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Review

Biological aspects of orthodontic tooth movement: A review of literature

Moshabab A. Asiry

Department of Paediatric Dentistry and Orthodontics, College of Dentistry, King Saud University, Building No 3500, Riyadh 12372-7325 Saudi Arabia

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ABSTRACT

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

Contents

1. Introduction

Orthodontics comprise of tooth movement in the jaw from one position to another to attain esthetics (Sabane, et al., 2016; Proffit and Fields, 2000a, 2000b; Al khateeb, et al., 1998). It has always been interesting for clinicians to understand the basic concept of tooth movement, so that the treatment time could be reduced, resulting in patient satisfaction (Kashyap, 2016). A lot of research has been done on the mechanical forces and tooth movement compared to the focus on cellular biology (Sabane, et al., 2016). The principle of tooth movement in which applied pressure results in remodeling is a microscopic fact (Kashyap, 2016). Although, there are lot of innovative mechanical devices for tooth movement but still we have not been totally successful in preventing periodontal injuries. This could be due to lack of complete cellular

E-mail address: masiry@gmail.com
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understanding (Sabane et al., 2016). The need to understand the specific remodeling pathways is essential to target those cells and achieve an impeccable prognosis (Al-Ansari et al., 2015). The advantage of understanding the remodeling pathways helps us to design a better appliance which targets the specific cell for a controlled and safe accelerated tooth movement (Al-Ansari et al., 2015; Oswal et al., 2015; Patil et al., 2012). The other advantage of knowing these cells can also help us to stimulate the body directly or indirectly to produce or activate these cells. The objective of this paper is to review the biological changes occurring at the molecular level during orthodontic tooth movement with special emphasis on chemical mediators and medication affecting the tooth movement.

2. Phases of tooth movement

Burstone in 1962 suggested three phases of tooth movement. They are:

(1) Initial phase
(2) Lag phase
(3) Post lag phase

Initial phase occurs immediately after the application of force to tooth. The movement is rapid due to the displacement of tooth in periodontal space. The time frame of the initial phase usually occurs between twenty-four hours to two days (Burstone, 1962). The movement of the tooth occurs within the bony socket. Due to the force applied on the tooth there is a compression and stretching of periodontal ligament which in turns causes extravasation of vessels, chemo-attraction of inflammatory cells and recruitment of osteoblast and osteoclast progenitors. After the initial phase, there is a lag phase in which the movement is minimal or sometimes no movement at all. The reason for this phase is the hyalinization of compressed periodontal ligament. The movement will not take place until the necrosed tissue is removed by the cells (Kashyap, 2016). In the lag phase the tooth movement stops for twenty to thirty days and during this time frame 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 are removed by macrophages, foreign body giant cells and osteoclast cells. 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 force application (Krishnan and Davidovitch, 2006). It has been hypothesized that during displacement of tooth, a continuous development and removal of necrotic tissue occurs (Melsen, 1999).

3. Theories of tooth movement

The orthodontic force applied on the tooth structure results in a tooth movement by deposition and resorption of alveolar bone called as remodeling. This force is converted into biological activity, although this activity is not fully understood but three possible theories of tooth movement are advocated. They are:

(1) Bone-Bending theory
(2) Biological Electricity Theory
(3) Pressure-Tension Theory

3.1. Bone-bending theory

Farrar (1888) stated that when an orthodontic force is applied to the tooth, it is transmitted to all tissues near the area of force application. These forces bend bone, tooth and the solid structures

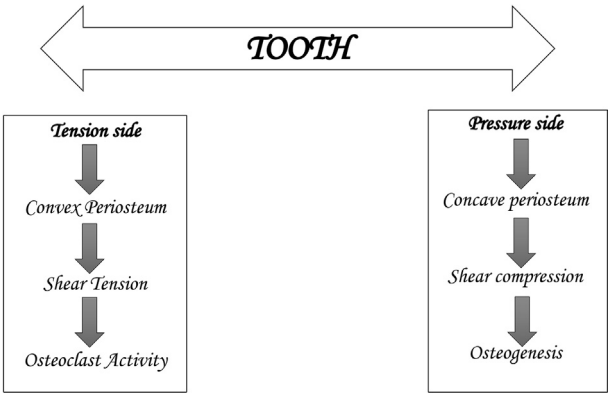

Fig. 1. Flowchart presenting the effect of applied forces on Periosteum.

