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RESEARCH ARTICLE

CURRENT KNOWLEDGE OF BIOLOGICAL PROCESSES INVOLVED IN THE ORTHODONTIC MOVEMENT OF TEETH

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ABSTRACT

Orthodontic tooth movement is a biological process involving interactions between physiological bone changes and chemical mediators such as growth factors, cytokines, arachidonic acid metabolites etc. Complex molecules are released by bone cells such as-osteoblasts, osteoclasts and osteocytes which cause bone changes/remodeling which are compatible with tooth movements. Various theories of tooth movement have been discussed in this article in conjunction with biological processes encompassing these.

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INTRODUCTION

Bone is dynamic tissue which undergoes remodeling as a response to biomechanical forces exerted by orthodontic appliances. Schwartz (1932) defined optimal force as "the force leading to changes in tissue pressure that approximate the capillary vessels' blood pressure, thus preventing their occlusion in a compressed periodontal ligament". Below optimal forces does not produce any reaction while forces, beyond optimum lead to necrosis of tissues. (Sharma *et al*., 2015) Root resorption (both apical and lateral resorption) can also occur as an undesirable effect of orthodontic force. (Miklas *et al*., 2013)

Theories of orthodontic tooth movement (Sharma *et al*., 2015)

Theories proposed include: 1) Pressure tension theory; 2) Bone bending theory and 3) Microdamage theory.

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1) Pressure tension theory: Sandstedt, 1904; Oppenheim, 1911 and Schwartz, 1932 hypothesized that tooth movement occurs in periodontal space and generates a "pressure" and "tension" side. On the pressure surface, the periodontal ligament undergoes disorganization and decrease in fiber synthesis. Also, cellular replication is decreased as the result of vascular constriction over the tension surface (Fig. 4). (Sharma *et al*., 2015)
2) Bone bending theory: Farrar (1808) suggested that "alveolar bone bending" has an important function in orthodontic tooth movement. On activation, an orthodontic appliance delivers forces to a tooth, which are then, transmitted to all surrounding tissues. Bone has more elasticity than any other tissue and bends on application of force. Biological processes accompanying bone bending involves turnover/ remodeling of bone. (Sharma *et al*., 2015)
3) Microdamage theory: According to this theory, microcracks develop in bone in response to material fatigue induced by application of orthodontic force. This leads to osteocytic apoptosis which attracts osteoclasts to the site. These microcracks reflect the

initial bone damage which then gets remodeled. (Henneman *et al*., 2008)

Tissue-related changes in response to orthodontic forces

Periodontal ligament is a physiological mediator of orthodontic treatment. Application of force triggers a cascade of cellular events within the periodontal ligament which aid in movement of teeth. (Sella *et al*., 2012) Orthodontic tooth movements are brought about by continuous and minimal magnitude forces. Minimal pressure required should be within the magnitude of 5-10 gm/cm^2. Tooth movement is the resultant of two types of resorption- frontal and undermining. (Topkara *et al*., 2012) Frontal resorption is caused by light forces which are minimally painful and harmful to periodontal tissues while undermining resorption is the result of heavy forces which are comparatively highly painful and more harmful to periodontal structures. External apical root-end resorption is a complication of orthodontic treatment resulting in permanent loss of root structure. Severe apical root resorption can be defined as "root end shortening measuring > 4mm or one-third root length". It is seen in 1 to 5% of teeth. (Topkara *et al*., 2012) Various risk factors contributing to multifactorial etiology of apical root-end resorption can be categorized into treatment-related and patient-related factors. Treatment-related factors may include- duration of treatment, magnitude of force application, tooth movement direction while the patient-related factors include systemic factors, genetics, severity of malocclusion, previous history root resorption, alveolar bone density etc. (Topkara *et al*., 2012) The tooth movement through bone is characterized by undermining resorption which starts from the adjacently localized bone marrow. During this period, there is no formative activity occurring on the tension side. Compression of periodontal ligament causes development of cell-free hyalinization which is the result of localized ischemia. As the resorptive process approaches the periodontal ligament, it eliminates the hyalinized tissue causing tooth movement due to periodontal ligament widening. Bone apposition begins at tension side (strain surface) due to heightened osteoblastic activity while on the opposing surface (stress surface), osteoclastic activity is seen. This simultaneous process maintains the width of the periodontal ligament. This tooth movement can occur outside the alveolar process outline while carrying its alveolus along with it. This corresponding stress-strain distribution is determined by multiple factors such as- magnitude of force, area of bone and force distribution. In tipping movements, these forces get concentrated on marginal and apical portions of alveolus, while in translation, there is uniform force distribution along the alveolar socket wall. (Melsen, 1999)

