

Enroute through Bone: Biology of Tooth Movement

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ABSTRACT

Biology of orthodontic tooth movement has always been an interesting field of orthodontist. Orthodontic tooth movement is divided into different phases and number of theories has been given for it, at present most of them are invalid. Gene-directed protein synthesis, modification and integration form the essence of all life processes, including OTM. Bone adaptation to orthodontic force depends on normal osteoblast and osteoclast genes that correctly express needed proteins at the right time and places. Prostaglandins, cytokines and growth factors play an important role in OTM.

Keywords: Tooth movement, Genes, Prostaglandins, Cytokines.

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INTRODUCTION

Orthodontic treatment is based on the principle that if prolonged pressure is applied to a tooth, tooth movement will occur as the bone around the tooth remodels. Bone is selectively removed in some areas and added in others, leading to tooth movement through the bone. Because the bony response is mediated by the periodontal ligament (PDL), tooth movement is primarily a periodontal ligament phenomenon³ (Proffit).

Physiological tooth movement is a slow process that occurs mainly in the buccal direction into cancellous bone or because of growth into cortical bone. In contrast, orthodontic tooth movement can occur rapidly or slowly, depending on the physical characteristics of the applied force and the size and biological response of the PDL.^{2,15} These force-induced strains alter the PDL's vascularity and blood flow, resulting in local synthesis and release of various key molecules, such as neurotransmitters, cytokines, growth factors, colony-stimulating factors and arachidonic acid metabolites. These molecules can evoke many cellular responses by various cell types in and around teeth, providing a favorable microenvironment for tissue deposition or resorption.^{1,2}

Factors, such as the type and magnitude of force (Storey and Smith 1952; Reitan 1985;¹⁹ Maltha et al 2004)^{11,12,14} or treatment duration (Pilon et al, 1996)¹³ are found to be

coherent with undesirable tissue reactions, such as sterile necrosis or root resorption. The appearance of necrotic tissue (also called hyalinization) is an important component in the process of tooth movement.²⁰

When forces are applied orthodontically, orthopedically or by functional appliances, its effect will be on gingiva, periodontal ligament, cementum, pulp, bone and sutures.

Periodontal and Bone Response to Normal Function

Periodontal ligament is a dense fibrous connective tissue which occupies periodontal space between the root of the tooth and alveolus. The connective tissue fibers of periodontal ligament are mainly collagenous. Under normal circumstances, the PDL occupies a space approximately 0.5 mm in width around all parts of the root. The principal cellular elements in the PDL are undifferentiated mesenchymal cells and their progeny in the form of fibroblasts and osteoblasts.⁴ The collagen of this ligament is constantly being remodelled and renewed during normal function.³

During masticatory function, the teeth and periodontal structures are subjected to intermittent heavy forces. Tooth contact last for 1 or 2 seconds or less, forces are quite heavy, ranging from 1 to 2 kg while soft substances are chewed up to as much as 50 kg based on the type of the food being masticated. When a tooth is subjected to heavy forces of this type, quick displacement of the tooth within the PDL space is prevented by the incompressible tissue fluid. Instead the force is transmitted to the alveolar bone which bends in response.

The resistance provided by tissue fluids allows normal mastication, with its force applications of 1 second or less, to occur without pain. Prolonged force, even of low magnitude, produces a different physiologic response remodeling of the adjacent bone. Orthodontic tooth movement is made possible by the application of prolonged forces.

Orthodontic Tooth Movement

PR Begg (1954) introduced the differential force concept and the light wire technique, in which tooth movements could be carried out using light continuous forces.

The concepts of differential forces were taken from Storey and Smith experiment (1952).¹¹

Thus, the concept of using low orthodontic force values and application of force to move teeth at the most favorable rate and with least tissue damage and pain was possible.