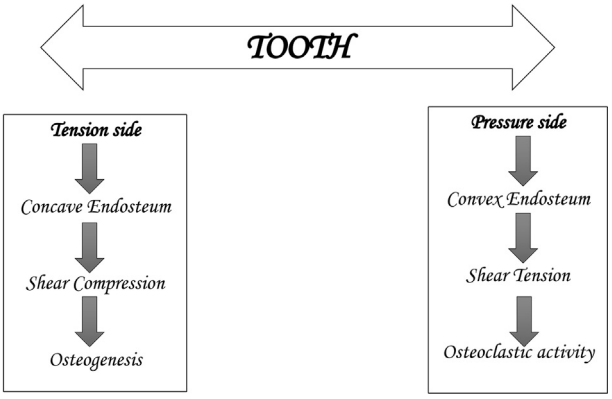

Fig. 2. Flowchart presenting the effect of applied forces on Endosteum.

of periodontal ligament (Kashyap et al., 2016). Since the bone is more elastic than the other structures it bends effortlessly and the process of tooth movement gets accelerated. This also explains the rapid tooth movement occurring at the extraction site and in pediatric patients, in which the bone is not heavily calcified and is more flexible (Baumrind, 1969). Fig. 1 and Fig. 2 presents the effect of applied forces on periosteum and endosteum respectively.

3.2. Biological electricity theory

This theory was proposed by Bassett and Becker in 1962. According to them, whenever the alveolar bone flexes or bends it releases electric signals and to some extent is responsible for tooth movement. Initially it was thought to be piezo-electric signals. The characteristic of these signals are:

(a) They have a quick decay rate which means it is initiated when the force is applied and at the same time it disappears quickly even with the force maintained.
(b) They produce equal signal on the opposite side when the force is released (Proffit et al., 1999).

After the bone bend, the ions interact with each other in the presence of the electric field causing electric signals and temperature change. A small voltage is observed called as "streaming potential". They are different from piezoelectric signals and they even can be generated by external electric field, which can modify the cellular activity. There is another type of signal present in bone that is not being stressed called as "bioelectric potential". The bone which is metabolically active shows electronegative changes that

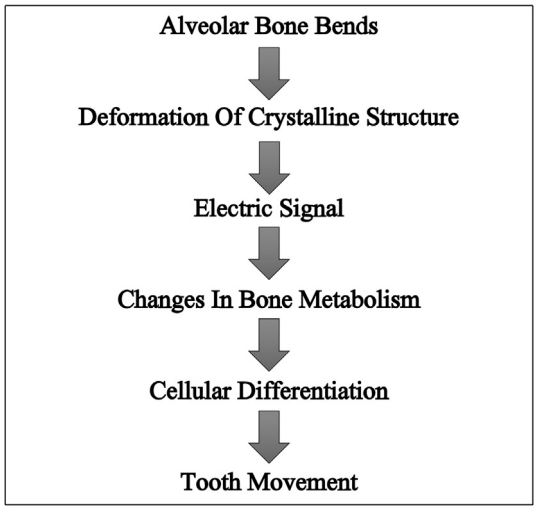

Fig. 3. Bio-electric theory of tooth movement.

are proportional to its activity (Sabane et al., 2016). The deflection of alveolar bone by orthodontic forces is accompanied by consequential change in periodontal ligament (Grimm, 1972). Fig. 3 explains the Bio-electric theory of tooth movement. The periodontal fibers generating stress on bone during orthodontic forces was evaluated with the nature of electro-chemical relationship between the orthodontic force and dento alveolar complex. It was concluded that the area with electronegative charge is characterized by elevated level of osteoclastic activity and the area of electropositive charge is characterized by elevated level of osteoblastic activity (Zengo et al., 1973). According to Davidovitch et al. (1980a, 1980b) the exogenous electric current along with orthodontic forces accelerates the orthodontic tooth movement. This suggests that the piezoelectric response due to bone bending might function as "cellular first messenger".

