Republic of Iraq
Ministry of Higher
Education and Scientific
Research
University of Baghdad

Biology of Tooth Movement

A Project Submitted to
The College of Dentistry, University of Baghdad, Department of orthodontic in Partial Fulfillment for the Bachelor of Dental Surgery

By

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B.D.S., M.Sc.

May 2022

DEDICATION

TO EVERY TIME I LOOKED TO PEOPLE I LOVED AND SEE TIREDNESS IN THEIR EYES TO EVERY TIME THEY PUT ME BACK IN THE WAY AND PUSH TO CONTINUE TO MY GRANDMOTHER, MOTHER ,FATHER AND MY UNCLE AHMED.

Certification of the supervisor

I certify that this project entitled "**Biology of Tooth Movement**" was prepared by the Fifth-Year student **Hibah Hitham Adnan** under my supervision at the College of Dentistry/University of Baghdad in partial fulfilment of the graduation requirements for the Bachelor degree in dentistry.

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Acknowledgment

First of all I would like to thank **God** for blessing me to here today.

I would like to thank *Prof.Dr. Raghad Abdulrazaq Al.Hashimi*, the Dean of College Of Dentistry, University Of Baghdad. My deepest thank and respect to *Prof. Dr.Yassir Abdul-khadem Yasser*, Head of Orthodontic Department. I would like to thank my Supervisor *Dr. Alaa Faleh* who helped me throw the course of my project. I really cannot find enough words to express my thanks for her support, help, advice and valuable instruction.

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List of Abbreviation

Abbreviation	Meaning
OTM	Orthodontic tooth movement
Cbfa 1	Core binding factor alpha 1
Runx-2	runt-related transcription factor 2 (protein)
ClCN7	Chloride channel 7
RANK	Receptor activator of nuclear factor k
RANKL	Receptor activator of nuclear factor k ligand
PDL	Periodontal ligament
PGE-2	Prostaglandin E2
CGRP	Calcitonin gene-related peptide
V	Versus
ATP	Adenosine tri phosphate
MMP	Matrix metaloprotenase
MMP-2	Matrix metaloprotenase
ECM	Extracellular matrix

Introduction

Tooth movement by orthodontic force application is characterized by Remodeling changes in dental and paradental tissues, including dental pulp, periodontal ligament (PDL), alveolar bone, and gingiva. These tissues, when exposed to varying degrees of magnitude, frequency, and duration of mechanical loading, express extensive macroscopic and microscopic changes. 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 **(Reitan, 1960)**.

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 **(Rygh and Brudvik, 1995)**.

Remodeling changes in paradental tissues are considered essential in effecting orthodontic tooth movement. 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 **(Krishnan and Davidovitch, 2006)**.

The underlying biomechanical and biological mechanisms of orthodontic tooth movement are essential for efficient and safe orthodontic treatment. However, the detailed mechanisms of OTM still remain to be elucidated. In recent years, abundant new findings related to biomechanical and biological changes in periodontium during OTM have been published. Orthodontic treatment is aiming to move malpositioned teeth to an appropriate position through the Remodeling of the periodontium stimulated by orthodontic force **(Will,2016).**

Aims of the study:

The aims of this study is to shed light on the biological effects of force of the orthodontic treatment and the effect of light and heavy force on the periodontal ligament and the alveolar bone.

Chapter One

Review of the literature

1.1Alveolar bone:

A better name for the alveolar bone is dental bone or tooth bone. Although the bulk of the alveolar bone is trabecular bone, it does contain a plate of compact bone adjacent to the periodontal ligament called the lamina dura. The PDL pierces through the lamina dura and anchors to the alveolar bone, with the other end connected to the cementum **(Blum, 2002)**. The inner (lingual) and outer (labial) cortical plates are also composed of compact bone. Alveolar bone is a mineralized connective tissue and consists of mineral tissue, organic matrix and water. In the alveolar bone, 23% is mineralized tissue; 37% is the organic matrix which mostly is collagen, and the other 40% is water **(Moss *et al.*, 1997).**

1.1.1 Cells

Multiple cell types are responsible for the homeostasis and functions of the alveolar bone. The most obvious cell types are osteoblasts, osteocytes and osteoclasts. However, other cell types are also important, including adipocytes, endothelial cells that form the lining of blood vessels and immune competent cells such as macrophages **(Teitelbaum, 2000).**

Osteoblasts are mononucleated and specialized cells that are responsible for bone apposition. Osteoblasts and fibroblasts share a key functional similarity in that they both synthesize type I collagen matrix. Osteoblasts, however, distinguish from fibroblasts by expressing Cbfa1 or Runx2 that is a master switch for the differentiation of stem/progenitor cells into osteoblasts **(Ehrlich and Lanyon, 2002)**. Although myriad genes control the complex process of osteogenesis, Cbfa1 or Runx2 is the earliest transcriptional factor and signals the initiation of bone formation **(Ducy *et al.*, 2000)** .

