. The definition includes the ILs, tumor necrosis factors (TNFs), interferons, growth factors, and colony-stimulating factors. Cytokines are regulated tightly during induction, gene transcription and translation, protein synthesis, and secretion. Once released, the cytokines are regulated in the circulation and at receptor level on target cells. Cytokines have been shown to be active participants in the process of OTM in studies conducted on animals. In human studies involving normal and periodontally inflamed tissue, TNF has been recovered and quantified from the gingival crevice. Studies showed an increase in the mean level of TNF and corroborated that it plays a role in tooth movement in human beings. Hence, it can be safely concluded that tooth movement in human beings is associated with an increase in TNF levels.[17]

PGs

The term PG was introduced by Von Euler, who first discovered the compound in semen of humans and believed the prostate

Table 1: Phases of orthodontic tooth movement given by Pilon *et al*

Phase I (initial)	24 h–2 days Initial tooth movement within the socket	Acute inflammatory response vasodilation – migrating of leukocytes-release of cytokines cell signaling molecules
Phase II (arrest)	20–30 days Movement stops	Chronic inflammation Continuation of migration of leukocytes Paradental remodeling
Phase III (acceleration)	40 days of accelerated tooth movement after initial force application	Another period of acute inflammation superimposing the on-going chronic inflammation
Phase IV (linear)	Overall tooth movement	Recruitment of macrophages, fibroblasts, osteoclasts, and osteoblasts

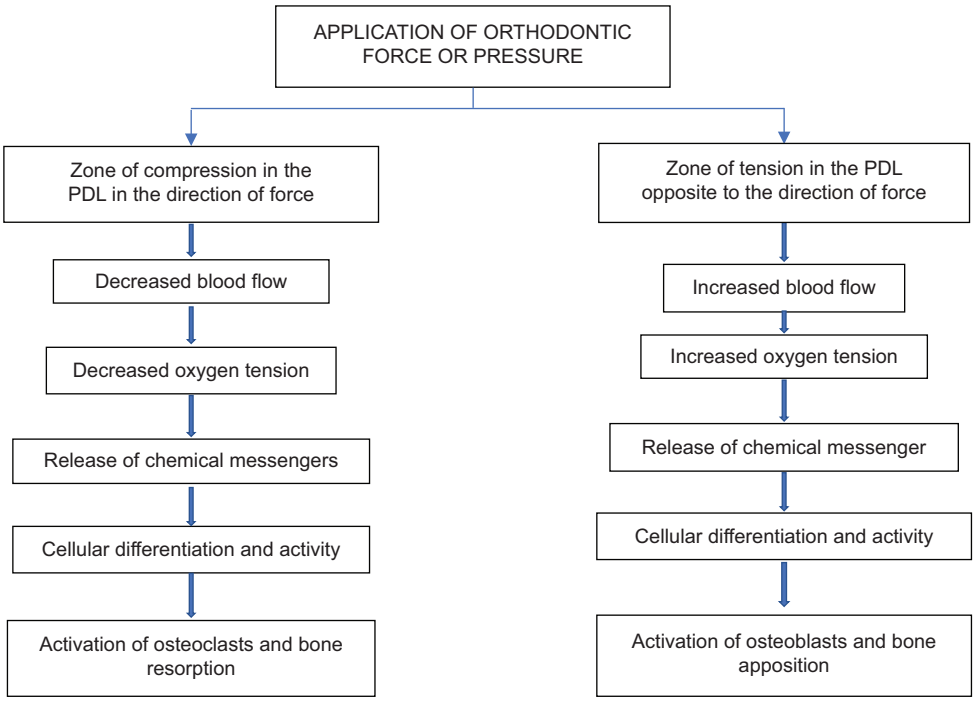

Figure 4: Histological representation of orthodontic tooth movement

gland to be the major source. Experiments showed that injection of PGs increased osteoclast numbers. Indomethacin, which inhibits PG synthesis, blocked the appearance of osteoclasts.[18] Further work showed that local PG injection could also increase the rate of OTM in primates. This culminated in the clinical use of PGE1 to increase the efficiency of orthodontic appliances. PGs appear important in the process of tooth movement under orthodontic forces (Figure 4), it is suggested that the use of over-the-counter non-steroidal anti-inflammatory drugs (NSAID's) by patients during orthodontic treatment significantly modulates the molecular pathways underlying tooth movement, leading to altered treatment efficacy.[19]

