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BIOLOGY OF TOOTH MOVEMENT

[1] Rohit Reddy S — [1] Post graduate
[2] Gowri sankar Singaraju — [2] Professor
[3] Prasad Mandava — [3] Professor and Head
[4] Vivek Reddy Ganugapanta — [4] Reader

[1-4] Department of Orthodontics, Narayana Dental College, Nellore, Andhra Pradesh, India.

ABSTRACT: Extrinsic forces applied to the crown of the tooth during physiological, therapeutic or pathological processes cause tooth movement. It is impossible for a tooth to be relocated without the remodeling of the periodontium. Bone remodeling brought about by proper techniques and protocol, will reduce the duration of treatment, resulting in quicker tooth movement, reduce pain and histologic damage and most importantly achievement of stable results. Even though the mechanical advances are used quite carefully during orthodontic tooth movement, traumatic effects on the periodontium have not been totally prevented. This may be because of a lack of complete understanding of the cellular complexities. Proper understanding of cellular and molecular biology and also the specific biochemical pathways will help design mechanics that will produce maximum benefits during tooth movement with minimal tissue damage. This reviews briefly the "Biology of tooth movement" to understand and update the knowledge on the latest research on biological changes occurring at the molecular level. This would in turn help in delivering better mechanics, producing quicker tooth movement with minimum tissue damage and maximum comfort to the patient.

KEYWORDS: Tooth movement, Biology, Orthodontic.

INTRODUCTION

The eruption and movement of a tooth occurs due to the translocation of the tooth from one position in the jaw to another. Teeth can be repositioned and retained in a new position in the jaw using orthodontic appliances, through the intervention of the cells of the periodontium. Proper understanding of cellular and molecular biology will help design mechanics that will produce maximum benefits during tooth movement with minimal tissue damage.

Orthodontic tooth movement differs markedly from physiological dental drift or tooth eruption. The former is uniquely characterized by the abrupt creation of compression and tension regions in the PDL.[1]

The force-induced tissue strain produces local alterations in vascularity, as well as cellular and extracellular matrix reorganization, leading to the synthesis and release of various neurotransmitters, cytokines, growth factors, colony-stimulating factors, and metabolites of arachidonic acid.[2, 3]

Contrary to the impression gained from the literature, tooth movement is not confined to events within the periodontal ligament. Recent research suggests that orthodontic tooth movement involves two interrelated processes: (1) deflection or bending of the alveolar bone and (2) remodelling of the periodontal tissues.

Fundamental principles of biology of tooth movement

Periodontium

The periodontium is an "organ" composed of functionally coordinated tissues: (1) attached gingiva, (2) epithelial attachment, (3) PDL and (4) alveolar bone .The specialized tissue that is the principal mediator of tooth movement is the PDL.

Assuming the periodontium is healthy and there is an adequate band of attached tissue, orthodontic tooth movement is a viable option. A cardinal contraindication for tooth movement is periodontitis.[4]

Dynamic Bone physiology:

As bone is a relatively rigid material, incapable of internal expansion or contraction, changes in osseous structure are via cell-mediated resorption and formation. Modeling, a change in shape or size of an osseous structure, is achieved by differential bone formation and resorption along the periosteal and endosteal surfaces. Internal turnover of osseous tissue is termed *remodeling*. Remodeling is controlled by both metabolic and biomechanical mechanisms, and is also an important element in the postoperative healing of cortical bone.[4]

The tissue biology associated with tooth movement:

It must be noted that the bones of the facial skeleton, particularly alveolar bones, are derived from the embryonic neural crest tissue. The bone that this tissue makes is intramembraneous and its utility is similar to an armor plate. It does not have significant weight-bearing or heavy muscular-supporting functions.

Tooth movement is an iatrogenically imposed traumatic event from which the bone and tooth recover and this localized wound healing episode occurs rapidly and efficiently with fewer intermediate steps. Through a complex signaling system involving many types of cells in and around the teeth and their supporting structures, teeth move through bone.[4]

Cell biology

The first structure of note is the cell membrane. This lipid bilayer **"double soap bubble skin"** separates the vast extracellular space outside of the cell from the closed compartmentalized and highly organized cytosol. The force system creates the movement of fluids in the extracellular matrix. This event will alter the macroscopic tissue called the *periodontal ligament.* These cells communicate with one another through the liberation of specific molecules called *chemokines* and *cytokines.* This alteration of cellular physiology can take the form of cell proliferation, cell differentiation, fabricating of a variety of cell products, changes in the cytoskeletal proteins, changes in cell shape, cell migration (chemotaxis), programmed cell death (apoptosis), and changes in cell surface adhesion. Ultimately, as each cell is activated, they act in concert or in combination as a tissue.[4]

Biological response to biomechanical signals:

An orthodontic appliance transfers mechanical stresses through the tooth to the periodontium where they are translated into physical, chemical, and electrical signals to cells that activate tissue remodeling to allow tooth movement. The quantity of force application can be adjusted by altering the magnitude of activation, and the quality of the force system depends on the direction, point of attachment, and the ratio of moment to force applied.[5]

Orthodontic mechanics to control tooth movement

In a purely mechanical system, acceleration is proportional to force (F = ma). Applying a greater force makes an object move faster. In a biological system such as is found in orthodontic treatment, more force may not necessarily equate to more or faster tooth movement.

It is not the force applied at the bracket that is important biologically, but the force per unit root surface that is transmitted at the level of the periodontal ligament. The force per unit area decreases for a given applied force as the amount of root surface increases. Therefore, for a large, multirooted tooth, the magnitude of force transmitted to the surrounding cells is less than for a small, single-rooted tooth in which the force is concentrated over a lesser area.[5]

Optimal orthodontic force

Traditionally, orthodontic forces have been categorized as “light” or “heavy,” and it was assumed that light forces are gentler and therefore more physiologic than heavy forces. Therefore it can be stated that, to produce adequate biological response in the periodontium, light forces are preferable. Unlike light forces, heavy forces often cause necrosis (hyalinization) of the PDL and undermining bone resorption[6], and have been implicated in root resorption.