Epker and Frost (1965) demonstrated that alteration in alveolar circumference is the result of periodontal fibers stretching which causes bending of bone in tension area. This bending results in bone apposition. "Regional accelerating phenomenon" reflects that the tissue reaction to regional and noxious stimulus gets distributed regionally while a continuous mechanical stimulus can lead to an increased bone density, which is termed as "structural adaptation to mechanical usage". Frost illustrated relationship between strain and net bone turnover balance. In low strain, net bone loss occurs due to increased strain, initiation of bone modeling takes place. This results in a positive balance. When the strain curve crosses the neutral line, both resorption and apposition remains in balance. The newly formed bone is mainly in response to a greater strain. Thus, a sustained force causes increased bone modeling. The bodily response to increased mechanical strain manifests as woven bone formation. Thus, Frost described the histopathological presence of woven bone whenever the stimulus exceeded a certain value. Tooth movement gets facilitated by alveolar bone resorption in direction of movement. This resorption starts as a reaction to hyalinization and has an indirect or an undermining effect. There is a rapid formation of woven bone in direction of tooth movement. (Melsen, 1999) According to the fluid shear stress theory, bone reaction to strain leads to fluid flow through bony canaliculi resulting in shear stress upon osteocytes. In areas of decreased canalicular fluid flow, apoptosis of osteocytes occurs. This attracts osteoclasts to the site. Also, activation of osteoprogenitors, osteoblasts and periodontal activation takes place. The newly formed periodontal ligament contains mainly higher amounts of type I collagen fibers specially, on the apposition side when compared with resorption side (Figure 2). (Henneman *et al*., 2008) Orthodontically-induced strain alters vascularity in periodontal ligament which stimulates release of various neurotransmitters, growth factors, cytokines, arachidonic acid metabolites etc. interactions between neurotransmitters and periodontal ligamental cells such as- fibroblasts and osteoblasts lead to a transient increase in intracellular levels of secondary messengers such as –cAMP, cGMP, IP3, Ca^{2+} etc. The secondary messengers pass signals to nucleus through series of kinases leading to release of various transcription factors which induce either cellular proliferation or differentiation. (Kashyap, 2016) Tooth movement on application of orthodontic force can be characterized by remodeling changes in dental as well as periodontal tissues which include dental pulp, alveolar bone and gingiva. When these tissues are exposed to varying degrees of frequency, magnitude and duration of mechanical loading, they express macroscopic as well as microscopic changes by release of factors such as Interleukin-1 and alkaline phosphatase. (Ariffin *et al*., 2013)

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme indicative of cell damage or death. Its presence in gingival crevicular fluid (GCF) is considered a potential marker for periodontal metabolism/inflammation in relation to movement of teeth. An "early phase response" during orthodontic tooth movement is characterized by an "acute inflammatory response" which is characterized by vasodilatation and leukocyte migration from capillaries in periodontal ligament. LDH-specific activity at tension and compression sites exhibit peak activity corresponding with forces of 1.5 N. Thus, it was suggested that in subjects with stabilized periodontal conditions a force of 1 N is more suitable. (Ariffin *et al*., 2013) The pressure and tension sides show histological variations. Biological events on the pressure side are reflected by disturbances in blood flow, compressed area hyalinization, hyalinized tissue resorption by macrophages and osteoclast-mediated bony resorption. (Narmada and Syafei, 2008) On tension side, blood flow activation promotes osteoblastic activity and deposition of osteoid. When hyalinization takes place, osteoclasts start undermining resorption in lamina dura. This undermining resorption results in delayed tooth movement and root resorption. Based upon these tissue changes, tooth movement has been divided into three phases- a) Initial movement due to compression of periodontal ligament, b) Period of hyalinization with no or little tooth movement and c) Tooth movement caused by undermining resorption and increased tissue oxygen concentration due to increase in capillaries. (Narmada and Syafei, 2008)