Osteoclastogenesis

Osteoclasts are multinucleated giant cell derived from hematopoietic stem cells in blood (Suda *et al*., 1992). At the compression site, osteoclast pre-cursor cell differentiates into osteoclast. As described earlier, the cells which mediate osteoclasts are cytokines especially TNF-alpha and IL-1. It is directly stimulated by IL-1R (Jimi *et al*., 1996) and indirectly by IL-1 and IL6 (O'Brien, 1999). IL6 and IL-1 stimulate local cells to manifest MCSF and RANKL. PGs mediate osteoclast formation by enhancing RANKL expression. In general, the local cells try to deregulate formation of osteoclast by producing RANKL decoy receptor which is OPG (osteoprotegerin) (Yasuda *et al*., 1998).[20]

Yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ) protein

YAP and TAZ are transcriptional coactivators encoded by paratactic homologous genes, shuttle-crossing between cytoplasm and nucleus to regulate the gene expression, and cell behavior and standing at the center place of the sophisticated regulatory networking of mechanotransduction.[21]

The process of OTM, which owes much to osteoblastogenesis and osteoclastogenesis, involves the proliferation and differentiation of many pluripotential cells including periodontal ligament cells (PDLCs), periodontal ligament stem cells, MSCs, and pre-osteoclasts in an artificial mechanical environment. Besides, osteocytes, osteoblasts, and PDLCs act as important mechanosensory cells and produce mediators, such as cytokines, growth factors, PG, and nitric oxide upon loading application to activate other cells in periodontal tissues.[21]

In view of this, researchers are searching for the connection between YAP/TAZ and OTM, and there is some direct evidence indicating that YAP/TAZ takes part in OTM. It has been found that the expression of YAP and TAZ is upregulated during OTM, and their expression is proportional to the orthodontic forces. Besides, how YAP/TAZ engages in the proliferation, differentiation, and functions of the cells engaged in OTM and YAP/TAZ has been explored to reveal the effects of YAP/TAZ in OTM.[21]

Role of Neurotransmitters in Tooth Movement

Sensory nerve fibers and neuropeptides have a role in the control and development of inflammation and, hence, a role in tooth movement. It has been recognized that apart from histamine, PGs, LTs, and cytokines, peripheral nerve fibers participate in inflammation. This neural contribution is termed neurogenic inflammation and involves release of neuropeptides and antidromic stimulation of afferent nerve endings and

initiation of an inflammatory reaction.[22] Since inflammation is an important part of OTM, neural modulation is an important factor in OTM. Neurotransmitters released in the periodontal ligament following the application of an orthodontic force interact with endothelial cells and lead to rapid vasodilation followed by extrusion of plasma and cells. Neurogenic mechanisms take part and modulate the development of the early inflammatory as well as the later reparatory processes incident to OTM.[23]

Medication and Tooth Movement

Orthodontists often prescribe drugs to manage pain from force application to biological tissues, manage temporomandibular joint problems, and tackle fungal and viral infections throughout the course of treatment. A recent review of pharmaceuticals commonly used in orthodontic practice, provided an insight into the dosage, pharmacological actions, and side effects of these agents. A part from these medication, patients who consume vitamins, minerals, and other compounds, for the prevention or treatment of various diseases, can also be found in every orthodontic practice. Some of these drugs may have profound effects on the short- and long-term outcomes of orthodontic treatment.

NSAIDs can be divided into different groups depending on their chemical composition such as salicylates, arylalkanoic acids, arylpropionic acids, oxicams, and coxibs. The mechanism of action of these different NSAIDs is almost similar and they tend to suppress production of all prostanoids (thromboxanes, prostacyclines, and PGs). Many animal studies have been done to know the effects of these NSAIDs on OTM but the effects were evaluated only for short administrations. The effect of these NSAIDs on OTM also depends on the dose and duration of these drugs which has to be considered during clinical application. The decrease in the rate of OTM may be related to the effect of these drugs on osteoclastic differentiation or in stimulating their activity. Many orthodontic patients take NSAIDs to overcome the initial discomfort caused by OTM. The previous studies reported that NSAIDs decrease the rate of tooth movement because of its effects on prostanoids.[24]

