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Effect of various biological ways on the orthodontic tooth movement: A review

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Abstract--The duration of orthodontic treatment is the primary concern of utmost patients. Unfortunately, long orthodontic treatment time poses several disadvantages like an advanced predilection to dental caries, gingival recession, and root resorption. Thus, there is an increase in the demand to find the best method of faster tooth movement. Orthodontic treatment is formed on the premise that when force is delivered to a tooth and thereby transmitted to the adjacent investing tissues, certain mechanical, chemical, and cellular events take place within these tissues, which allow for the structural difference that contributes to the tooth movement. Conventionally, this process is slow, and orthodontic treatment time can range anywhere from 36-48 months. The body's responses to these forces are the crucial controllers of inflammation and tissue turnover. So, in this article, various pharmacological means are discussed that can enhance the rate of tooth movement.

Keywords--accelerated orthodontic tooth movement, RANK, prostaglandins, interleukins, vitamin D & E.

Introduction

Orthodontic treatment in the present day does not just bear meeting the demands of creating functional harmony in occlusion and perfecting the aesthetic outlook. But also, the treatment should complete in the most effective duration which can be accepted by the patient and the orthodontist. We live in a fast-paced world where there is an increased tendency for experimenters to concentrate on accelerating means for tooth movement due to the huge demand for adults for a

shorter orthodontic treatment time.¹ Prostrating this challenge will dramatically ameliorate the quality of orthodontic care and motivate further people toward the conception of orthodontic treatment. Lengthy orthodontic treatment prompts numerous cases, especially grown-ups, to either avoid treatment or seek shorter indispensable results. Therefore, there has been an increased hunt for ways that accelerate the orthodontic tooth movement (OTM) without compromising the treatment outcome is an active area of exploration in orthodontics today.

OTM is mainly because of the remodeling of surrounding bone periodontal ligament (PDL) caused by the mechanical stimuli. Bone remodeling is a process of bone formation on the tension site and bone resorption on the pressure site.² OTM can be regulated by the magnitude of the applied force and the biological responses from the PDL.³ Changes in the environment around the PDL due to alterations in blood flow are caused by force applied to teeth and leading to the release of various mediators like cytokines, growth factors and arachionic acid metabolites. Due to these secretions, remodeling of the bone occurs causing faster tooth movement.⁴

Frost in 1983 explained the regional acceleratory phenomena (RAP) which is a local response to a noxious stimulus, that describes a process by which tissue forms faster than the normal regional regeneration process. By enhancing the various healing stages, this phenomenon makes healing occur 2–10 times faster.⁴ So, the purpose of this article is to review the various methods of accelerated OTM and their clinical applicability.

Accelerated OTM is broadly classified into:

- I. Based on these biological principles: Classified into two types⁵
 - Indirect: Activate target cells that control the rate of tooth movement by adding the release of upstream cytokines. The indirect techniques range from minimally invasive techniques like micro osteoperforations (MOPs) to invasive techniques like piezocision and aggressive technique corticotomy.
 - Direct: Utilize various stimulants to directly activate the target cells. The direct techniques include vibration, laser, and ultrasound.
- II. According to Ghada et al 2013¹
 - Biological
 - Physical
 - Biochemical
 - Surgical Approaches
- III. According to RoyChodhury et al 2015⁶
 - Surgical Methods
 - Physical/ Mechanical stimulation methods
 - Molecular methods
 - Drugs
- IV. According to Raja et al 2016⁷
 - Drugs
 - Surgical Methods

- Physical/ Mechanical stimulation methods
- V. According To Alkhani et al 2017⁸
 1. Stimulating the Artificial Pathway to Increase the Rate of Tooth Movement
 - Chemical Agents
 - Physical Stimulation
 2. Stimulating the Natural Pathway to Increase the Rate of Tooth Movement
 - Corticotomy
 - Piezoincision
 - Micro-osteoperforations
- VI. According to Maheshwari et al 2015⁹
 - Non- Surgical / Non- Invasive
 - Surgical / Invasive

In this article, we mainly focus on the various biological methods that accelerate orthodontic tooth movement.