According to Schwarz, forces below optimum force produce no reaction, whereas forces above that level lead to tissue necrosis, thus preventing frontal resorption of the alveolar bone.[7]

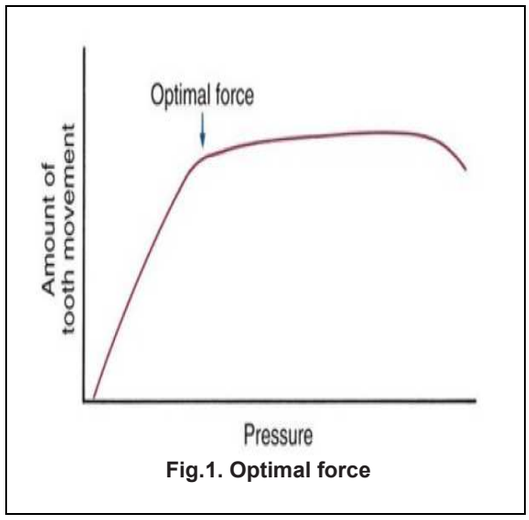


Fig.1. Optimal force

The current concept means that there is a force of certain magnitude and temporal characteristics (continuous v/s intermitted, constant v/s declining) capable of producing a maximal rate of tooth movement, without tissue damage, and with maximum patient comfort.[8-9] According to this concept, the optimal force might differ for each tooth and for each patient.(**Table 1**)

Phases of orthodontic tooth movement

In 1962, Burstone[11] suggested that, if the rates of tooth movement were plotted against time, there would be 3 phases of tooth movement--

1. Initial phase,
2. Lag phase, and
3. Postlag phase.

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.

Table.1. Optimum forces for orthodontic tooth movement

Type of movement	Force*(gm)
Tipping	35-60
Bodily movement (translation)	70-120
Root uprighting	50-100
Rotation	35-60
Extrusion	35-60
Intrusion	10-20

**values depend in part on the size of the tooth; smaller values appropriate for incisors, higher values for multirooted posterior teeth.*[10]

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.

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

Current concepts

The studies,[12,13] performed on beagles, divided the curve of tooth movement into 4 phases.

Cellular and tissue reactions start in the initial phase of tooth movement, immediately after force application. Because of the compression and stretch of fibers and cells in PDL pressure and tension areas, respectively, the complex process of recruitment of osteoclast and osteoblast progenitors, as well as extravasation and chemo attraction of inflammatory cells, begins.

In the second phase, in areas of compression disruption in blood flow occurs which leads to the development of hyalinized areas and the arrest of tooth movement, which can last from 4 to 20 days. Only removal of necrotic tissue and bone resorption from adjacent marrow spaces (indirect resorption) and from the direction of the viable PDL (undermining resorption) allow the resumption of tooth movement.

This comprehensive process requires the recruitment of phagocytic cells such as macrophages, foreign body giant cells, and osteoclasts from adjacent undamaged areas of the PDL and alveolar bone marrow cavities. These cells act in tandem to remove necrotic tissues from compressed PDL sites and adjacent alveolar bone.

In areas of PDL tension, quiescent osteoblasts (bone surface lining cells) are enlarged and start producing new bone matrix (osteoid).

The third and fourth phases of orthodontic tooth movement, also known as the acceleration and linear phases, respectively, start about 40 days after the initial force application.

The pressure sides of teeth exhibit collagen fibers without proper orientation indicating direct or frontal resorption which could be considered part of the remodeling process." The tension sides in the third and fourth phases clearly show bone deposition, as evidenced by alkaline phosphatase positive osteoblastic cells.[14]

Theories of tooth movement

Orthodontic tooth movement has been defined as the result of a biologic response to interference in the physiologic equilibrium of the dentofacial complex by an externally applied force.[8] The 3 main mechanisms for tooth movement proposes were —

1. The application of pressure and tension to the PDL,
2. Fluid dynamic theory
3. Bending of the alveolar bone

1. The pressure-tension theory

Classic histologic research about tooth movement by Sandstedt (1904), [15]Oppenheim (1911),[16] and Schwarz (1932)[7] led them to hypothesize that a tooth moves in the periodontal space by generating a "pressure side" and a "tension side."

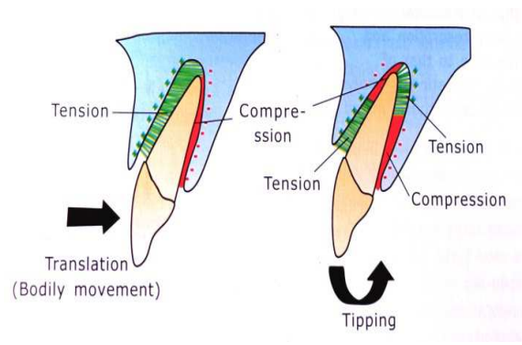


Fig.2. Picture showing the areas of compression

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. On the tension side, stimulation produced by stretching of PDL fiber bundles results in an increase in cell replication. This enhanced proliferative activity leads eventually to an increase in fiber production.[17]

The theory proposes that force-subjected PDL progenitor cells differentiate into compression-associated osteoclasts and tension-associated osteoblasts, causing bone resorption and apposition, respectively. The width changes in the PDL cause changes in cell population and increases in cellular activity.

Inflammation might be at least partly responsible for cellular recruitment and tissue remodeling in areas of force application. This process might in turn lead to frontal resorption (where osteoclasts line up in the margin of the alveolar bone adjacent to the compressed PDL, producing direct bone resorption) and undermining resorption.

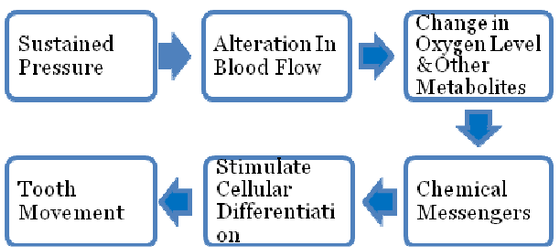
The third phase of bone remodeling consists of loss of bone mass at PDL pressure areas and apposition at tension areas.[18]This succession of events formed the central theme of the pressure-tension hypothesis.

Flaws in pressure tension theory

However, there are two major conceptual problems associated with the hypothesis. First, does stretching of the principal fibre bundles generate tension and second, can differential pressures be developed within the tissues of the periodontium.

2. **Fuid Dynamic theory**

Given by Bien[19] in 1966 also called blood flow theory of tooth movement occurs as a result of alterations in fluid dynamics in periodontal ligament. Peridontal space is a confined space and passage of fluid in and out of this space is limited A hydrodynamic condition is created that resembles a hydraulic mechanism and a shock absorber. On application of force 'squeeze film effect' results**.** This results in reduced oxygen level on the compression side, escaping of blood gases into interstitial fluid creating a favorable environment for resorption.