Further, inhibition of the inflammatory reaction produced by the PGs tends to slow down OTM (Diravidamani *et al*., 2012). Paracetamol (Acetaminophen) is not taken under NSAIDs, although they have similar chemical structure. They are commonly used analgesics but lack in anti-inflammatory effect and has no effect on blood clotting and no side effect on the stomach. Two important animal studies done on the effect of paracetamol on OTM in rabbit show that there is no significant effect on rate of OTM. Therefore, paracetamol can be considered as a safe drug to be used for managing pain associated with orthodontic treatment (Tyrovola and Spyropoulos, 2009).[25]

Another important group of drugs which affect OTM is bisphosphonates, because of its direct effect on calcium homeostasis thereby affecting the bone metabolism, thus having an inhibitory effect on the orthodontic treatment and tooth movement (Adachi *et al*., 1997). Bisphosphonates are used in the treatment of bone diseases such as osteoporosis, Paget's disease, and bone metastasis. The half-life of bisphosphonates is 10 years; therefore, they continue to affect the bone metabolism even after completion of therapeutic dose (Tyrovola and Spyropoulos, 2009). Corticosteroids may increase OTM but it depends on dosage and timing of steroids (Verna *et al*., 2000) in contrast to others (Swanson *et al*., 2006) who claimed that the corticosteroids inhibit tooth movement by stimulating *in vitro* bone resorption which is also time and dose dependent. Parathyroid hormone (PTH) is secreted by parathyroid glands, which is released when there is low concentration of calcium content in blood. The main effect of PTH is to increase the concentration of calcium by stimulating bone resorption. Therefore, PTH increases the rate of OTM by stimulating bone resorption. Estrogens are female sex hormones which are decreased after menopause in female patients leading to osteoporosis. Therefore, it is suggested that estrogens seems to reduce tooth movement rate.[26]

Thyroid gland releases two hormones thyroxine and calcitonin which plays an important role in the calcium regulation and reabsorption. Although, there are no studies which has shown the effect of calcitonin on the rate of tooth movement, but there are animal studies to show Thyroxin increases rate of tooth movement if injected locally by activating osteoclasts.

Vitamin D3 (1,25 dihydroxycholecalciferol) is a hormone which regulates the serum calcium and phosphate levels by promoting intestinal absorption and reabsorption. The deficiency of Vitamin D3 can be due to low intake of calcium combined with inadequate exposure to sunlight, eventually leading to osteoporosis, and decreased bone mineralization. The effect of Vitamin D3 on the rate of OTM has been studied in rats and the results concluded that Vitamin D3 can increase the rate tooth movement (Al-Ansari *et al*., 2015). These effects of medication and drug abuse on tooth movement indicate that orthodontists should enquire about the prescribed medication, over-the-counter drugs and dietary supplements taken by the orthodontic patients before initiation of treatment.[26]

Conclusion

Rapid advances in all biological fields have enabled the better understanding of the mechanisms involved in the OTM. It is evident that, at different stages of tooth movement, different combinations of cell-cell and cell-matrix interactions occur; which determine the nature of the remodeling changes.[27] The research trend is now directed toward elucidating molecular level interactions during these confounding events. A better understanding of the relationship between genes and transcription factors in controlling bone and PDL remodeling will expand knowledge and might strengthen our clinical capabilities. Above all, this growing body of knowledge on the response of cells to mechanical loads should illuminate useful paths in clinical orthodontics and assist us in identifying

and discarding harmful methods of mechanotherapy. The future orthodontics will, therefore, increasingly become biologically correct and consequently patient-friendly. This ongoing development will move orthodontics closer to the goal of being optimal, where teeth are moved efficiently, without causing discomfort to the patient or damage to the teeth and their supporting tissues.[28]