Bone is a dynamic tissue and constantly remodels by osteoblasts and osteoclasts, the two of which function by cross talk and signaling. The number of osteoblasts decreases with age, affecting the balance of bone deposition and resorption and potentially leading to osteoporosis **(Dippolite *et al.*,1999)** .

Osteocytes are the most numerous cells in mature bone, and can live as long as the organism itself (**Mullender *et al.*, 1996).**Osteocytes are derived from functional osteoblasts that are embedded in mineralized bone in the process of bone apposition. The space that an osteocyte occupies is called a lacuna. Hydroxyapatite, calcium carbonate and calcium phosphate is deposited around osteocytes (**Noble, 2008).**Whereas osteoblasts (and osteocytes) derive from the mesenchymal/mesodermal lineage, osteoclasts originate from an entirely different source: the hematopoietic/monocyte lineage (**Nijweide *et al.*,1986).**

Osteoclast are formed by the fusion of multiple monocytes, and, therefore, multinucleated **(Boyle *et al.*, 2003)** .Their unique properties include adherence to endosteal bone surfaces, and secret acid and lytic enzymes that destroy mineral and protein structures. An array of transcription factors controls osteoclast differentiation (**Teitelbaum, 2000)**. Osteoclasts are characterized by robust expression of tartrate resistant acid phosphatase, specified osteoprotegerin, cathepsin K, and chloride channel 7 (ClCN7) (**Harada and Rodan, 2003)** . Osteoprotegerin blocks nuclear factor kappa B (RANK) and RANK ligand (RANKL) docking; cathepsin K destroys bone matrix proteins, whereas chloride channel 7 maintains osteoclast neutrality by shuffling chloride ions through the cell membrane. RANKL, a key regulator of osteoclast function is synthesized by osteoblasts and promotes osteoclast differentiation, suggesting that osteoblasts control osteoclast differentiation, but not function **(Karsenty, 2003).**

1.1.2 Matrix Proteins:

In the alveolar bone, the most abundant extracellular matrix component is collagen type I**.** In addition, alveolar bone contains noncollagenous proteins such as osteocalcin, osteopontin, osteonectin, bone sialoprotein and fibronectin as well as proteoglycans including lumican, fibromodulin, decorin, biglycan and versican **(Delaisse *et al.*, 1993).**

Osteocalcin acts as a hormone and causes pancreatic beta cells to release more insulin, and at the same time directs adipocytes to release adiponectin, which increases sensitivity to insulin **(Lee *et al.*, 2007).**

Osteopontin is a phosphorylated, sialic acid containing glycoprotein that can be from the mineralized bone matrix. Matrix metalloproteinase-1, metalloproteinase-2 and cathepsin are considered to be particularly important in bone resorption (**Bossard *et al.*, 1996).**

They cleave type I collagen most efficiently within the triple-helical body of the native conformation and is active at neutral pH, whereas cathepsin K degrades type I collagen in a similar manner but is active at low pH in the acidic microenvironment beneath the ruffled border of osteoclasts **(Mao, 2010).**

Osteonectin is found in many tissues. This does not exclude the possibility that it is "essential" for mineralization and bone deposition while bone sialoprotein appear to be sites of initial mineralization **(Bianco, 1994)**.

Decorin and biglycan, the small proteoglycans of bone and cartilage both bind to apatite crystals, but biglycan binds with greater specificity and higher affinity than decorin **(Bidanset et al., 1992).**

1.2 Periodontal ligament:

The PDL connects the cementum to the alveolar bone by bundles of type I collagen named Sharpey's fibers. The width of a periodontal ligament in

homeostasis is approximately 0.15–0.38 mm, depending on the tooth type **(Mao *et al.*, 2012)** .