3.3. Pressure-tension theory

The histological research by Sandstedt (1904), Oppenheim (1911) and Schwarz (1932), hypothesized that a tooth moves in the periodontal space by creating a pressure and tension side (Table 1). It explains the alteration of blood flow in periodontal ligament. This alteration results in less oxygen levels on the pressure side due to compression of the periodontal ligament and vice versa. Tuncay et al. (2006) observed that low oxygen tension causes decreased Adenosine triphosphate (ATP) activity. These changes can directly or indirectly act on cellular activity and differentiation. Schwarz (1932) correlated the tissue response to the magnitude of force with capillary blood pressure. If the force exceeds the pressure (20–25 g/cm^2 of root surface), tissue necrosis can occur due to the strangulated periodontium (Krishnan and Davidovitch, 2006).

Table 1
Factors affecting tooth movement according to Pressure-Tension theory.

Factors affecting tooth movement	Pressure side	Tension side
Blood flow	Decreases	Increases
Oxygen level	Decreases	Increases
Carbon dioxide level	Increases	Decreases
Cell replication	Decreases	Increases
Fiber production	Decreases	Increases

4. Role of chemical mediators in tooth movement

4.1. Chemokines

As the blood flow reduces on the pressure side due to compression of the periodontal ligament, some of the cells undergo apoptosis while others die resulting in necrosis (Al-Ansari et al., 2015). These cell deaths also include some osteocyte and osteoblast in the adjacent alveolar bone. This causes acute inflammatory response with release of chemokines, which are small proteins that could attract other inflammatory and precursor cells into the extravascular space from the vasculature (Al-Ansari et al., 2015). During orthodontic movement, the chemokines known as monocyte chemo attractant protein-1 (MCP-1) is released attracting the monocytes (Taddei et al., 2012). These monocytes become either macrophages or osteoclasts once they exit the blood stream and enter into the tissue. The release of other inflammatory mediators is seen within first few hours of tooth movement (Al-Ansari et al., 2015).

4.2. Cytokines

These short range extracellular proteins modulate the activity of other cells. They are pro-inflammatory cells (Proffit et al., 1999). First it was thought that only lymphocytes produce these cells and named them as "lymphokines". Later it was known that many different cells produce these proteins and hence renamed it as "cytokines" (Sabane et al., 2016). There are over 50 cytokines which are recognized. These proteins are seen in various stages of inflammation. Some of the cytokines which mediate the bone remodeling during orthodontic tooth movement are interleukin-1, alpha1 beta, tumour necrosis factor (TNF), IL-6 (Garlet et al., 2007). The inflammatory cells which produce cytokines are osteoblast, fibroblast, endothelial cells and macrophages (Al-Ansari et al., 2015).

4.3. Prostaglandins

Prostaglandins were first isolated from human semen by Von Euler (Samuelsson et al., 1975). It was believed that prostate gland was the major source but now it is known that nearly all tissues produce it. They are derived from the metabolism of arachidonic acid. They help in inflammatory mediation by vasodilation, adhesion of inflammatory cells and vascular permeability. Yamasaki demonstrated that osteoclast number increases after injecting prostaglandin (Yamasaki et al., 1980). Bhalaji et al., (1996) conducted studies on rabbits and was found that the rate of tooth movement increased after injecting prostaglandin locally. During mechanical stimulation, prostaglandins are produced directly by inflammatory cells or indirectly by cytokines like TNF-alpha (Perkins and Kniss, 1997).