Based on Storey and Smith experiment, Sandstedt¹⁶ presented the concept of undermining resorption which was later supported by Schwarz.¹⁷ According to it, when excessive orthodontic force is applied, there is compression of periodontal membrane and tooth investing bone. This leads to occlusion of blood vessels and blood supply is cut-off. Due to inadequate supply, there is necrosis. No tooth movement can occur until necrosed tissue is phagocytosed.

Thus, they pointed out that teeth, which are subjected to heavy/excessive orthodontic forces, show marked resorption of investing structures and teeth become loosened, after which light forces can readily move the teeth.

Frontal resorption—steady attack on outer surface of lamina dura—smooth continuous tooth movement.

Undermining resorption—delay until bone adjacent to tooth can be removed, at which point the tooth moves to a new position. If high forces are maintained, again a delay follows until further undermining resorption occurs.

According to Proffit,³ forces are classified as follows:

Continuous: Force maintained at some appreciable fraction of the original from one patient visit to the next.

Interrupted: Force levels decline to zero between activation.

Intermittent: Force levels decline abruptly to zero, intermittently, when appliance is removed or when fixed appliance is temporarily deactivated.

Phases of Tooth Movement

In 1962, Burstone¹⁸ suggested that if the rates of tooth movement were plotted against time, there would be three phases of tooth movement as follows:

- Initial phase
 - A lag phase and
 - A postlag phase.
1. The initial phase is characterized by rapid movement immediately after the application of force to the tooth. This rate can be largely attributed to the displacement of the tooth in the PDL space.
 2. Immediately after the initial phase, there is a lag period, with relatively low rates of tooth displacement or no displacement. It has been suggested that the lag is produced by hyalinization of the PDL in areas of compression. No further tooth movement occurs until cells complete the removal of all necrotic tissues.

3. The third phase of tooth movement follows the lag period, during which the rate of movement gradually or suddenly increases.

Theories of Orthodontic Mechanisms

There are two main proposed mechanisms for tooth movement as follows:

1. The application of pressure and tension to the PDL.
2. Bending of the alveolar bone.

The Pressure-Tension Theory

Classic histologic research about tooth movement by Sanstedt (1904),¹⁶ Oppenheim (1911)²⁶ and Schwarz (1932)¹⁷ led them to hypothesize that a tooth moves in the periodontal space by generating a 'pressure side' and a 'tension side'.

This hypothesis explained that on the pressure side, the PDL displays disorganization and diminution of fiber production. Here, cell replication decreases seemingly due to vascular constriction.

This classic hypothesis on the mechanism of tooth movement, based on the work of Oppenheim (1911), Sandstedt (1905) and Schwarz (1932), postulates the movement of the tooth within the periodontal space, generating a 'pressure side' and a 'tension side'. Schwarz hypothesized that the PDL space is a continuous hydrostatic system, and forces applied to this environment by means of mastication or orthodontic appliances create a hydrostatic pressure that would be, in accordance with Pascal's law, transmitted equally to all regions of the PDL. On the 'pressure side', cell replication is said to decrease as a result of vascular constriction, causing bone resorption. On the 'tension side', cell replication is said to increase because of the stimulation afforded by the stretching of the fiber bundles of the PDL, thus causing bone deposition. In terms of fiber content, the PDL on the 'pressure side' is said to display disorganization and diminution of fiber production, while on the 'tension side', fiber production is said to be stimulated.

The Bone-Bending Theory

Farrar²⁴ was the first to suggest, in 1888, that alveolar bone bending plays a pivotal role in orthodontic tooth movement. This hypothesis was later confirmed with the experiments of Baumrind in rats and Grimm²⁵ in humans. According to these authors, when an orthodontic appliance is activated, forces delivered to the tooth are transmitted to all tissues near force application. These forces bend bone, tooth and the solid structures of the PDL. Bone was found to be more elastic than the other tissues and to bent far more readily in response to force application.