The PDL has two primary functions to transmit and absorb mechanical stress and to provide vascular supply and nutrients to the cementum, alveolar bone and the PDL itself **(Krishnan and Davidovitch, 2006**). The PDL is a connective tissue and shares certain similarities with tendons and other ligaments in the appendicular skeleton (**Nanci and Bosshardt, 2006).**

1.2.1 Cells

Fibroblasts constitute about 50–60% of the total PDL cellularity **(McCulloch and Bordin, 1991)**. PDL fibroblasts consist of multiple subpopulations and thus are heterogeneous. PDL cells experience and respond to mechanical stresses such as those in orthodontic tooth movement **(York and Hunter, 2004).**

Other PDL cells include macrophages, lymphocytes and endothelial cells that form the lining of blood vessels **(Naveh *et al.*, 2012)**. When forces are applied to the tooth, PDL fibroblasts react by activating stretch-sensitive Ca 2+ - permeable channels and increase actin polymerization and yield a rapid and transient increase in C-Fos expression that in turn stimulates their proliferation and differentiation **(Yamaguchi *et al.*, 2001)** . Activated fibroblasts secrete plasminogen activator as well as its inhibitor, matrix metalloproteases and their inhibitors, cytokines (PGE-2) and interleukin-6 **(Lekic *at al.*, 2001)**.

The PDL further consists of defense cells such as macrophages and mast cells. Epithelial remnants of Malassez are descents of dental epithelium cells in the PDL, following amelogenesis **(Mao *et al.*, 2012)**.

In addition, osteoblasts, osteoclasts and cementoblasts are present in the PDL and participate in the homeostasis of the periodontium. The osteoblasts and

osteoclasts reside in the PDL on the surface of lamina dura and in endosteal surfaces of the alveolar bone, and are also responsive to mechanical stresses. PDL and alveolar bone readily remodel in homeostasis and orthodontic tooth movement. Osteoblasts in the PDL and alveolar bone are replaced every few months **(Davidovitch,1991)**.

Most biological tissues adapt and self-renew, serving as an indication that there must be stem cells, which replenish and replace terminally differentiated cells that periodically undergo apoptosis. Stem cells are immature and unspecialized cells that can

(1) self-renew

(2) undergo asymmetrical differentiation:

producing precise copies of stem cells and at the same time differentiate into specialized cell types such as fibroblasts and osteoblasts (**Sonoyama *et al.*, 2006)**.

There are two types of dental stem cells: epithelial stem cells and mesenchymal stem cells. Epithelial and mesenchymal stem cells intimately interact during tooth development: epithelial stem cells giving rise to ameloblasts, where as mesenchymal stem cells differentiating into fibroblasts, odontoblasts, cementoblasts, osteoblasts, and perhaps other cells in the periodontal ligament (**Bluteau *et al.*, 2008)**.

Periodontal ligament cells have been studied for decades, due to their significance inperiodontal disease and also orthodontic tooth movement. Dental follicle cells, which originate from neural crest derived mesenchyme, differentiate into cells that form the periodontium and are present in the developing tooth germ prior to root formation **(Yao *et al.*, 2008)**.

Among fibroblast-like cells in the periodontal ligament, stem/progenitor cells have been identified **(Seo *et al.*, 2004)** . Typically, soft tissue is scraped from the root of an extracted tooth and enzyme-digested to release a small number of cells. Morphologically, it is impossible to separate PDL fibroblasts from PDL stem/progenitor cells. Nonetheless, certain PDL cells yield progenies upon single cell colony assay and can differentiate into multiple cell lineages in vitro. In chemically defined culture conditions, specific PDL cells differentiate into cementoblast-like cells, adipocytes, and collagen-forming cells. When transplanted into immune-compromised rodents, PDL fibroblast-like cells generated a cementum/PDL-like structure. To date, little is known how PDL stem/progenitor cells respond to mechanical forces such as those in orthodontic tooth movement **(Yao *et al.*, 2008)**.

1.2.2 Fibrous Matrix

Collagen fibers, reticulin fibers and oxytalan fibers form the PDL fibrous matrix. Collagen accounts for over 90% PDL fibers. Type I collagen fibers in the PDL are 45–55 nm in diameter and have somewhat uniform morphology **(Macneill *e1 al.*, 1998)**.

PDL fiber bundles are arranged in directions that reflect their functional properties. PDL collagen fibers grow separately from bone and cementum surfaces, and gradually elongate and approximate each other **(Sawhney and Howard, 2004)**. Upon application of orthodontic forces, PDL nerve fibers release calcitonin gene-related peptide (CGRP) and substance P **(Hall *et al.*, 2001)** .