Phases of orthodontic tooth movement (Fig. 5)

When a force of varying magnitude, frequency and duration is applied on a tooth to bring about an orthodontic tooth movement, a series of macroscopic and microscopic events are observed in and around periodontal ligament fibers and alveolar bone. This mechanical loading of periodontal ligament and alveolar bone results in the formation of areas of tension and pressure which further generates the cascade of events leading to bone formation and resorption respectively. Thus, an orthodontic tooth movement can be divided into three phases i.e., *initial phase, lag phase and post lag phase.* (Ariffin *et al*., 2011) The Initial phase of orthodontic tooth movement is characterized by rapid movement of the tooth within 24-48 hours after the first application of the force. It is generally attributed to the movement of tooth in the periodontal ligament space and slight bending of the bone is also seen. The periodontal ligament fibers in the direction of force are compressed and those in the opposite direction are tensed. Studies have shown that any amount of light and heavy forces can bring about the tooth movement to the same extent during this phase. The amount of tooth movement achieved depends on various factors like width of periodontal ligament fibers, length and anatomical configuration of root, amount of force applied and periodontal status of the tooth. Tooth can be moved approximately between 0.4 mm to 0.9 mm and it usually last for 7 days. (Ariffin *et al*., 2011) Next phase is the lag phase which marked by little or no displacement of the tooth. It is characterized by the presence of areas of hyalinization in the periodontal ligament. No subsequent movement can take place until these areas are removed completely. If light forces are used, amount of hyalinized tissue formed is less and frontal resorption occurs. However, if heavier forces are used, amount of hyalinized tissue formed is more. Resorption in this case would be rearward thus, longer time-period would be required to bring about the tooth movement. This phase usually last for 20-30 days but may extend as long as 10 weeks. Duration of this phase depends on various factors like density of alveolar bone, age of the patient and of hyalinized tissue formed. (Ariffin *et al*., 2011) The post lag phase represents the final phase in which tooth movement progresses rapidly due the removal of areas of hyalinization. During this phase, osteoclasts are found in larger amounts resulting in direct resorption of bony surface facing the periodontal ligament. Bone resorption is seen on the pressure side and bone formation is dominant on the tension side. (Ariffin *et al*., 2011)

Bioelectric signal generation on orthodontic tooth movement

Bassett and Becker (1962) have proposed that there is generation of electric signals in "stressed" tissues. These signals may change macromolecules localized in specified sites within cell membranes or may cause ionic mobilization across all membranes. The concave surface of orthodontically-treated bone is electronegative that favors bone deposition (via osteoblast activity) whereas, the opposing convex surfaces exhibit neutrality and show osteoclastic activity. Bone bending creates two types of bio-electrical responses- "piezoelectricity" and "streaming potentials". 'Piezoelectricity' is a phenomenon limited to crystalline substances wherein deformation of crystal structure leads to electric current production. This phenomenon can be seen in both organic and inorganic crystals. (Sharma *et al*., 2015)

Signaling molecules generated in orthodontic tooth movement
Various signaling molecules are generated in orthodontically-induced tooth movement include-

a) Arachidonic acid (eicosatetraenoic) metabolites: These are released on activity of enzyme, phospholipase.
b) Prostaglandins: Prostagladins E1 and E2 (PGE1 and PGE2) play a central role in bone resorption process (compression side). Prostaglandins act on osteoclasts by an increase in their number and formation of ruffled borders. Prostaglandin binding to cellular membranous receptors leads to conversion of ATP as well as GTP into cAMP and cGMP, respectively. PGE2 and COX2 are upregulated on compression side.