The active biologic process that follow bone bending involve bone turnover and renewal of cellular and inorganic fractions. These processes are accelerated while the bone is held in the deformed position. These authors further stated that 'reorganization proceeds not only at the lamina dura of the alveolus but also on the surface of every trabeculum within the corpus of bone'. With the help of this theory and gaining support from Wolff's law, these authors could explain factors, such as:

1. The relative slowness of en masse tooth movement, when much bone flexion is needed for the rapidity of alignment of crowded teeth and when thickness makes bone flexion easier.
2. The rapidity of tooth movement toward an extraction site and
3. The relative rapidity of tooth movement in children, who have less heavily calcified and more flexible bones than adults.

Bioelectric Signals in Orthodontic Tooth Movement

It has been shown that distortion of cells and extracellular matrix is associated with alteration in tissue and cellular electric potentials. Bones generally have a remarkable ability to remodel their structure in such a way that the stress is optimally resisted. It has been hypothesized that mechanical deformation of the crystalline structure of the hydroxyapatite and the crystalline structure of collagen induce migration of electrons that generate local electric fields. This phenomenon is called piezoelectricity.

Such signals die away quickly even though the force is maintained. But when the force is released and the crystal lattice returns to the original shape, a reverse flow of electrons occurs. Rhythmic activity would cause a rhythmic flow of electrons in both directions.

Cells are sensitive to this piezoelectric effect. It has been assumed that bending of bone may create negative fields occurring in the concave aspect of the bone surface leading to deposition. Areas of convexity are associated with positive charges and evoke bone resorption. Further, ions in the fluids surrounding the living bone interact with these electrical fields. These currents of small voltages are called streaming potentials.^{27,28} Recent *in vivo* experiments conducted by Roberts et al (1981-JDR)⁷ have revealed that a negative electrical field is created in the areas where the PDL is widened.

GENETIC CONTROL MECHANISMS

Several genes, linked to mechanical activation of bone, produce enzymes, such as glutamate/aspartate transporter (GLAST), inducible nitric oxide synthetase (iNOS) and prostaglandin G/H synthetase (PGHS-2). Inducible gene

products compose an intricate series of endocrine, paracrine, and autocrine mechanisms for controlling bone modeling.^{5,6}

- Parathyroid hormone (PTH) and PTH-related protein (PTHrP) enhance expression of insulin-like growth factor I (IGF-I).
- *In situ* hybridization under conditions of physiologic tooth movement in rats demonstrated site-specific expression of mRNAs for osteonectin (OSN), osteocalcin (OCN) and osteopontin (OPN).^{31,34} In response to orthodontic force, OPN mRNA is elevated within the tissue by 12 hours and can be demonstrated at 48 hours by *in situ* hybridization in >50% of osteoclasts and >87% of osteocytes in the interdental septum of maxillary molars (JBMR-1999).³²
- Msx1 is a regulator of bone formation during development and postnatal growth. It is involved in the control of neural crest cell migration but also appears to be important for bone modeling activity.

Osteoclast differentiation and activation is controlled by a group of genes related to tumor necrosis factor (TNF)³⁰ and its receptor (TNFR). Genes involved are osteoprotegerin (OPG), receptor activator of nuclear factor (RANK) and RANK ligand (RANKL).

Colony stimulating factor 1 (CSF1) and RANK induce differentiation of hematopoietic precursor cells, which results in osteoclast precursors with RANK receptors. Local bone related cells secrete RANKL, which binds with RANK on the preosteoclast cell surface to induce the development of a functional osteoclast. As a feedback control, the same regulatory cells produce OPG, which blocks the RANK receptor and thus downregulates osteoclasts.¹⁰

- In addition to the well-established 'RANK-RANKL-OPG axis', another gene (TREM-2)³³ has been implicated in control of bone modeling.
- Another gene, the P2X7 receptor, has been reported to play an important role for initiating and sustaining all types of anabolic bone modeling.