CGRP and substance P serve as vasodilators and stimulate plasma extravasation and leukocyte migration. CGRP has been shown to induce bone formation through stimulation of osteoblasts and inhibition of osteoclast activity **(Anderson and Seybold, 2004).**

1.3 Orthodontic versus orthopedic force

Orthodontic force has been defined as "force applied to teeth for the purpose of effecting tooth movement, generally having a magnitude lower than an orthopedic force," whereas orthopedic force is defined as "force of higher magnitude in relation to an orthodontic force, when delivered via teeth for 12 to 16 hours a day, is supposed to produce a skeletal effect on the maxillofacial complex. These definitions show that there is no clear distinction between orthodontic and orthopedic forces, even in terms of magnitude; furthermore, many widely variable arbitrary suggestions about the characteristics of orthodontic forces abound in the literature **(Oshiro *et al.*, 2002).**

Orthodontic mechanotherapy is mainly aimed at tooth movement by remodeling and adaptive changes in paradental tissues **(Verna and Melsen, 2003).**To effect this outcome, only small amounts of force—20 to 150 g per tooth—might be required but craniofacial orthopedics is aimed at delivering higher magnitudes of mechanical forces— more than 300 g—in attempts to modify the form of craniofacial bones **(Kanzaki *et al.*, 2004).**

The appliances, called craniofacial orthopedic devices, deliver macro-scale mechanical forces, which produce micro-structural sutural bone strain and induce cellular growth response in sutures **(Roberts *et al.*, 2006).**

1.4 Optimal Orthodontic force

Orthodontic tooth movement is mediated by coupling bone resorption and deposition in compressed and stretched sides of the PDL, respectively. Orthodontic forces, by virtue of altering the blood flow and localized electrochemical environment, upset the homeostatic environment of the PDL

space. This abrupt alteration initiates biochemical and cellular events that reshape the bony contour of the alveolus **(Toms *et al.*, 2002)**

It is assumed that an optimal orthodontic force moves teeth efficiently into their desired position, without causing discomfort or tissue damage to the patient. Primarily, an optimal force is based on proper mechanical principles, which enable the orthodontist to move teeth without traumatizing dental or paradental tissues, and without moving dental roots redundantly (round tripping), or into danger zones (compact plates of alveolar bone). 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 **(Karsenty, 2003).**

However, Burstone, reported that orthodontic forces are never distributed equally throughout the PDL, and Storey, observed that some trauma is always associated with applied orthodontic forces, even light ones. Moreover, it is impossible, with the available instrumentation, to measure precisely the amount of force applied to roots or parts thereof under any mode of treatment **(Storey, 1973; Burstone, 1990).**

At present, it can be stated that, to engender adequate biological response in the periodontium, light forces are preferable, because of their ability to evoke frontal resorption of bone. Unlike light forces, heavy forces often cause necrosis (hyalinization) of the PDL and undermining bone resorption and have been implicated in root resorption **(Daskalogiannakis, 2000).**

They studied distal movement of canines in orthodontic patients and suggested that there is an optimum range of pressure (150-200 g) on the tooth-bone interface that produces a maximum rate of tooth movement. Pressure below this range produced no tooth movement. When the force was increased above

optimum, the rate of tooth movement was decreased and finally approached zero within a week as in (**figure 1) (Karsenty, 2003)**.

The current concept of optimum force views it as an extrinsic mechanical stimulus that evokes cellular response that aims to restore equilibrium by remodeling periodontal supporting tissues. So the mechanical input that leads to the maximum rate of tooth movement with minimal irreversible damage to root, PDL, and alveolar bone is considered to be optimal **(Oppenheim, 1998).**