Biological methods (Figure 1 & 2)

Local application or systemic intake of certain medicines, vitamins, minerals might have an impact on OTM. ¹⁰ Drugs consumed by orthodontic patients can have a wide range of effects on the tooth movement process, either decelerating or accelerating it, depending on the medication effects on cells involved in bone and periodontal ligament (PDL) remodeling.¹¹ Molecules present in medicines and nutrients consumed regularly by patients can reach the mechanically stressed paradental tissues through the circulation and interact with local target cells.^{12,13}

Various cell-signaling pathways are actuated, leading to stimulation of periodontal ligament metabolism, and localized bone resorption and bone deposition.¹² The combined effect of mechanical forces and one or more of these agents may be inhibitory, additive, or synergistic.¹³

Promoter and Suppressor Drugs

Promoter drugs are the agents that enhance bone resorption. They coupled with the secondary and primary inflammatory mediators and enhance tooth movement while suppressor drugs are agents that reduce bone resorption and reduce tooth movement.¹³

<i>PROMOTER DRUGS</i>	<i>SUPPRESSOR DRUGS</i>
PROSTAGLANDINS	BISPHOSPHONATES
VITAMIN D3	NON- STEROIDAL ANTI-INFLAMMATORY DRUGS
CALCIUM	
CYTOKINE – IL-1, EGF & TNF	
OSTEOCALCIN	
VITAMIN -E	
CORTICOSTEROIDS	

HORMONES	FLUORIDE
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Promoter Drugs

- A. Prostaglandins: It stimulates bone resorption by increasing directly the number and activity of osteoblast. The hyperactive osteoblast through the OPG-RANKL-RANK pathway activates osteoclasts. Lee et al. in 1990 stated that systemic and local administration of PGE1 in rats has an impact on tooth movement, the former is more efficient.¹⁴ Spielmann et al. 1989 observed after weekly PGE1 injections individual differences in the rate of movement. No side effects and no pathologic damage could be observed, as PGEs might be involved in root resorption.¹⁵ Besides the higher risk of root resorption another disadvantage of using prostaglandins clinically is the pain during the injection process.¹⁶
- B. Active vitamin D (1,25 dihydroxy vitamin D3 (1,25[OH]2D3)): It plays an important role in calcium homeostasis with calcitonin and parathyroid hormone stated by Kale (2004) and it increases bone formation as said by Huang (2014)¹⁹. In the study of Kawakami et al. (1990)¹⁷ local vitamin D3 injections in the submucosal palatal area in rats caused accelerated tooth movement without obvious side effects. Against this, Tyrovola et al. (2001)¹⁸ state that vitamin D metabolites can reduce the speed of tooth movement.
- C. Calcium: The additional use of calcium in local injections of PGEs, reduces the speed of tooth movement but also stabilizes the root resorption in the process of accelerated orthodontic tooth movement as stated by Seifi (2003).¹⁹
- D. Cytokine: High concentration of cytokines such as interleukins IL-1, IL-2, IL3, IL-6, IL-8, and tumor necrosis factor α (TNF), growth factors, and macrophage colony- stimulating factors were found to play a major role in bone remodeling.
- Interleukin-1(IL-1): This stimulates osteoclast function by increasing prostaglandin synthesis, hyperactive osteoblast activates osteoclasts through the OPG-RANKL-RANK pathway.
- Tumour necrosis factor (alpha, beta) (TNF): stimulates bone resorption and inhibits bone collagen and non-collagenous protein synthesis. Ohori et al. proved that systemic injections of TNF- α enhance bone resorption and therefore tooth movement.²⁰ However, IL-1 and TNF- α have a promoting impact on mechanically induced root resorption.
- Epidermal growth factors (EGF): have a catabolic effect on bones and an osteoclasts recruitment effect. The study of Savenkov et al. (2003)²¹ proved in rats that high-dose intraperitoneal EGF injections increase the osteoclast rate.
- E. Osteocalcin: It is released from thyroid C-cells in response to high serum calcium. It is a bone protein synthesized by osteoblasts and odontoblasts and is conducive to the activation of bone resorption. Research data have demonstrated that the injections have stimulated osteoclasts on pressure side of alveolar bone. The results suggest that osteocalcin has an additive effect on the rate of orthodontic tooth movement through the enhancement of osteoclastogenesis on the pressured side Kobayashi and Hashimoto et al. 2001 proved in rats that daily local osteocalcin injections accelerate orthodontic tooth movement, especially in the early phase of treatment.²²