4.4. Osteoclastogenesis

Osteoclasts are multinucleated giant cell derived from hematopoietic stem cells (Suda et al., 1992). At the compression site osteoclast pre-cursor cell differentiate into osteoclast. As described earlier, the cells which mediate osteoclasts are cytokines especially TNF-alpha and Interleukin 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 M-CSF and RANKL. Prostaglandins mediate osteoclast formation by enhancing RANKL expression. Generally the local cells try to deregulate formation of osteoclast by producing RANKL decoy receptor which is OPG (osteoprotegerin) (Yasuda et al., 1998). Therefore,

for tooth movement to occur the OPG levels should be less at the compression site (Al-Ansari et al., 2015).

5. Role of neurotransmitters in tooth movement

Dental and paradental tissues are innervated by neurons, originating from trigeminal ganglion. These neurons contain many neuropeptides like substance P (SP), vasoactive intestinal polypeptide (VIP) and Calcitonin gene-related peptide (CGRP) (Norevall et al., 1995; Yamaguchi et al., 2004). These neurons are passive under normal physiological conditions (Krishnan and Davidovitch, 2009). During orthodontic treatment the neutral condition changes leading to release of active proteins, which in turns cause local inflammation and releases the above mentioned neuropeptides (Vandevska and Radunovic, 1999). Since these neurons are closely associated with capillaries, the endothelial cells are the first to interact with these neuropeptides. These neuropeptides can increase the vascular permeability and affect the bone directly (Sabane et al., 2016). This permeability helps leukocyte to migrate from the capillaries and initiate the acute inflammation (Middleton et al., 2002). These leukocytes release signaling factors like growth factor, cytokines which helps in tissue remodeling (Yamaguchi et al., 2004). The other inflammatory cells which help in releasing cytokines are mast cells, monocyte and lymphocytes (Lee et al., 2007). Studies have shown that substance P elevate the level of prostaglandin-E and collagenase (Davidovitch et al., 1988). VIP is a potent vasodilator which encourages bone resorption (Sabane et al., 2016).

6. Medication and tooth movement

An analysis of forces and vectors does not completely explain the mechanism of orthodontic tooth movement. The complex interaction of different strain, gene expressions and activation of signaling pathways sets a new paradigm for explaining the mechanism of orthodontic tooth movement (Masella and Meister, 2006). The effect of medications on signaling molecules such as eicosanoids or prostanoids is important to regulate pathways and pathological responses, which directly or indirectly affects orthodontic biological tooth movement (Bartzela et al., 2009).

Leukotrienes are the only eicosanoids that are formed independently from COX. Leukotrienes have an important role in inflammation and allergic diseases like asthma, however, based on an animal study done on rats, it also has some influence on OTM. The study demonstrated a significantly decrease in OTM after selective inhibition of leukotriene synthesis (Mohammed et al., 1989). Therefore, these findings suggest that the drugs which inhibit leukotrienes indirectly decrease OTM. The medications such as Zafirlukast and Montelukast block the leukotriene receptor which has the same effect as inhibition of leukotriene synthesis. Another approach to inhibit leukotriene synthesis is by selective blocking of lipoxygenase enzyme which helps in conversion of arachidonic acid to leukotrienes. This is achieved by drugs such as Zileuton. So these drugs Zafirlukast, Montelukast and Zileuton which inhibit leukotrienes synthesis also decrease OTM (Bartzela et al., 2009).

NSAIDs (Non-Steroidal Anti-inflammatory Drug) are used by many patients for different conditions such as headache, migraine, gout, rheumatoid arthritis, osteoarthritis, post-operative pain, cardiovascular diseases and colorectal cancer. Although these drugs are used for different conditions, the doses vary from high to low dose, long term to short term prescriptions. 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 are almost similar, they tend to suppress production of all prostanoids (thromboxanes, prostacyclines, and prostaglandins). Many animal studies have been done to know the effects of these NSAIDs on OTM but the effects were evaluated for short administrations. Based on these animal studies, the effect of different NSAIDs on OTM has been summarized in the below Table 2. 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 (Bartzela et al., 2009; Chumbley and Tuncay, 1986; Vayda et al., 2000; Zhou et al., 1997). Many orthodontic patients take NSAIDs to overcome the initial discomfort caused by orthodontic tooth movement. Previous studies reported that NSAID's decrease the rate of tooth movement because of its effects on prostacyclines and thromboxanes (Laudano et al., 2001; Bartzela et al., 2009; Seibert et al., 1994). Further, inhibition of the inflammatory reaction produced by prostaglandins tends to slow orthodontic tooth movement (Diravidamani et al., 2012).