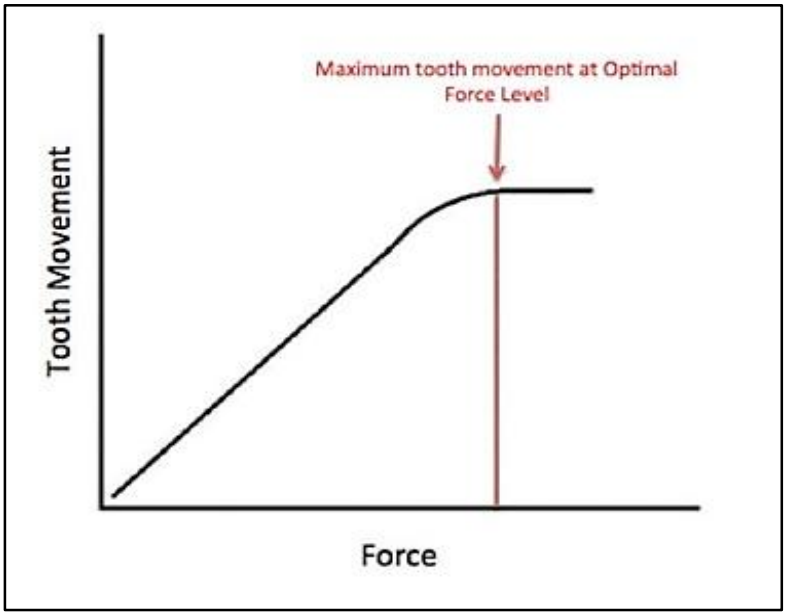


Figure 1: Optimal orthodontic force **(Proffit *et al., 1999)***

This concept means that there is a force of certain magnitude and temporal characteristics (continuous v intermitted, constant v declining) capable of producing a maximal rate of tooth movement, without tissue damage, and with maximum patient comfort. According to this concept, the optimal force might differ for each tooth and for each patient **(Proffit *et al* 1999; Ren *et al.*, 2003)**

1.5 Theories of tooth movement:

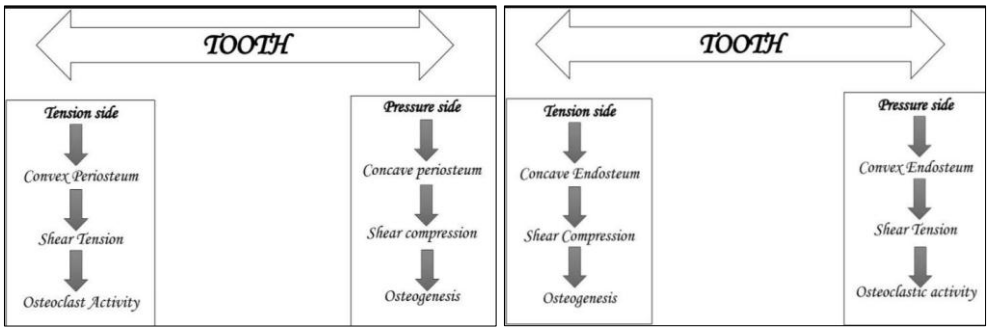
The orthodontic force applied on the tooth structure results in a tooth movement by deposition and resorption of alveolar bone called as remodeling. This force is converted into biological activity, although this activity is not fully understood but three possible theories of tooth movement are advocated. They are: **(Sabane et al., 2016).**

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

1. Bone-bending theory

Farrar, stated that when an orthodontic force is applied to the tooth, it is transmitted to all tissues near the area of force application **(Farrar, 1888).** These forces bend bone, tooth and the solid structures of periodontal ligament **(Kashyap, 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 as in (**Figure 2)** presents the effect of applied forces on periosteum and endosteum respectively **(Baumrind, 1969).**



(a) **(b)**

Figure 2: Flowchart (a) presenting the effect of applied forces on Periosteum (b) presenting the effect of applied forces on Endosteum **(Perinetti *et al.*, 2003).**

2. Biological electricity theory

This theory proposed that 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 piezoelectric signals **(Bassett and Becker in 1962).**

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 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 as shown in **Figure 3** which explains the Bio-electric theory of tooth movement. The periodontal fibers generating stress on bone during orthodontic forces was evaluated with the nature of electrochemical 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).**

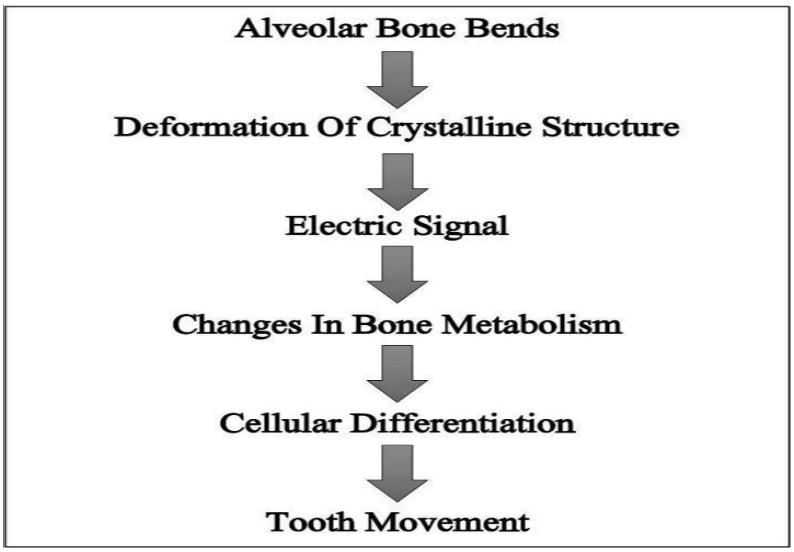


Figure3: bioelectric theory **(Sabane et al., 2016).**

The exogenous electric current along with orthodontic forces accelerates the iorthodontic tooth movement. This suggests that the piezoelectric response due to bone bending might function as "cellular first messenger" **(Davidovitch et al., 1980a; Davidovitch et al., 1980b)**