3. The bone-bending theory

Farrar[20] was the first to suggest, in 1888, that alveolar bone bending plays a pivotal role in orthodontic tooth movement. 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 bend far more readily in response to force application.

Bioelectric signals in orthodontic tooth movement

In 1962, Bassett and Becker [21] proposed that, in response to applied mechanical forces, there is generation of electric potentials in the stressed tissues. These potentials might charge macromolecules that interact with specific sites in cell membranes or mobilize ions across cell membranes.

The concave side of orthodontically treated bone is electronegative and favors osteoblastic activity, whereas the areas of positivity or electrical neutrality—convex surfaces—showed elevated osteoclastic activity**. (Fig.3)**

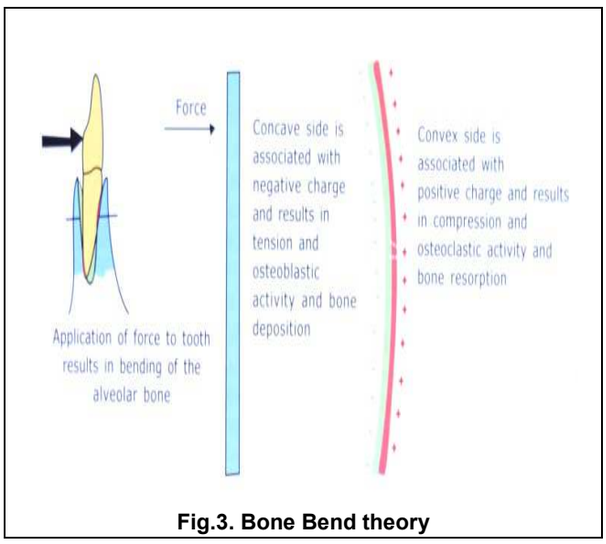


Fig.3. Bone Bend theory

Taken together, these findings suggest that bioelectric responses (piezoelectricity and streaming potentials) propagated by bone bending incident to orthodontic force application might function as pivotal cellular first messengers.

Piezoelectricity

Piezoelectricity is a phenomenon observed in many crystalline materials, in which a deformation of a crystal structure produces a flow of electric current as electrons

are displaced from one part of the lattice to another. Apart from inorganic crystals, it was found that organic crystals could also exhibit piezoelectricity.

The two unusual properties of piezoelectricity, which seem to not correlate well with orthodontic tooth movement are (1) a quick decay rate, where the electron transfer from one area to another after force application reverts back when the force is removed, which does not or should not happen once orthodontic treatment is over; and (2) production of an equivalent signal in the opposite direction upon force removal.[8] **(Fig.4)**

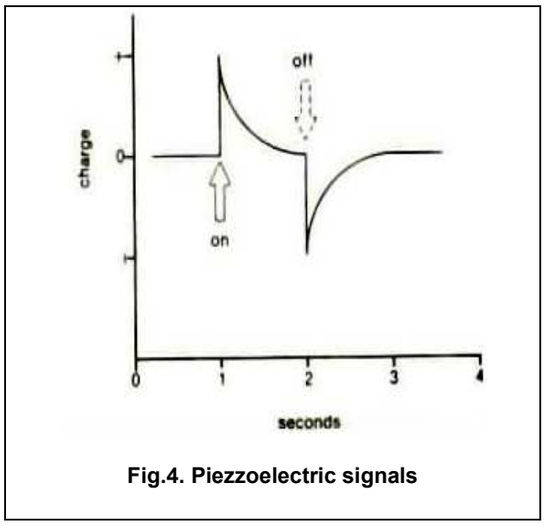
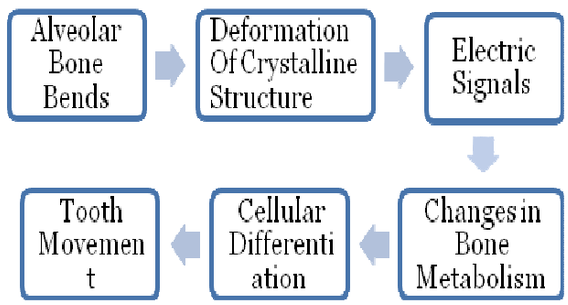


Fig.4. Piezzoelectric signals

Davidovitch et al., [22, 23] suggested recently that piezoelectric potentials result from distortion of fixed structures of the periodontium—collagen, hydroxyapatite, or bone cell surface. But in hydrated tissues, streaming potentials (the electrokinetic effects that arise when the electrical double layer overlying a charged surface is displaced) predominate as the interstitial fluid moves.
They further reported that mechanical perturbations of about one minute per day are apparently sufficient to cause an osteogenic response, perhaps due to matrix proteoglycan related strain memory.



Various signaling molecules and metabolites in orthodontic tooth movement

The acute inflammatory process that typifies the initial phase of orthodontic tooth movement is predominantly exudative, in which plasma and leukocytes leave the capillaries in areas of paradental strain. A day or 2 later, the acute phase of inflammation subsides and is replaced by a chronic process that is mainly proliferative, involving fibroblasts, endothelial cells, osteoblasts, and alveolar bone marrow cells. During this period, leukocytes continue to migrate into the strained paradental tissues and modulate the remodeling process.

Chronic inflammation prevails until the next clinical appointment, when the orthodontist activates the tooth-moving appliance, thereby starting another period of acute inflammation, superimposing it on the ongoing chronic inflammation.

For the patient, the periods of acute inflammation are associated with painful sensations and reduced function (chewing). A reflection of these phenomena can be found in the gingival crevicular fluid (GCF) of moving teeth, where significant elevations in the concentrations of inflammatory mediators, such as cytokines and prostaglandins, occur temporally.[24-26]

Prostaglandins as mediators of orthodontic tooth movement

Prostaglandins are a group of chemical messengers belonging to a family of hormones called eicosanoids(derived from arachidonic acid). They have reported a direct action of prostaglandins on osteoclasts in increasing their numbers and their capacity to form a ruffled border and effect bone resorption. Like other bone-resorbing agents, PGE_2 also stimulates osteoblastic cell differentiation and new bone formation, coupling bone resorption in vitro.