ROLE OF PROSTAGLANDINS IN MEDIATING OTM

Arachidonic acid can be released either by phospholipidases activated by direct cellular damage or by any nondestructive perturbation of the membrane, be it physical, chemical, hormonal or neurohormonal. Prostaglandins can also be termed as local hormones functioning to coordinate effects of those other hormones which induce prostaglandin synthesis and function through G-protein linked receptors to elicit their cellular effects. Classically, prostaglandins as one of the mediators of inflammation cause an increase in intracellular cAMP and calcium accumulation by monocytic cells which then modulate and activate osteoclastic activity.^{8,9}

Klein and Riasz in 1970 reported first time the involvement of prostaglandins in orthodontic teeth movement (OTM). Recent studies observed that with both light continuous force and interrupted force for a duration of 24 hours, there was a significant elevation in both IL-1 β and PGE2 levels.

The effects of local administrations of PGE2 and 1, 25-dihydroxycholecalciferol (1, 25-DHCC) on orthodontic tooth movement was compared in a recent study and 1, 25-DHCC was found to be more effective in modulating bone turnover during orthodontic tooth movement.¹⁹

CYTOKINES AND GROWTH FACTORS IN OTM

Cytokines secreted by leukocytes may interact directly with bone cells or indirectly, via neighboring cells, such as monocytes/macrophages, lymphocytes and fibroblasts, through their production of cytokine or a variety of growth factors.^{21,22} Cytokines released have multiple activities, which include bone remodeling, bone resorption, new bone deposition.

Prominent cytokines include as follows:

- Interleukin I
- IL-6
- Tumor necrosis factor
- Granulocyte-macrophage colony stimulating factor (GM-CSF)
- Macrophage colony stimulating factor (M-CSF)
- Growth factors are also released during inflammation and repair by the cells of PDL and bone
- Another theory stated that the growth factors may secreted by bone cells and stored (bound to bound matrix).²³

Growth factors involved are as follows:

- Fibroblast growth factor (b-FGF and a-FGF)
- Insulin like growth factors (IGF-I, IGF-II)
- Transforming growth factor (TGF)
- Platelet growth factor (PDGFS)
- Bone morphogenic proteins (BMP)

Bone Formation

Promoter	Inhibitor
CGRP, BMP, NOS, GH, GLAST, CTGF, PTH, Ostrix, androgen	Osteocalcin, HOXA-2 MSZ-2, Leptin, SOST, aging, disuse
OPG, CICN-7, TNF, RANK RANKL, IL-1 β , IL-6, PTH, CSF-1, estrogen deficiency, cathepsin-K, disuse	Testosterone, estrogen bisphosphanates, calcium, vit D, CGRP

Markers of Orthodontic Treatment-related Tissue Remodeling in the GCF

Inflammation is the integral component of the tissue response to the application of orthodontic forces.

Inflammatory mediators are the marker of tissue response as follows:

- IL-1 β
- IL-1RA
- Matrixmetalloproteinase-1 (MMP-1)
- Matrixmetalloproteinase-2 (MMP-2)
- Prostaglandins.

Progress in Diagnosis and Treatment Planning

- Interpatient variability in mechanical response is common in orthodontic practice.
- The ENCODE (ENCYclopedia of DNA Elements) projected has started identifying, ‘all structural and functional elements of human genome’. This will allow orthodontist to identify biological promoters and inhibitor of OTM and plan molecular intervention to maximize adaptive responses.^{29,30}

If gene expression in tissue subjected to mechanical force shows patterns of alteration in secreted protein in blood or GCF (gingival crevicular fluid). This may be the media can serve as window for diagnosis and prognosis and sources of active treatment biomarker for assessing mechanics.

CONCLUSION

Tooth movement is a highly conserved physiological mechanism for continuous adaptation of the dentition. Orthodontic tooth movement is a biomechanical exploitation of the physiologic mechanisms for developing and maintaining optimal occlusal function. The tooth continues to move until it achieves equilibrium with natural and applied loads.

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