- F. **Vitamin E:** Vitamin E is a popular antioxidant that affected bone turnover. However, its effects were unknown. So, Seong et al 2022 aimed to evaluate tooth movement and bone remodeling in rats receiving a vitamin E enriched diet. It presented an increased OTM rate on days 4 and 14 and showed an increased osteoclastic cell and decreased bone volume. In addition, there was increased expression of the microphthalmia-associated transcription factor in the alveolar bone on the experimental side and, no difference in bone remodeling on the control side.²³
- G. **Corticosteroids:** The main effect is on bone tissue which is direct inhibition of osteoblastic function and thus decreases total bone formation. The bone formation is decreased due to elevated PTH levels caused by inhibition of intestinal calcium absorption which is induced by corticosteroids. Corticosteroids increase the rate of tooth movement, and since new bone formation can be difficult in a treated patient, they decrease the stability of tooth movement.⁶ Umashankar et al evaluated the rate of tooth movement in rats during short and long-term corticosteroid therapy and concluded that bone remodeling seemed to slow down in acute administrations, whereas the rate of tooth movement increased in chronic treatment.¹²
- H. **HORMONES**(Table 1)
- Parathyroid hormone (PTH):** it is released from the parathyroid gland in response to low serum calcium, phosphate, or vitamin D3. PTH increases bone resorption by increasing osteoclasts as stated by Huang (2014).¹⁶ The continuous systemic or local administration of PTH over a month can shorten the treatment time because undesired resorptions in other bones like vertebrae cannot be excluded, local injections could be more advantageous than the systemic administration as said by Soma (1999).²⁴ Due to the long-term risks, the application of PTH and thyroid hormones for the acceleration of tooth movement is not practicable clinically.
- Relaxin:** The role of Relaxin is known in the re-modeling of soft tissue rather than remodeling of bone, it is a peptide hormone of the insulin/relaxin family. It has been shown that it increases collagen in the tension site and decreases it in the compression site during orthodontic movement stated by Madan (2007)²⁵, so it enhances tooth movement by enhancing fiber and bone remodeling at the tension site. However, McGorray et al. (2012)²⁶ stated that weekly injections of relaxin for eight weeks did not affect the speed of tooth movement.
- Thyroid Hormone:** Thyroxine and Calcitonin are produced by the thyroid gland. Administration of thyroxine will lead to an increase in bone remodeling activity and reduces bone density. Thyroxine produces interleukin 1 (IL-1 β), a type of cytokine which involves in bone formation through osteoclastic reaction.⁶ However, low dosage and short-term thyroxine administration lower the frequency of “force-induced” root resorption, and a reinforcement of the protection of the cementum and dentin to the osteoclastic resorption.¹³
- Estrogen:** The rate of periodontal tissue remodeling is influenced by estrogen level. It influences the composition and degradation of collagen fibers in the periodontal ligaments and the remodeling of the alveolar bones. It also enhances the alkaline phosphatase activity and the secretion of osteocalcin (OCN) and osteoprotegerin (OPG) in the periodontal ligament cells.²⁷ Low estrogen levels stimulate the osteoblastic production of bone resorption-related

factors, such as interleukin-1 and -6, tumor necrosis factor-alpha (TNF- α), and macrophage colony-stimulating factor; these factors may induce bone loss by affecting the differentiation and activity of osteoclasts.