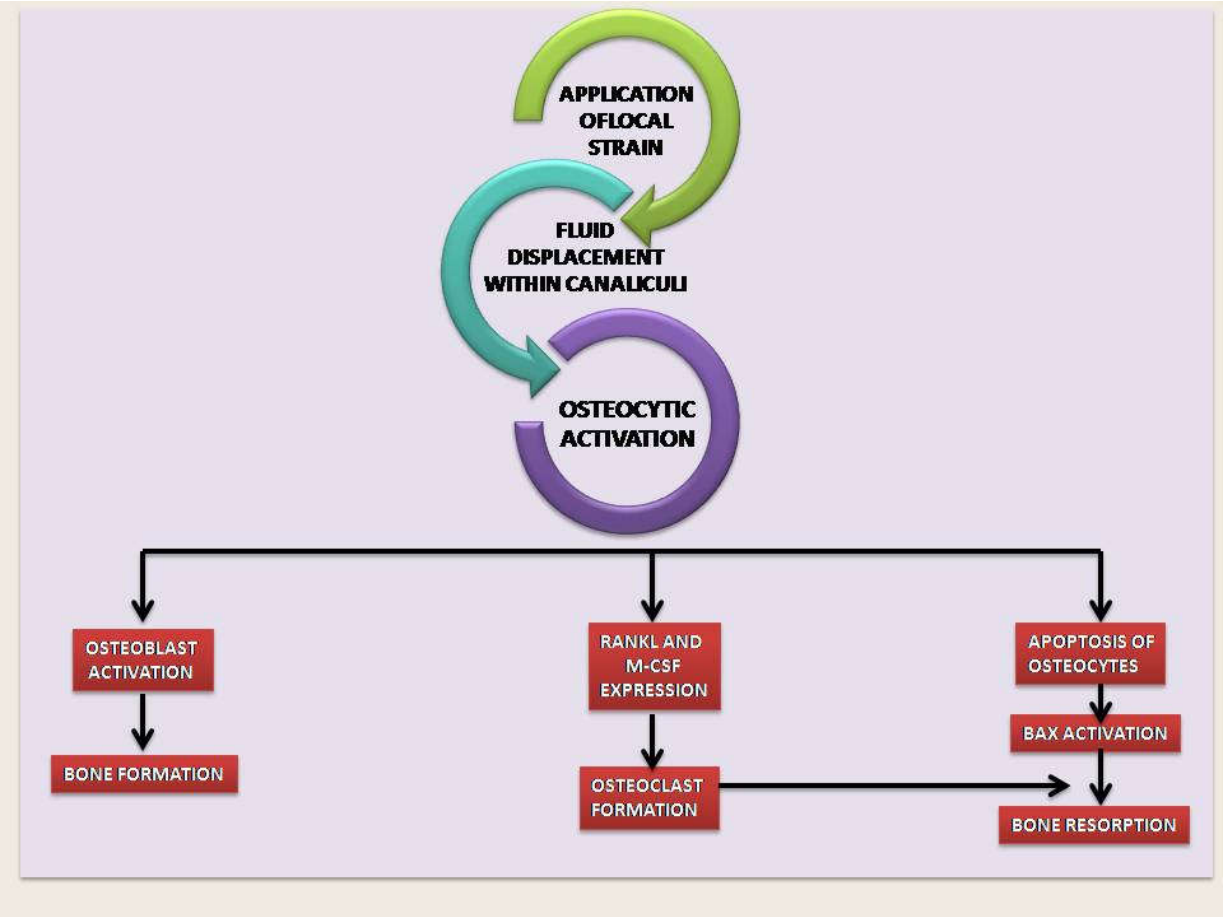
1,25-dihydroxycholecalciferol plays a central role in calcium homeostasis by acting as first messenger. It acts as a stimulator of bone resorption by initially osteoclast differentiation. Sox-9 regulates type II collagen gene by preventing chondrocytic differentiation. Cytokines affecting bone metabolism include-interleukins-1, -2, -3, -6, -8, TNF-α, IFN-γ and osteoclast differentiation factor. Most importantly, IL-1 causes direct osteoclast stimulation through IL-1 type receptor. IL-1 acts by drawing leukocytes by stimulation of fibroblasts, endothelial cells, osteoclasts and osteoblasts. Tumor Necrosis Factor-α (TNF-α) causes stimulation as well as differentiation of osteoclastic progenitors to osteoclasts in the presence of macrophage-CSF. TNF-related ligand- RANKL and its two receptors, RANK (Receptor Activator of Neutral Kinases) and OPG (Osteoprotegrin) are important for bone remodeling. Osteoprotegrin (OPG), a receptor present on osteoblasts competes with 'RANK' for RANKL binding.