3. Pressure-tension theory

The tooth moves in the periodontal space by creating a pressure and tension side **(Schwarz, 1932).** It explains the alteration of blood flow in periodontal ligament as shown in **table 1**. This alteration results in less oxygen levels on the pressure side due to compression of the periodontal ligament and vice versa. **(Tuncay, 2006).**

Table 1: Factors affect the pressure and tension side **(Jason and cauto,1999).**

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

Low oxygen tension causes decreased Adenosine triphosphate (ATP) activity. These changes can directly or indirectly act on cellular activity and differentiation **(Schwarz, 1932).**

The tissue response to the magnitude of force with capillary blood pressure. If the force exceeds the pressure (20–25 g/cm2 of root surface), tissue necrosis can occur due to the strangulated periodontium **(Krishnan and Davidovitch, 2006).**

1.6 Phases of tooth movement:

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, 1999).**

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 **(Jason and cauto,1999).**

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**.** 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 **(Kashyap, 2016)**.

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).**

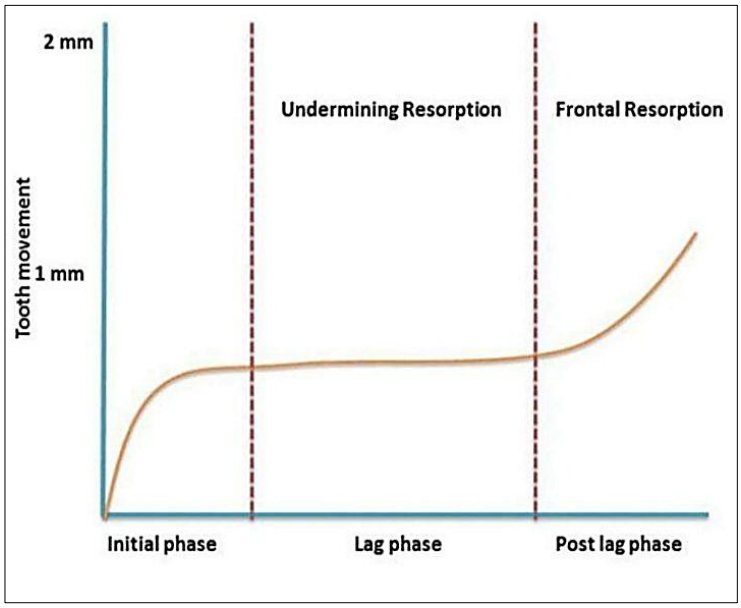


Figure 4: Phases of tooth movement **(Arffin *et al.*, 2011).**

1.7 Periodontal ligament and Alveolar Bone remodeling

Two interrelated processes in orthodontic tooth movement are deflection (bending) of the alveolar bone and remodeling of the periodontium: the periodontal ligament, alveolar bone and cementum **(Masella and Meister, 2006).**

Force magnitude has been associated with biological events, although most of these associations are conjectures. 'Direct resorption' is associated with light force application,tissue and cellpreservation, and vascular potency.
'Indirectresorption' and hyalinization are associated with heavy forces that cause crushinginjury to PDL tissues, cell death, hemostasis, and cell-free PDL and adjacentalveolar bone zones **(Henneman *et al.*, 2004)**.

Mechanical forces often cause hyalinization leading to necrosis in the PDL and lead todelayedbone resorption. Hyalinization occurs in the PDL and is proposed to indicatehyaline-like tissue formation that no longer has normal tissue architecture. Macrophages are responsible for removing the hyalinized tissues prior to which little tooth movement occurs **(Sprogar *et al.*, 2008).**

Extracellular matrix and cell distortion causes structural and functional changes in cell membrane, and cytoskeletal proteins. At the same time, numerous submembrane proteins associate in cellular focal adhesions. These complex structural or functional adaptations will transmit signals to the cytoplasm and mediate cell adhesion by integrin activation **(Mclean et al, 2004).**