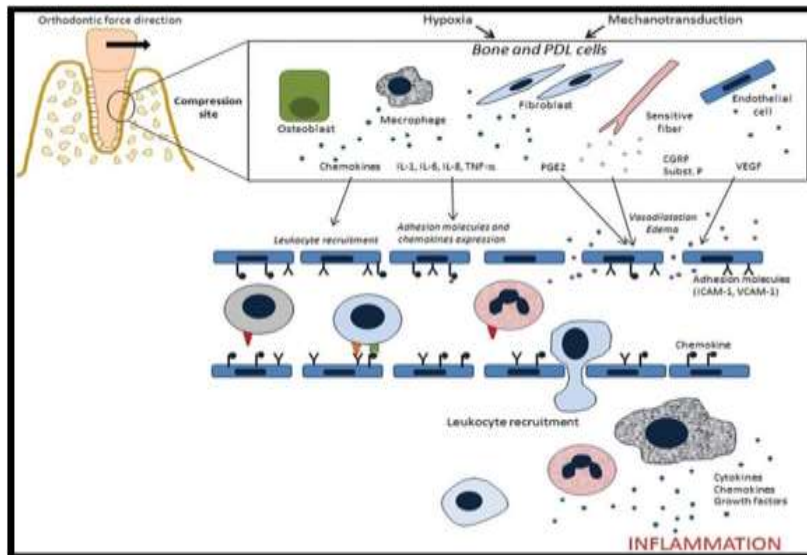


Figure1: Inflammation and Mechano-transduction for the tooth movement

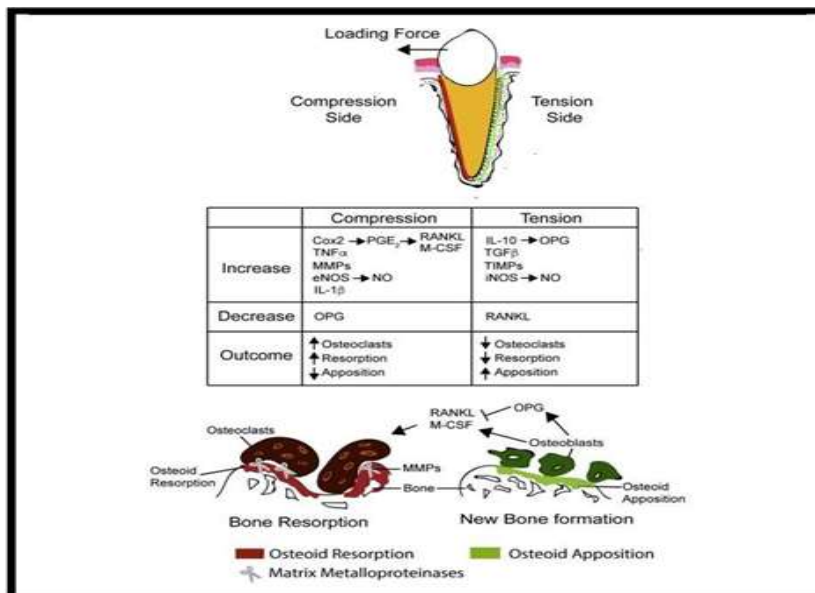


Figure 2: Cellular pathway associated with orthodontic tooth movement

Suppressor Drugs (Table 2)

- A. Bisphosphonates: are widely used in treating osteoporosis, Paget’s disease, bone metastases, and bone pain from some types of cancer. They inhibit osteoclasts and decrease them. This leads to inhibition of orthodontic tooth

movement and hence delays orthodontic treatment.¹² However, by inhibiting bone resorption, this drug may have positive effects on periodontal health. Fujimura Y (2009) investigated the effect of bisphosphonates on orthodontic tooth movement and root resorption in mice. It was found that the orthodontic appliance increased the number of osteoclasts on the pressure side and, reduced the amount of tooth movement and the root resorption on the pressure side.²⁸