It inhibits osteoclast differentiation, osteoclast suppression and apoptosis induction. Thus, remodeling of bone is an interplay between RANK-RANKL binding and OPG production (Figure 3). (Ariffin *et al*., 2013) Tooth movement rate is directly controlled by bone resorption rate. Resorption is influenced by an increase in activity of inflammatory cytokines and chemokines through prostaglandins E2 and the RANK/ RANKL pathways which cause osteoclastic differentiation (Figure 1). (Alikhari *et al*., 2013)

Interaction between cytoskeleton-extracellular matrix

Forces from extracellular matrix are transduced to the cytoskeletal structures via cell surface proteins which causes the cytoskeletal reorganization, cytokine secretion, activation of ribosomes and gene transcription. Nociceptors are high-threshold mechanoreceptors which are activated by heavy forces and tissue injury. They belong to unmyelinated C and/or small myelinated Aδ fibers containing neuropeptides such as-"calcitonin gene-related peptide" and "substance P". These neuropeptides are released whenever these end terminals are strained. Mechanoreceptors are low-threshold, slow responding nerve fibers. (Miklas *et al*., 2013) Osteocytes were earlier thought to provide support and nutrition to bone.

However, they have also been shown to exhibit propioceptive properties. (Patil *et al*., 2013) Orthodontic tooth movements affect the numbers, functions and distribution of mechano- and nociceptive nerve fibers affecting tooth movement. (Patil *et al*., 2013)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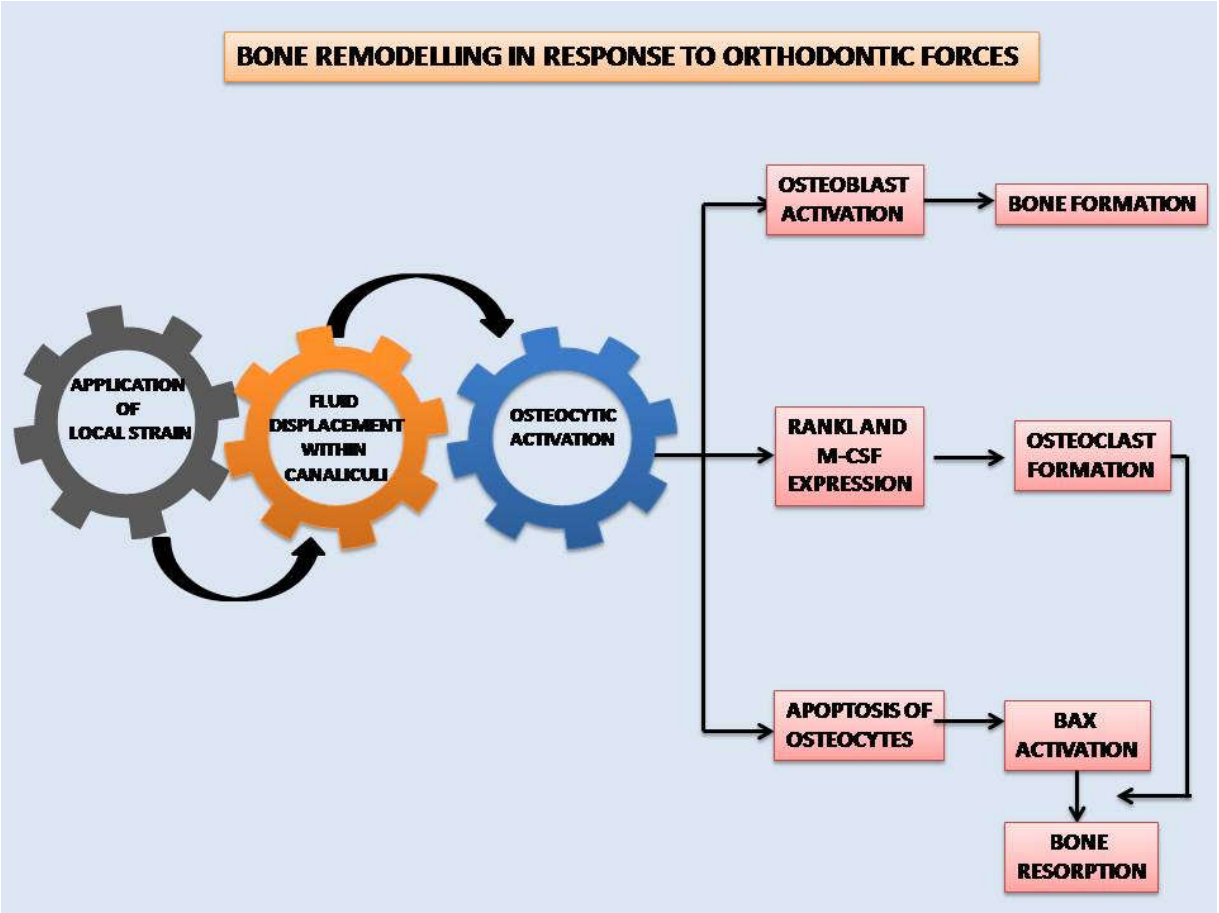
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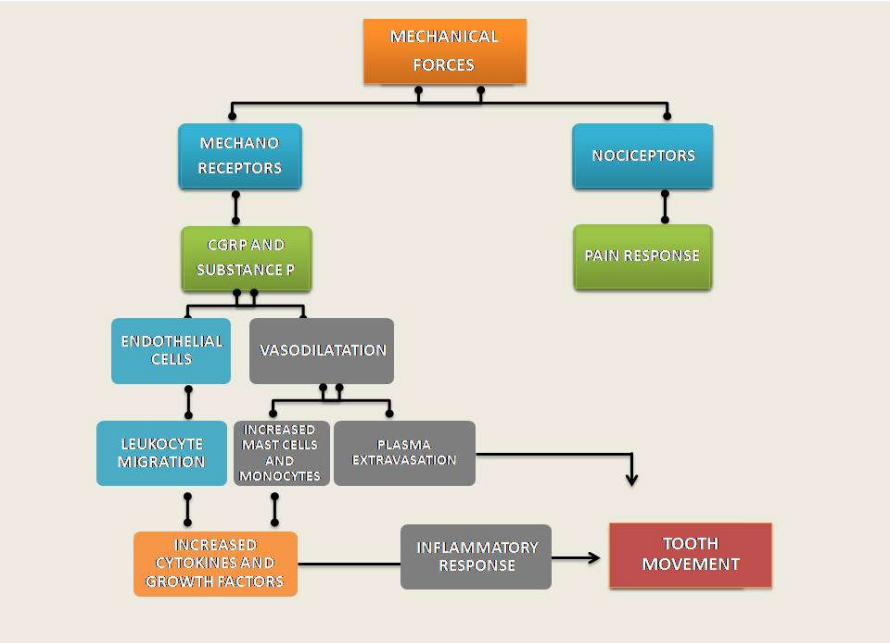
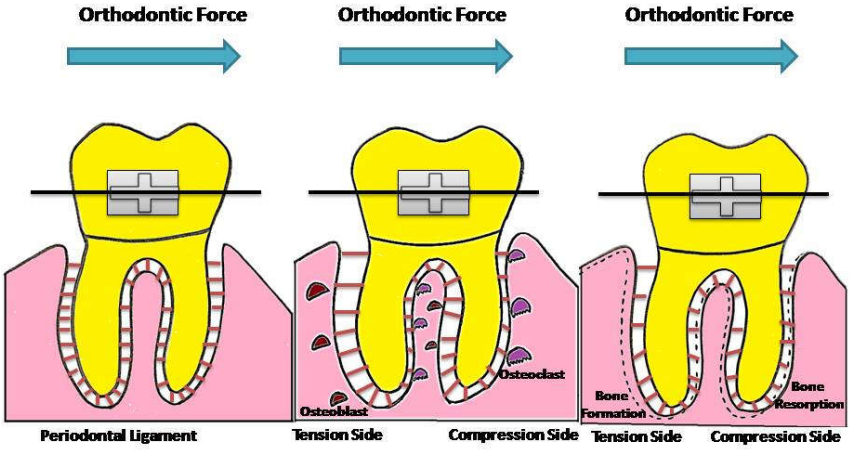
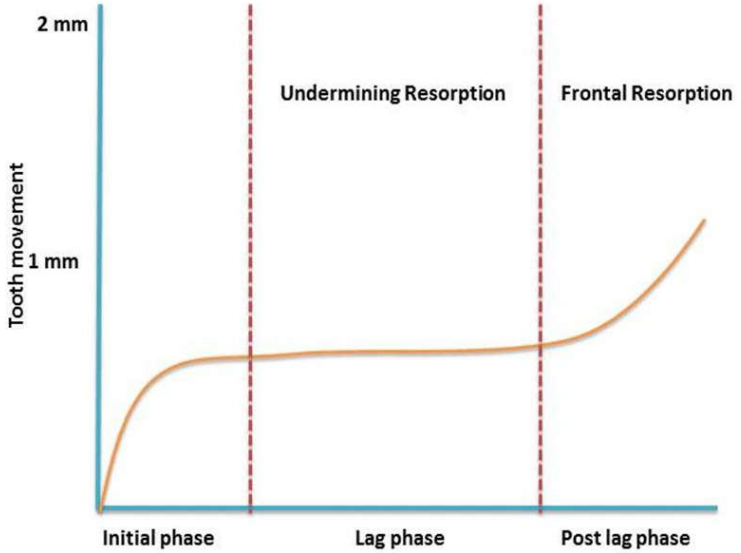