Leukotrienes

Leukotrienes(LTs) are also metabolites of arachidonic acid and are potent stimulators of bone resorption(Meghji et al[27] 1988). Within minutes, as paradental tissues become progressively strained by applied forces, the cells are subjected to other first messengers, the products of cells of the immune and the nervous systems. The binding of these signal molecules to cell membrane receptors leads to enzymatic conversion of cytoplasmic ATP and GTP into adenosine 3′, 5′-monophosphate (cyclic AMP [cAMP]), and guanosine 3′, 5′-monophosphte (cyclic GMP [cGMP]), respectively. These latter molecules are known as intracellular second messengers.[28]

The first messenger (a hormone or another stimulating agent) binds to a specific receptor on the cell membrane and produces an intracellular chemical second

messenger. This second messenger then interacts with cellular enzymes, evoking a response, such as protein synthesis or glycogen breakdown.

Two main second-messenger systems are now recognized—

1. The cyclic nucleotide pathway and the
2. Phosphatidyl inositol (PI) dual signaling system.[76]

These systems mobilize internal calcium stores and activate protein kinase C, respectively. The activation of specific protein kinases, together with an increase in intracellular calcium concentrations, might trigger a number of protein phosphorylation events, eventually leading to a cellular response. This response might comprise motility, contraction, proliferation, synthesis, and secretion.[28]

Vitamin D and Diacylglycerol

Another agent that has been identified as an important factor in orthodontic tooth movement is 1, 25, dehydroxychloecalciferol (1, 25, DHCC).[29,30] This agent is a biologically active form of vitamin D and has a potent role in calcium homeostasis.

The latter molecule has been shown to be a potent stimulator of bone resorption by inducing differentiation of osteoclasts from their precursors. In addition to bone-resorbing activity, 1, 25 DHCC is known to stimulate bone mineralization and osteoblastic cell differentiation in a dose-dependent manner.[31]

The local applications of 1,25(OH)2D3 could enhance the reestablishment of dental supporting tissues, especially alveolar bone, after orthodontic treatment.[84]

Evidently, increasing its concentration around paradental cells while they are subjected to orthodontic forces can evoke synergistic reactions by the cells, leading to rapid tooth movement.

Mechanotransduction

Involves two events

1. Detection of mechanical strain by bone cells
2. Transduction of mechanical strain into biochemical signal

1. Detection of mechanical strain by bone cells

After an orthodontic force is applied, the initial step is the detection of a mechanical strain. The cells responsible for sensing mechanical strains in bone have been considered to be osteoblasts, osteocytes, or both. These cells sense the strain in different ways which include streaming potential, strain sensitive ion channels and cytoskeleton reorganization.

2. Transduction of mechanical strain into biochemical signal

Applied mechanical forces are transduced from the strained extracellular matrix (ECM) to the cytoskeleton through cell surface proteins. The ECM molecules involved in this process include collagen, proteoglycans, laminin, and fibronectin. The transduction occurs by ECM binding to cell adhesion molecules (integrins) and other cell surface receptors. Adhesion of the ECM to these receptors can induce reorganization of the cytoskeleton, secretion of stored cytokines, ribosomal activation, and gene transcription.

Current concepts

Of the 3 components of the cytoskeleton—microfilaments, microtubules, and intermediate filaments—microfilaments are best suited to detect these changes. The major subunit protein of microfilaments is actin.

A family of integral proteins know as integrins, which are present on the cell membrane, connect the cytoplasm and nucleus to the ECM.

The integrins bind to fibronectin extracellularly and talin intracellularly, to provide a signal transduction pathway. A recent study identified expressions of integrins (specifically αVβ3 subunit) in osteoclasts associated with bone resorption and in odontoclasts associated with root resorption and in epithelial cell rests of Malassez in the PDL.[32]**(Fig.5)**

Translation of mechanical strain into biological signal

Regardless of how a mechanical signal is received, it must somehow influence the biochemical machinery of the cell. In the signaling cascade process, receptor activation is followed by second-messenger generation (adenosine 3',5' cyclic monophosphate [cAMP] and inositol trisphosphate [IP3]). These advance the signal to the nucleus through a series of kinases. In the nucleus, different second messengers account for the differential pattern of immediate early gene (IEG) expression. IEGs are among the earliest responses that can be measured at the transcription level. These can produce either cellular proliferation or differentiation.[33]

Different signalling molecules involved in load induced remodeling

Neurotransmitters

Leucocytes, other PDL cell types, including osteoblasts, fibroblasts, epithelial cells, endothelial cells, and platelets, can also synthesize and secrete the neurotransmitter molecules. The products of these cells can be classified into different categories, such as cytokines, growth factors, and colony-stimulating factors. Each of these ligands might act in an autocrine or a paracrine fashion, causing activation of target cells.

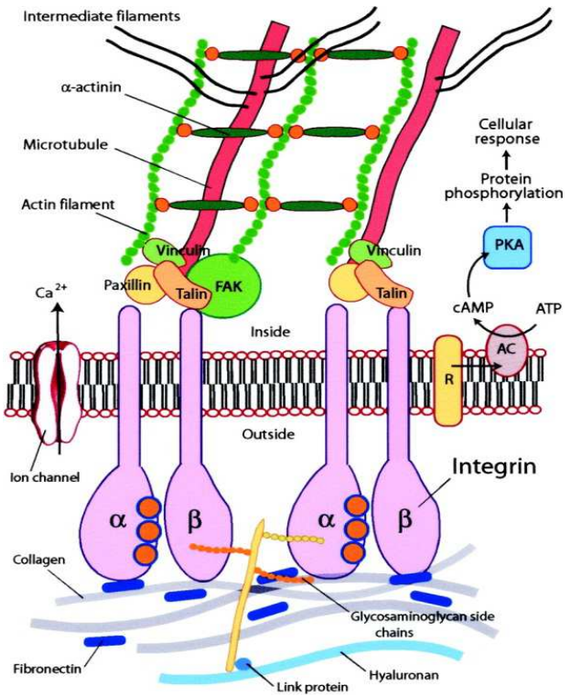


Fig.5 (From Murray C. Meikle 2006, The tissue, cellular, and molecular regulation of orthodontic tooth movement: 100 years after Carl Sandstedt, The European Journal of Orthodontics.Murray C MeikleEur J Orthod 2006;28:221-240)

Pain and tooth movement

Tooth movement-associated tissue remodeling, an inflammatory process, might induce painful sensations, particularly after activation of the orthodontic appliance. After 24 hours of force application, C-fos (immunoreactive neurons known to be involved in transmission of nociceptive information) expression is noted ipsilaterally in the trigeminal subnucleus caudalis and bilaterally in the lateral parabranchial nucleus.