Alveolar bone resorption occurs on the compression side during tooth movement. Bone resorption occurs through osteoclastic activity, thus creating irregular cavities in bone that later will be filled by newly formed bone owing to osteoblast activity. Two processes involved in bone resorption are the dissolution of minerals and the degradation of the organ matrix, which consists of type I collagen. These processes are driven by enzymes, including matrix metalloproteinase and lysosome cysteine proteinases **(Zainal *et al.*, 2011).**

Orthodontic forces result in the deformation of blood vessels and disarrangement of surrounding tissues. Subsequently, blood flow and periodontal tissue adapt to the compression force, or when they fail are responsible for cell death and tissue necrosis the rate of orthodontic tooth movement is affected by multiple factors such as the magnitude, frequency, and duration of mechanical forces that are applied to the teeth or bone. Mechanical forces change vascularity and blood flow, resulting in the synthesis and release of molecules such as neurotransmitters, cytokines, growth factors, colony-stimulating factors that regulate leucocyte, macrophage, and monocyte lines . Protein phosphorylation mediated by protein kinase enzymes is critical to th understanding of orthodontic tooth movement **(Arffin *et al.*, 2011).**

Cytoplasmic signaling proteins Hh, transforming growth factor-β superfamily, and many transcriptional factors and ions(Ca^{2+} , PO^{3-}) enhance or suppress gene expression. Matrix metalloproteinases (MMP) is an indispensable enzyme in bone remodeling. MMP-2 protein is induced by

compression and increases significantly in a time-dependent fashion, reaching a peak after 8 h of force application **(York and Hunter, 2004).**

On the tension side, MMP-2 significantly increases after one hour of force application but gradually returns to baseline within eight hours as shown in figure no.5. The cleavages of procollagen yields procollagen type I C-terminal propeptide and procollagen type I N terminal propeptide that may serve as bone formation markers **(Hannon and Eastel, 2006).**

Normal chloride channels play a key role in osteoclastic alveolar bone resorption in orthodontic toothmovement Cystic fibrosis, a pathological bone condition is characterized by mutated cellular chloride channels encoded by polymorphic nucleotide sequences in the ClCN7 gene **(York and Hunter, 2004).**

1.8 Cellular event in tooth movement

Cellular events in response to mechanical loading It is now well established that during normal everyday function there is a balance maintained between bone resorption and bone deposition, with the osteoblast controlling these processes. The exact cellular and molecular biological events that occur during orthodontic tooth movement are the subject of extensive research **(Karsenty, 2003).**

Mechanical load, for example force on a tooth from an orthodontic appliance, leads to deformation of the alveolar bone, possibly due to the effects of fluid movement within the viscoelastic PDL as the tooth is displaced, and stretching or compression of the collagen fibres and extracellular matrix **(Krishnan and Davidovitch, 2006)**.

These distortions are detected by the cells (fibroblasts, osteoblasts, and osteocytes) because their cytoskeleton as shown in (**table .2)** is connected to the

extracellular matrix (ECM) by integrins embedded in their cell walls. Osteocytes communicate with each other via gap junctions **(Blum, 2002).**

There is evidence that the shape of a cell can influence its activity; rounded cells tend to be catabolic where as flattened cells are anabolic as shown in (**figure .5)** it is possible that the changes in shape of the cells in the PDL are at least partly responsible for the chain of events seen in areas where the PDL is compressed or under tension **(Arffin *et al.*, 2011).**

A recent review of the mechanobiology of tooth movement has suggested the following four stages may be described **(Verna and Melsen, 2003).**

(1) Matrix strain and fluid flow in the alveolar bone and PDL.

(2) Cell strain, as a result of matrix strain and fluid flow.

(3) Cell activation and differentiation (osteoblasts, osteocytes, fibroblasts and osteoclast precursor.

(4) Remodeling of PDL and alveolar bone.