PRESSURE TENSION THEORY



Differentiation markers associated with bone cells (Karsenty, 1999)

Pre-osteoblasts

Pre-osteoblasts are characterized by expressions of 'alkaline phosphatase', 'type I collagen' and 'bone sialoprotein'. (Miklas *et al*., 2013)

Osteoblasts

Osteoblasts are mesenchymal cells which synthesize as well as secrete extracellular matrix comprising of 'type I' collagen, 'osteonectin', 'osteopontin', 'osteocalcin', 'alkaline phosphatase', 'growth factors' and 'proteoglycans'. These growth factors act by promoting osteoblast precursors' proliferation and new bone mineralization. (Patil *et al*., 2013)

Markers associated with osteoblastic differentiation are as follows: (Patil *et al*., 2013; Silva *et al*., 2015)

a) Cbfa 1: The osteoblastic differentiation is controlled by Cbfa1 gene which is expressed preceding its appearance.
b) Osf1: This gene is expressed during early stages of osteoblastic differentiation.

Osteoblasts synthesis requires bone morphogenetic protein, 'Wingless' (Wnt) pathways, Runt-related transcription factor, Distal-less homeobox 5 (Dlx5) and Osterix (Osx) expressions. Osterix is a gene responsible for downstreaming Runx2 activity. Runx2/Osterix deletion results in absence of osteoblastic synthesis. Other factors include- Connexin 43, fibroblast growth factor-18 (FGF-18) and microRNAs and ephrin B2. (Patil *et al*., 2013; Silva *et al*., 2015)

Osteoclasts

Osteoclasts are 'multinucleated' giant cells derived from monocytic-hematopoietic origin. These cells exhibit high tartarate-resistance acid phosphatase (TRAP). Osteoclastic differentiation markers include:

a) Pu.1: This is the earliest known marker of osteoclastic differentiation. Pu.1 deletion results in multi-lineage defects in progenitors of B- and T-lymphocytes, granulocytes and monocytes. It regulates c-fms transcription encoding the M-CSF receptors.
b) c-fos: This is the cellular homolog of "v-fos" oncogene. Deletion of c-fos gene has been shown in mice, an early onset of osteoclast differentiation.
c) NF-κβ: It plays an early role in osteoclast differentiation.
d) Microphthalmia (mi): Microphthalmia (mi) is a basic "helix-loop-helix" transcription factor.