Thus, there appears to be an indirect nociceptive mechanism operating during tooth movement that evokes a delayed and continuous nociceptive response, which is expected to limit masticatory function during active tooth movement.[34]

Role of cytokines in the RANKL/RANK/OPG system

The role of cytokines in the RANKL/RANK/OPG system in inducing bone remodeling was demonstrated recently.[35] The TNF-related ligand RANKL (receptor activator of nuclear factor-Kappa ligand) and its 2 receptors, RANK and osteoprotegrin (OPG), have been shown to be involved in this remodeling process. In the bone system, RANKL is expressed on osteoblast cell lineage and exerts its effect by binding the RANK receptor on osteoclast lineage cells. This binding leads to rapid differentiation of hematopoietic osteoclast precursors to mature osteoclasts.

OPG is a decoy receptor produced by osteoblastic cells, which compete with RANK for RANKL binding. The biologic effects of OPG on bone cells include inhibition of terminal stages of osteoclast differentiation, suppression of activation of matrix osteoclasts, and induction of apoptosis. Thus, bone remodeling is controlled by a balance between RANK-RANKL binding and OPG production**. (Fig.6)**

M-CSF (CSF-1) acts directly on osteoclast precursor cells to control their proliferation and differentiation. Stimulators of bone resorption such as $1,25(OH)_2$ vitamin D_3, parathyroid hormone, and interleukin-1 increase osteoclast formation by stimulating the expression of RANKL by osteoblasts/stromal cells **(Fig.6)**

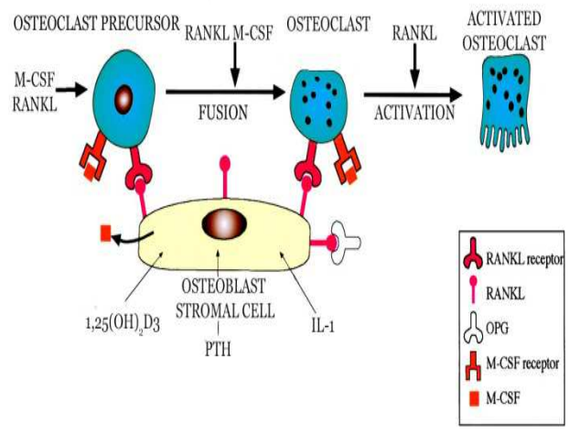


Fig.6(From Murray C. Meikle 2006, The tissue, cellular, and molecular regulation of orthodontic tooth movement: 100 years after Carl Sandstedt, The European Journal of Orthodontics.Murray C Meikle Eur J Orthod 2006;28:221-240)

Genetic mechanisms

Mechanical activation of bone cells is linked to many genes, which produce various enzymes, such as glutamate/aspartate transporter, inducible nitric oxide synthase, and prostaglandin G/H synthetase.

In-situ hybridization under conditions of physiologic tooth movement in rats showed site-specific expression of mRNA for osteonectin, osteocalcin, and osteopontin. Osteoclast and osteoblast progenitor cells had positive signals for osteonectin and osteocalcin. Osteopontin was expressed in osteoblasts and adjacent osteocytes along bone-resorbing surfaces. According to the investigators,[36] the primary responses to osteogenic loading are induction of differentiation and increased cell function, rather than an increase in cell numbers.

Orthodontic force-induced system adaptation occurs in the context of five related microstructures: PDL and alveolar bone ECM, cell membrane, cytoskeleton, matrix of nuclear proteins, and genome. Orthodontic force causes physical distortion of PDL and alveolar bone cells and the ECM, triggering many biochemical reaction cascades that affect all 5 micro-entities. ECM and cell distortion initiate structural and functional changes in extracellular, cell membrane, and cytoskeletal proteins.

Cytoplasmic signaling proteins Hh, sonic hedgehog, the TGF superfamily, and many TFs and ions (Ca, PO3) reach the nuclear matrix and then genome, resulting in enhanced or suppressed gene expression. Input becomes output as gene-expressed proteins, or protein synthesis inhibition, mobilize mitosis, cell motility, secretion of other proteins, and programmed cell death (apoptosis) that further modify cytoskeleton, cell membrane, and ECM. The process is continuous.

Recent reports proposed a role for nitric oxide as a marker of vascular signal transduction during the initial state of orthodontic tooth movement.[37-39] Nitric oxide is produced by various cells and is present in blood vessels, nerves, and PDL fibroblasts. This molecule has been reported to take part in bone remodeling and in the regulation of blood vessels and nerves.

The factors, systemic and local, affecting the remodeling process are listed in the Table II.

Pathways of tooth movement

On the basis of research in basic biology and clinical observations, Mostafa et al.,[18] proposed an integrated hypothetical model for tooth movement. This model consists of 2 pathways—I and II—that work concurrently to induce tooth movement.

According to these authors, pathway I represents the more physiologic response, because it is usually associated with normal bone growth and remodeling, whereas pathway II represents the generation of a local inflammatory response by orthodontic forces.

Pathway I

In pathway I, orthodontic force creates vectors of pressure and tension, leading to bone bending, generation of tissue bioelectric polarization, and subsequent bone remodeling. With the circumstantial evidence of prostaglandin synthesis, and with the evoked electric signals, Mostafa et al.,[18] stated that these phenomena, along with membrane electrical polarization by piezoelectric processes, act on the cell surface cyclic nucleotide pathway, generating changes in the levels of intracellular second messengers. This effect, in turn, leads to alterations in cell proliferation, differentiation, and activation.

Pathway II

The alternative pathway proposed by Mostafa et al.,[18] attributes orthodontic tooth movement to a classic inflammatory response after force application. Lymphocytes, monocytes, and macrophages invade these tissues, enhancing prostaglandin release and hydrolytic enzyme secretion. The local elevation in prostaglandins and a subsequent increase in cellular cAMP concentrations increase osteoclast activity. Secreted hydrolytic enzymes, such as collagenase, dissolve the mechanically strained ECM.