- B. Non-Steroidal Anti-Inflammatory Drugs: NSAID acts by inhibiting the production of all prostanoids (thromboxanes, prostacyclins, and prostaglandins) by blocking an enzyme called cyclooxygenase during the transformation of arachidonic acid.^{6,12} Prostaglandin inhibition by NSAIDs triggers a cascade of events, leading to a reduction in the numbers of osteoclast-like cells, Howship lacunae, and blood vessels throughout the treatment. It lowers the rate of collagen maturation in the PDL and so, the rate of tooth movement.¹¹ However, acetaminophen controls discomfort without inhibiting prostaglandin synthesis.
- C. Fluorides: It increases bone mass and mineral density, and because of these, it has been used in the treatment of metabolic bone disease, such as osteoporosis. Sodium fluoride treatment might delay orthodontic tooth movement and increase the course of treatment. Sodium fluoride has been shown to inhibit osteoclastic activity and reduce the number of active osteoclasts.¹⁰

Systemic factor	Effects on bone metabolism	Effects on tooth movement
Vitamin D	Increase rate of bone remodeling	Increase tooth movement
Thyroid hormone	Increase rate of bone remodeling	Increase tooth movement
Androgen	Decrease bone resorption	Unproven
Calcitonin	Inhibit bone resorption	Inhibit tooth movement
Estrogen	Decrease bone resorption	Decrease tooth movement
Relaxin	Increase bone resorption	Increase tooth movement

Table 1: Influence of systemic factors on bone metabolism and tooth movement

- D. Miscellaneous: Jianru et al. (2012) hypothesized that coffee intake could influence tooth movement in a way that caffeine can break the calcium balance in bone and directly inhibit the development of osteoblasts, leading to temporarily decreased bone mineral density and consequently inducing faster orthodontic tooth movement.²⁹ Patients with chronic alcohol consumption may result in inhibited bone formation. Alcohol-induced oxidative stress resulted in increased nicotinamide adenine dinucleotide phosphate oxidase activity in bone cells leading to increased osteoclastogenesis. Cigarette smoking increases the progression of periodontal disease as well as carious lesions. An increase in COX-2 gene and prostaglandin E2 is seen with nicotine use. This increases bone resorption. All these factors will effectively increase the pace of orthodontic tooth movement in a dose-dependent manner.¹¹

DRUGS	Effects on bone metabolism	Effects on tooth movement
Corticosteroids	Increase bone resorption	Increase tooth movement

Bisphosphonates	Decrease bone resorption	Decrease tooth movement
Prostaglandins	Stimulate bone resorption	Enhancing tooth movement
Leukotrienes	Stimulate bone resorption	Enhancing tooth movement
Fluorides	Inhibit osteoclastic activity	Decrease tooth movement
Aspirin	Decrease bone resorption	Decrease tooth movement
Diclofenac	Decrease bone resorption	Decrease tooth movement
Ibuprofen	Decrease bone resorption	Decrease tooth movement
Celecoxib	Decrease bone resorption	No influence
Paracetamol	No influence	No influence

Table 2: Influence of drugs on bone metabolism and tooth movement

Conclusion

A better understanding of the biology of tooth movement and treatment outcomes individually is a complex process that requires knowledge in many different areas of biomedicine. Publications on the outcomes of well-planned investigations in every field of medicine inspire researchers who have selected the areas that may help to address orthodontic clinical issues faced by the clinician daily. The administration of exogenous biological molecules to accelerate tooth movement during orthodontic treatments has been intensively tested in animal experiments. However, administration of the following molecules has demonstrated promising results; cytokine, PTH, vitamin D.

Future Scope

Current researches tend to focus on areas such as monitoring a patient's reaction to mechanical forces by searching bone remodeling markers in the GCF, saliva, and blood serum. Speed of tooth movement could be enhanced by various physical and chemical agents. Moreover, current knowledge raises the possibility of enhancing biological anchorage at specific sites, thereby decreasing the rebound effect and assisting with the prevention of root resorption.

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