Table 2
NSAIDs effect on orthodontic tooth movement.

Sl. No.	NSIADs	Dosage	Effect on orthodontic tooth movement
1	Salicylates	High and low dose	Effect controversial and not clear
2	Aryalkanoic acids	Low dosage	Decrease in OTM rate
3	Arylpropionic acid	High dosage	Decrease in OTM rate
4	Oxicams	Nil	No studies
5	Coxibs	High dosage (local Injection)	Induced OTM

Paracetamol (Acetaminophen) is not considered under NSAIDs, although they have similar chemical structure. They are commonly used analgesics but lack in anti-inflammatory effect, 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 shows that there is no significant effect on rate of OTM (Arias and Marquez-Orozco, 2006; Roche et al., 1997). Therefore, paracetamol can be considered as a safe drug to be used for managing pain associated with orthodontic treatment. (Bartzela et al., 2009).

Another important group of drugs which affect orthodontic tooth movement are bisphosphonates, because of its direct effect on calcium homeostasis thereby affecting the bone metabolism, thus having an inhibitory effect on orthodontic treatment and tooth movement (Adachi et al., 1997). Bisphosphonates are used in the management 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 bone metabolism even after completion of therapeutic dose (Bartzela et al., 2009).

Corticosteroids may increase orthodontic tooth movement but it depends on dosage and timing of steroids (Verna et al., 2000) in contrast to others (Swanson et al., 2006) who claim that corticosteroids inhibits tooth movement by stimulating in vitro bone resorption (increased activity and/or formation of osteoclasts) 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 in blood. The main effect of PTH is to increase the concentration of calcium by stimulating bone resorption. Therefore, PTH increases the rate of orthodontic tooth movement by stimulating bone resorption (Soma et al., 1999, 2000).

Estrogens are female sex hormones which are decreased after menopause in female patients leading to osteoporosis. Therefore, it can be suggested that Estrogens seems to reduce tooth movement rate (Haruyama et al., 2002; Yamashiro and Takano-Yamamoto, 2001).

Thyroid gland releases two hormones thyroxine and calcitonin which play an important role in calcium regulation and reabsorption. Although, there are no studies to show the effect of calcitonin on the rate of tooth movement, there are animal studies to show Thyroxin increases rate of tooth movement if injected locally by activating osteoclasts (Shirazi et al., 1999; Verna et al., 2000).

Vitamin D3 (1,25 dihydroxycholecalciferol) is a hormone which regulates serum calcium and phosphate levels by promoting intestinal absorption and reabsorption. The deficiency of vitamin D3 can be due to low intake 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 suggested that Vitamin D3 can increase the rate tooth movement (Al-Ansari et al., 2015). These confounding effects of medication and drug abuse on tooth movement indicates that clinicians should enquire about the prescribed medication, over-the-counter drugs and dietary supplements taken by the orthodontic patients before initiation of treatment.

7. Conclusion

Based on the interpretations of previous data on the biology of tooth movement, it can be concluded that rate of tooth movement depends on bone remodeling which is a result of inflammatory process after orthodontic forces are applied on the teeth. The role of chemical mediators such as cytokines, interleukins, growth factors, RANKL receptors and osteoprotegerins in the processes of bone remodeling should be considered when planning orthodontic tooth movement. Also, care should be taken when prescribing medications during orthodontic tooth movement because some medications like NSAIDs, Bisphosphonates, exogenous thyroxin, steroids, etc. can increase or decrease tooth movement. In summary, the research on biology of tooth movement is on the right track and can accommodate new theories as well as better accelerating techniques.

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