References

1. Asbell MB, Hill C. A brief history of orthodontics. Am J Orthod Dentofacial Orthop 1990;98:176-83.
2. Lindauer SJ, Britto AD. Biological response to biomechanical signals: Orthodontic mechanics to control tooth movement. Semin Orthod 2000;6:145-54.
3. Norton LA. Fundamental principles of the biology of tooth movement. Semin Orthod 2000;6:139-44.
4. Meikle MC. The tissue, cellular, and molecular regulation of orthodontic tooth movement: 100 years after Carl Sandstedt. Eur J Orthod 2006;28:221-40.
5. Vandevska V. Neural modulation of inflammatory reactions in dental tissues incident to orthodontic tooth movement. Eur J Orthod 1999;21:231-47.
6. Roberts WE, Huja S, Roberts JA. Bone modeling: Biomechanics, molecular mechanisms, and clinical perspectives. Semin Orthod 2004;10:123-61.
7. Chelărescu S, Șurlin P, Decusară M, Oprică M, Bud E, Teodorescu E, *et al*. Evaluation of IL1β and IL6 gingival crevicular fluid levels during the early phase of orthodontic tooth movement in adolescents and young adults. Appl Sci 2021;11:521.
8. Insoft M, King GJ, Keeling SD. The measurement of acid and alkaline phosphatase in gingival crevicular fluid during orthodontic tooth movement. Am J Orthod Dentofac Orthop 1996;109:287-96.
9. Krishnan V, Davidovitch ZE. Cellular, molecular, and tissue-level reactions to orthodontic force. Am J Orthod Dentofac Orthop 2006;129:469-e1.
10. Kumar AA, Saravanan K, Kohila K, Kumar SS. Biomarkers in orthodontic tooth movement. J Pharm Bioal Sci 2015;7:S325.
11. Sandy JR, Farndale RW, Meikle MC. Advances in mechanically induced bone remodeling. Am J Orthod Dentofac Orthop 1993;103:212-22.
12. Profitt WR, Fields HW, Sarver DM. Contemporary Orthodontics. 4th ed. St. Louis: Elsevier; 2007.
13. Bien SM. Hydrodynamic damping of tooth movement. J Dent Res 1966;45:907-14.
14. Moyers RE. Handbook of Orthodontics. 4th ed. United States: Year Book Medical Publisher; 1988.
15. Grimm FM. Bone bending, a feature of orthodontic tooth movement. Am J Orthod 1972;62:384-93.
16. Mohammed AH, Tatakis DN, Dziak R. Leukotrienes in orthodontic tooth movement. Am J Orthod Dentofac Orthop 1989;95:231-7.
17. Kehoe MJ, Cohen SM, Zarrinnia K, Cowan A. The effect of acetaminophen, ibuprofen, and misoprostol on prostaglandin E2 synthesis and the degree and rate of orthodontic tooth movement. Angle Orthod 1996;66:339-50.
18. Leiker BJ, Nanda RS, Currier GF, Howes RI, Sinha PK. The effects of exogenous prostaglandins on orthodontic tooth movement in rats. Am J Orthod Dentofac Orthop 1995;108:380-8.
19. Chumbley AB, Tuncay OC. The effect of indomethacin (an aspirin-like drug) on the rate of orthodontic tooth movement. Am J Orthod 1986;89:312-4.
20. Yamaguchi M. RANK/RANKL/OPG during orthodontic tooth movement. Orthod Craniofac Res 2009;12:113-9.
21. Deng L, Chen Y, Guo J, Han X, Guo Y. Roles and mechanisms of YAP/TAZ in orthodontic tooth movement. J Cell Physiol 2021;236:7792-800.
22. Vandevska-Radunovic V. Neural modulation of inflammatory reactions in dental tissues incident to orthodontic tooth movement. A review of the literature. Eur J Orthod 1999;21:231-47.
23. Neubert JK, Dolce C, Toro EJ, Holliday LS, Caudle RM, Bokrand-Donatelli Y. Neural Modulation of Orthodontic Tooth Movement. India: INTECH Open Access Publisher; 2011.
24. Karthi M, Anbuslevan GJ, Senthilkumar KP, Tamizharsi S, Raja S, Prabhakar K. NSAIDs in orthodontic tooth movement. J Pharm Bioallied Sci 2012;4:S304.
25. Tyrovola JB, Spyropoulos MN. Effects of drugs and systemic factors on orthodontic treatment. Quintessence Int 2001;32:365-71.
26. Klaushofer K, Hoffmann O, Gleispach H, Leis HJ, Czerwenka E, Koller K, *et al*. Bone-resorbing activity of thyroid hormones is related to prostaglandin production in cultured neonatal mouse calvaria. J Bone Mineral Res 1989;4:305-12.
27. Vâţă LI. The influence of orthodontic forces on bone remodeling mediated by cellular response. A review. Int J Med Dent 2020;24:45-51.
28. Asiry MA. Biological aspects of orthodontic tooth movement: A review of literature. Saudi J Biol Sci 2018;25:1027-32.