Recent model

Recent reports by Jones et al[40,41]detailed events in bone cells immediately after the application of mechanical stress. That report is based on the assumption that stresses in any form either compressive, tensile, or shear will evoke many reactions in the cell, leading to the development of strain.

Table.2. Factors affecting bone-remodeling process

Hormones	• Polypeptides • Parathyroid hormones • Calcitonin • Insulin • Growth hormone • Steroid • 1,25, dihydroxy vitamin D_3 • Glucocorticoids • Sex steroids • Thyroid hormones		These are basically responsible for Bone homeostasis
Growth factors	• Insulin-like growth factors I and II • Transforming growth factor β • Fibroblast growth factor		These three are involved in many biologic activities, including cell growth, differentiation, and apoptosis, as well as in developmental processes and bone remodeling.
	• Platelet derived growth factor		This is important in the process of mitogenesis in bone cells.
	• Connective tissue growth factors		It stimulates proliferation of osteoblast precursors, and promotes mineralization of new bone by osteoblasts
Cytokines	**Bone resorption** • Interleukin-1 • Interleukin-6 • Interleukin-11 • Tumor necrosis factor • Osteoclast differentiating factor	**Bone Apposition** • Interleukin-4 • Interleukin-13 • Interleukin-18 • Interferon-γ • Osteoprotegrin	They interact with the other factors in bone remodeling.
Colony-stimulating factors	• M-CSF • G-CSF • GM-CSF		These have implication in bone remodeling through osteoclast formation and thereby during tooth movement
	• Prostaglandins • Leukotriens		These two are involved in bone resorption
Others	• Nitric oxide		involved in bone Remodeling

The sequence of events after the application of mechanical forces with the help of orthodontic appliances can thus be outlined as:

- Movement of PDL fluids from areas of compression into areas of tension.
- A gradual development of strain in cells and ECM in involved paradental tissues.
- Direct transduction of mechanical forces to the nucleus of strained cells through the cytoskeleton, leading to activation of specific genes.
- Release of neuropeptides (nociceptive and vasoactive) from paradental afferent nerve endings.
- Interaction of vasoactive neuropeptides with endothelial cells in strained paradental tissues.
- Adhesion of circulating leukocyte to activated endothelial cells.
- Plasma extravasation from dilated blood vessels.
- Migration by diapedesis of leukocytes into the extravascular space.
- Synthesis and release of signal molecules (cytokines, growth factors, and CSFs) by the leukocytes that have migrated into the strained paradental tissues.
- Interaction of various types of paradental cells with the signal molecules released by the migratory leukocytes.
- Activation of the cells to participate in the modeling and remodeling of the paradental tissues.

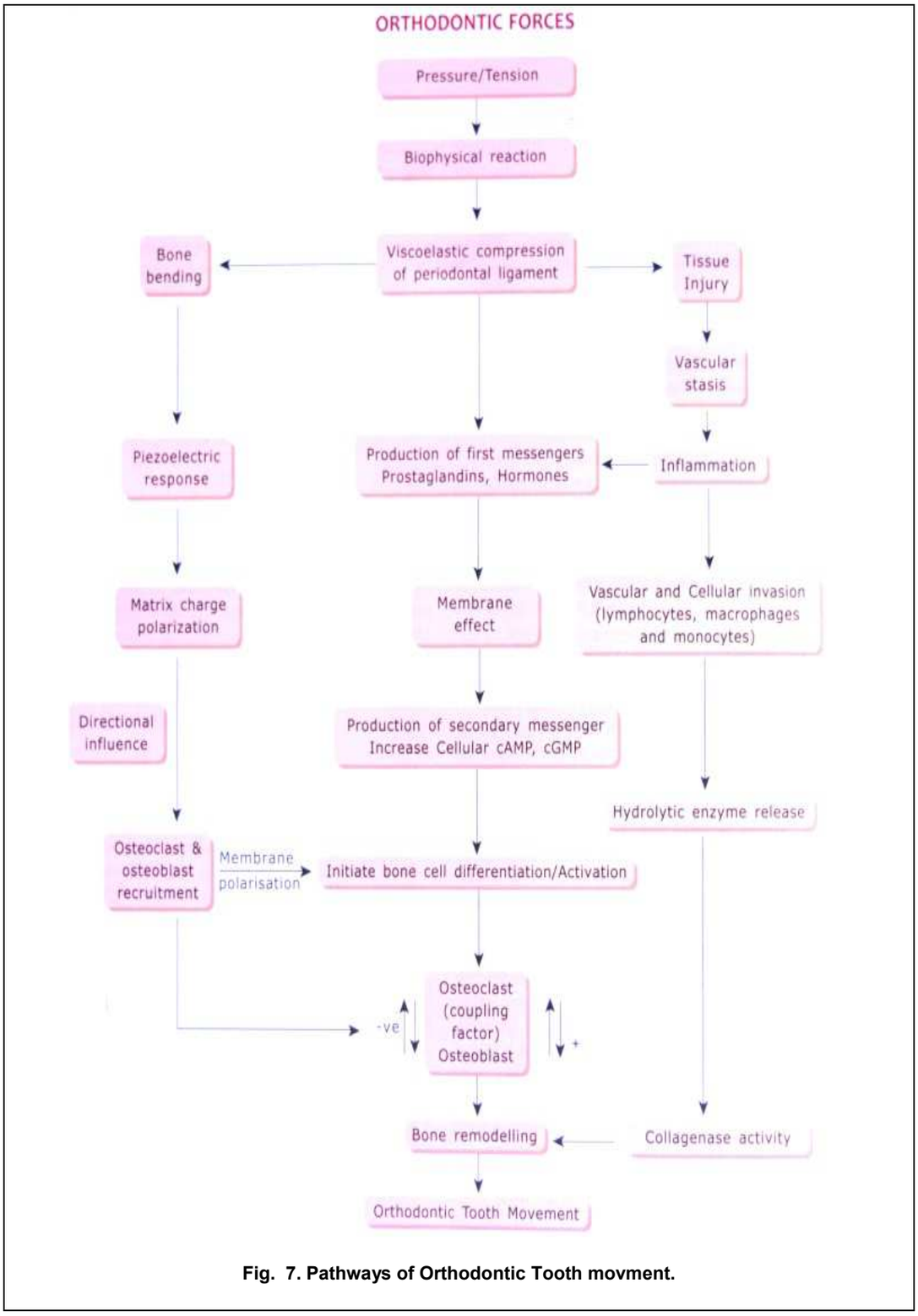


Fig. 7. Pathways of Orthodontic Tooth movment.