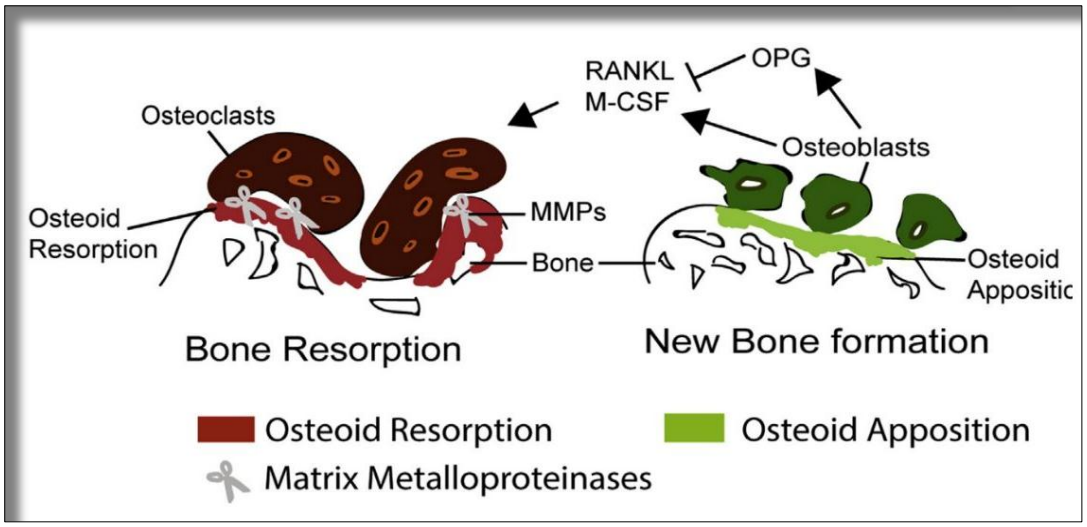


Figure 5: Cellular events during tooth movement **(Andrade *et al.*, 2007).**

Table2: Factors involved in regulation of bone remodeling during tooth Movement **(Yen*et al., 2005*).**

Name	Function
RUNX-2	One of the most important bone-specific genes, vital for mesenchymal differentiation into osteoblasts
Interleukin-1 (IL-1)	Potent stimulator of bone resorption, acting both directly and by increasing prostaglandin synthesis. Also an inhibitor of bone formation. Produced by macrophages and osteoblasts
RANKL (Receptor activator of nuclear factor (NF-kB) ligand)	Secreted by osteoblasts and binds the RANK receptors found within the cell membrane of osteoclast precursors. It is an essential stimulatory factor for the differentiation, fusion, activation and survival of osteoclastic cells
OPG (osteoprotegerin)	Secreted by osteoblasts and blocks the effects of RANKL, thereby decreasing the activity of osteoclasts. Acts as a decoy receptor by binding RANKL extracellularly
M-CSF (macrophage-colony stimulating factor) aka CSF-1	Polypeptide growth factor found in bone matrix and produced by osteoblasts. Acts directly on osteoclast precursor cells to control proliferation and differentiation
PGE-2 (prostaglandin E2)	Potent mediator of bone resorption found in sites of inflammation. Produced by cells in response to mechanical loading. Elevates intracellular messengers
Leukotrienes	Actions on both bone destruction and bone formation, found in sites of inflammation. Produced by cells in response to mechanical loading. Elevates intracellular messengers
MMPs (matrix metalloproteinases)	Range of enzymes e.g. collagenase, gelatinase, produced by various cell types to break down unmineralised extracellular matrix
TIMPs (tissue inhibitors of metalloproteinases)	Produced by various cell types to bind to MMPs extracellularly to reduce/inhibit their activity
ERKs (extracellular signal-related kinases)	Members of the MAP kinase family of intracellular messengers that provide a key link between membrane bound receptors and changes in the pattern of gene expression

Chapter two

Discussion:

Orthodontic treatment is to move malpositioned teeth to an appropriate position through the remodeling of the periodontium stimulated by orthodontic force **(Andrade *et al.*, 2007).**

Several theories had been proposed, the pressure –tension theory is well accepted and proposes that cellular responses are modulated by chemical messengers, released from blood flow or cells in situ, in response to mechanical stress imposed on the periodontal ligament and alveolar bone **(Sprogar *et al.*, 2008).**

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. The duration and character of force have great influence in orthodontic mechanotherapy, alterations in which can produce varied tissue reactions **(Yen *et al., 2005).***

Chapter three:

Conclusion and suggestion:

Conclusion

From This review we conclude that:

- The applied force from orthodontic appliance affect and change the homeostasis of the periodontium and alter the blood flow and this will activate enzymes and mediators that are responsible for the differentiation of osteoblast and Osteoclast on the pressure and tension side.
- Heavy force causes hyalinization of the tissues surrounding the tooth
- Light force is better for Orthodontic tooth movement
- The Optimal orthodontic force depends on the type of the tooth and on the patient condition

Suggestion

We suggest and hope that in the future more studies should occur on how to accelerate tooth movement by electrical effect and how to make a device that can measure accurately the optimal force for each tooth and patient.

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