Biomarkers of bone remodeling in gingival crevicular fluid

GCF arises at the gingival margin and can variously be described as a transudate or an exudate. The total fluid flow is between 0.5 and 2.4 mL per day. Recent studies in orthodontic tooth movement have used GCF because of its noninvasive nature and ease of repetitive sampling from the same site with the help of platinum loops, filter paper strips, gingival washings, and micro pipettes.

The fluid is used to analyze various biochemical markers such as prostaglandin production and the action of various extracellular and intracellular factors, such as IL-1, IL-6, TNF-α, epidermal growth factors, β_2 microglobulin, cathepsin, aspartate aminotransferease, alkaline phosphatase, and lactate dehydrogenase.

Tissue reactions with varied force applications

Orthodontics is based on application of force on the teeth, under the influence of which tooth movement occurs. The duration and character of force have great influence in orthodontic mechanotherapy, alterations in which can produce varied tissue reactions.

Continuous, Interrupted, and Intermittent forces

Most contemporary fixed orthodontic appliances use light continuous forces as part of orthodontic mechanotherapy to effect tooth movement. However, a continuous force can subside rapidly and thus be interrupted after a limited period of time, such as in torquing movements by an edgewise archwire or labial movement of blocked-out maxillary lateral incisor with the help of ligation. It is not always possible to distinguish between continuous and interrupted movements, and the latter act for only comparatively short periods.

Nevertheless, it appears that this kind of a force, that starts in a continuous mode and then becomes interrupted, is biologically favorable, particularly when its initial magnitude is low. In such a case, hyalinized zones might develop in sites of compressed PDL, but, as soon as this necrotic tissue is eliminated and the tooth moves, the force decreases quickly. Finally, the archwire retains its passivity for a while, during which time (rest period) there will be an opportunity for calcification of the newly formed osteoid layer.

This rest period between appliance activations is the time used by the tissues for reorganization. This rest can promote favorable cell proliferation for further tissue changes when the appliance is activated again. The characteristic feature of continuous/interrupted tooth movement is formation of new bone layers in the richly cellular tissue at the entrance of open marrow spaces as soon as the tooth movement stops.

Typical intermittent forces act as either an impulse or a shock of short duration, or for short periods with a series of interruptions. These forces are mainly produced by removable appliances, which deliver force periodically. Examples of such a system are springs resting on tooth surfaces. Intermittent force results in small compression zones in the PDL, short hyalinization periods, and lengthy rest periods when the appliance is removed intermittently. During this time, the tooth moves back to the tension side and remains in normal function. This mode of treatment can improve the paradental circulation and promote an increase in the number of PDL cells, because its fibers usually retain a functional arrangement.

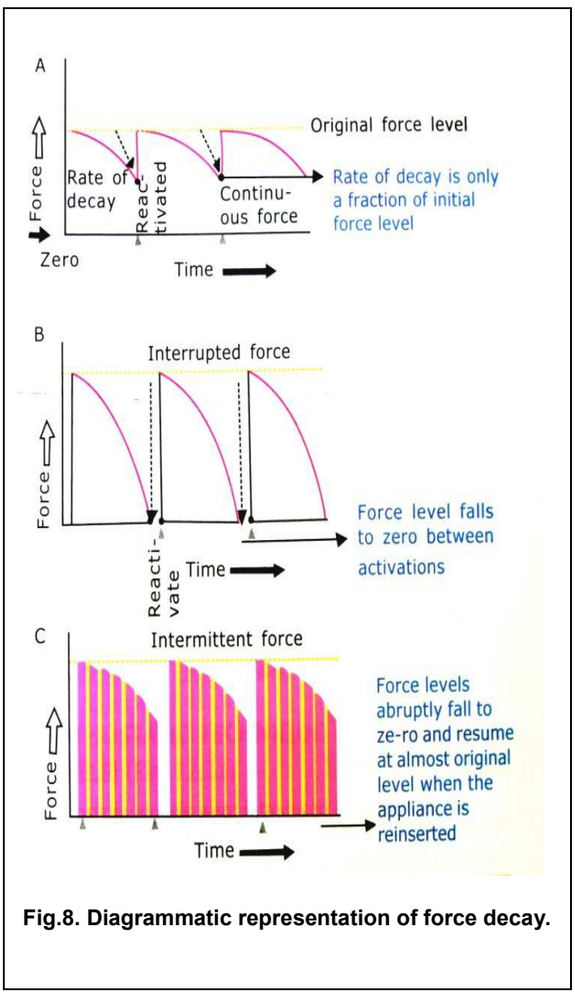


Fig.8. Diagrammatic representation of force decay.

Duration of Clinical application

Clinical experience suggests that successful tooth movement requires a threshold of force duration of about 6 hours per day. It was determined in an experiment on cats that it takes about 3 hours for significant elevations in cAMP in extracts of alveolar bone and PDL, after sustained applications of tipping forces to the maxillary canines.[42]

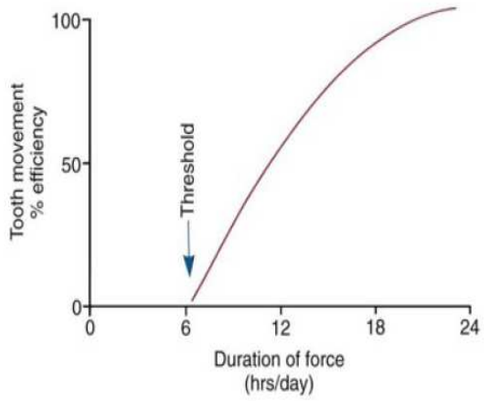


Fig.9. Theoretical plot of tooth movement efficiency versus duration of force in hours per day. Continuous force, 24 hours per day, produces the most efficient tooth movement, but successful tooth movement can be produced by shorter durations, with a threshold at about 6 hours.

ADVERSE EFFECTS OF ORTHODONTIC FORCE

The deleterious effects include caries, gingivitis, marginal bone loss, pulpal reactions, root resorption, and allergic reactions to appliance materials. Can be classified as

Gingival problems
Root resorption
Pulpal reactions

Gingival problems

Fixed-appliance orthodontics has been shown to produce deleterious effects on the periodontium, ranging from gingivitis to bone loss. The cementation of orthodontic bands or resin-bonded attachments can evoke local soft tissue response. This response is mainly due to plaque accumulation and the proximity of these attachments to the gingival sulcus. Another long-term complication of orthodontic treatment is gingival recession. The bacterial plaque was composed mainly of spirochetes and motile rods.

Root resorption

Orthodontic force application can sometimes evoke excessive resorption of root cementum, proceeding into the dentin, eventually shortening the root length—a process called root resorption.

The magnitude of an orthodontic force and rigid fixation of the archwire to the brackets could be considered the most important factors predisposing a tooth to the root resorption.[43]Maxillary central incisors, are the most prone to the process, followed by the maxillary molars and the canines. In the mandibular arch, the most prone teeth are the lateral and central incisors.[44,45]Some repair occurs, including smoothing and remodeling of cemental surfaces and the return of the PDL width to normal. Original root contours and lengths are never reestablished, but the function of the tooth apparatus is usually not severely affected by the loss of root length.

Pulpal reactions

Various experiments have demonstrated an initial decrease in blood flow, lasting approximately 32 minutes, followed by an increase in blood flow (lasting 48 hours). It may lead to congested and dilated blood vessels, and edema of pulpal tissue in their histologic observations. The progression of the inflammatory process in human pulp fibroblasts apparently depends on stimulation by neuropeptides and production of inflammatory cytokines, such as IL-1, IL-3, IL-6, and TNFα.

A recent report described apoptosis in dental pulp tissues of rats undergoing orthodontic treatment.[46] Perinetti et al[47] demonstrated that an enzyme, aspartate aminotransferase (which is released extracellularly upon cell death), is significantly elevated after orthodontic force application.

The other deleterious effects include

- Pain
- Allergic reactions
- Mobility
- Alveolar bone height

Pain

If appropriate force (not heavy) is applied, the patient feels little pain or nothing immediately. However pain develops after several hours. The patient feels mild aching sensation and the teeth are quite sensitive to pressure.The pain usually lasts for 2 – 4 days and disappears until the appliance is reactivated. For most of the patients, the pain associated with the initial activation of the appliance is most severe. Pain is due to the development of ischemic areas in the PDL.The pain is directly proportional to the area of PDL that has undergone sterile necrosis (hyalinization). So heavier forces produce larger areas of hyalinization and greater pain. Pain can be managed using analgesics like acetaminophen.[48]

Allergic reaction

Some patients may develop allergic reactions to stainless steel which contains nickel. Allergic reactions manifest as widespread erythema and swelling of oral tissue which develops 1 – 2 days after starting the treatment . In such patients, stainless steel appliances (brackets, bands, wires etc) should be substituted with titanium appliances and nickel titanium or steel wires should be substituted with beta titanium.[49]

Mobility

Mobility is due to widening of PDL space during orthodontic treatment and temporary disorganization of the fibers in the PDL. Moderate increase in mobility is an expected response of orthodontic treatment. Heavier Force causes greater degree of undermining resorption which leads to excessive mobility.

Excessive mobility indicates that there is heavy force acting on the tooth. If the tooth becomes extremely mobile, force should be discontinued until the mobility decreases to moderate levels. Excessive mobility will usually correct itself without permanent damage.

Effect on alveolar bone height:

Excessive loss of crestal bone height is almost never seen as a complication of orthodontic tooth movement. Loss of alveolar crest height in one large series of patients averaged less than 0.5mm and almost never exceeded 1mm, with the greatest changes at extraction site.[50]

Post treatment changes in periodontium.

Orthodontic forces are known to produce pressure and tension regions in the PDL and alveolar bone. This strain alters the affected tissues' vascularity and blood flow, providing a favorable microenvironment for either tissue deposition or resorption.

During the recovery period, the return of periodontal dimensions to normal values is regulated by the rate and direction of alveolar bone turnover.[51] Capability of adaptive response to applied orthodontic force rests in the DNA of periodontal ligament (PDL) and alveolar bone cells.

CONCLUSION

After 100 years, we have reasonably good understanding of the sequence of events involved in orthodontic tooth movement at the tissue and cellular levels on both the tensile and compression sides of the periodontium.

Rapid advances in all biological fields have enabled us to better understand the mechanisms involved in orthodontic tooth movement. It is evident that, at different stages of tooth movement, different combinations of cell-cell and cell-matrix interactions occur; these determine the nature of the remodeling changes.

A better understanding of the relationship between genes and transcription factors in controlling bone and PDL remodeling will expand our knowledge, and might strengthen our clinical capabilities.

Above all, this growing body of knowledge on the response of our cells to mechanical loads should illuminate useful paths in clinical orthodontics and assist us in identifying and discarding harmful methods of mechanotherapy.

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. Future orthodontics will, therefore, increasingly become biologically correct and, consequently, patient-friendly.

EFFECTS OF DRUGS ON INDUCED TOOTH MOVEMENT

	EFFECTS ON BONE METABOLISM	EFFECTS ON TOOTH MOVEMENT
Non-Steroidal Anti-Inflammatory Drugs		
Aspirin	↓ bone resorption	↓ tooth movement
Diclofenac	↓ bone resorption	↓ tooth movement
Ibuprofen	↓ bone resorption	↓ tooth movement
Indometacin	↓ bone resorption	↓ tooth movement
Celecoxib	↓ bone resorption (in vitro)	no influence
Corticosteroids	↑ bone resorption (chronic use)	↑ tooth movement
Bisphosphonates	↓ bone resorption	↓ tooth movement
Acetaminophen	unproven	no influence

EFFECTS OF SYSTEMIC FACTORS ON INDUCED TOOTH MOVEMENT

	Effects on Bone Metabolism	Effects on Tooth Movement
Estrogen	↓ bone resorption	↓ tooth movement
Androgen	↓ bone resorption	unproven
Relaxin	↑ bone resorption	↑ tooth movement
Thyroid hormones	↑ rate of bone remodeling	↑ tooth movement
	↑ bone resorption	↓ root resorption
Parathyroid hormone	↑ bone resorption	↑ tooth movement
Vitamin D	↑ rate of bone remodeling	↑ tooth movement
	↑ bone resorption	

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Corresponding Author

Dr. Sivareddy Rohit Reddy
Post Graduate student
Department of Orthodontics,
Narayana Dental College and Hospital,
Nellore.
Email: rohitreddy190@gmail.com