Osteoclasts produce RANK, EGFR, CCR2 and CCR5. Their differentiation is inhibited by IL-12, -18, -33 and interferon. (Wajid *et al*., 2014)

Osteocytes

Osteocytes are constituent cells of bone mainly responsible for sustaining bone homeostasis and metabolism. Selerostin is a glycoprotein which acts as a negative regulator of osteoblastic differentiation. Additionally, osteocytes promote mineralization through Dentin matrix phosphoprotein-1 (Dmp1, a member of SIBLING family) and Phex (trans-membrane endopeptidase) and also, inhibit mineralization through Sost and MEPE, an extracellular matrix phosphoglycoprotein. (Silva *et al*., 2015) On exposure to hypoxic conditions, these cells secrete TGF-β, c-fos, nitric oxide (NO), hypoxia induced factor-1 (HIF-1) and Insulin Growth Factor (IGF) and promote angiogenesis. (Wajid *et al*., 2014) Osteocytes are mechanosensory while osteoblasts and periodontal fibroblasts are mechano-responsive cells. (Wajid *et al*., 2014) Effects of drugs on orthodontic tooth movement (Kakadiya *et al*., 2014). Drugs can promote as well as inhibit tooth movement during orthodontic mechanotherapy. Drugs which promote orthodontic tooth movement include- Prostaglandins, Parathyroid hormone (PTH), vitamin D and L-arginine. (Kakadiya *et al*., 2014)

a) Prostaglandins: These compounds are metabolized in the arachidonic acid pathway. They mediate periodontal ligamental inflammation which aids in tooth movement. They act by stimulating bone resorption by increased osteoclast activity. (Kakadiya *et al*., 2014)
b) Vitamin D: Vitamin D has a stimulatory effect on osteoblasts localized on pressure side of periodontal ligament. Thus, balancing overall bone turn-over. (Kakadiya *et al*., 2014)
c) Parathyroid hormone: Parathyroid hormone causes an increase in calcium ion concentration in blood because it stimulates bone resorption. (Kakadiya *et al*., 2014)

Drugs which suppress orthodontic tooth movement include- calcitonin, bisphosphonates, corticosteroids, estrogen, NSAIDs, fluorides, anti-cancer drugs and anti-rheumatoid arthritis drugs. (Kakadiya *et al*., 2014)

a) Estrogen: Estrogen acts by inhibition of cytokine production responsible for bone resorption. It also acts by inhibiting osteoblastic response to parathyroid hormone. (Kakadiya *et al*., 2014)
b) Corticosteroids: Corticosteroids act by inhibition of osteoblastic activity. Decrease in bone formation is due to elevated parathyroid hormone which is affected by decreased calcium reabsorption in intestine which in turn is influenced by corticosteroids. (Kakadiya *et al*., 2014)
c) Bisphosphonates: Bisphosphonates cause inhibition of bone resorption, thus, hindering tooth movement. (Kakadiya *et al*., 2014)
d) Calcitonin: This is a peptide hormone secreted by thyroid gland in hypocalcemic conditions. It inhibits calcium and phosphate absorption from proximal renal tubules. It inhibits bone resorption by osteoclastic activity and increases osteoblastic activity. It has an inhibitory role in tooth movement. (Kakadiya *et al*., 2014)
e) Fluoride: This is a trace element which increases bone mass by increasing mineralizing capacity. Topical fluoride therapy using sodium fluoride might cause a delay in tooth movement by inhibiting osteoclastic activity. (Kakadiya *et al*., 2014)
f) Anticancer drugs: These therapeutic agents cause damage to precursor cells involved in bone modeling thereby, complicating tooth movement. (Kakadiya *et al*., 2014)

Adverse effects of orthodontic treatment

The various adverse effects encountered commonly during orthodontic treatment are root resorption, pain, pulpal changes, periodontal disease, decalcification and temporomandibular joint dysfunction. These harmful effects can be attributed to patient or a practitioner. Thus, considering the common risk factors prior to the treatment is of prime importance to an orthodontist.

1) **Root resorption:** It was first discussed by Ketchamm in 1927. The risk of root resorption increases with the increase in treatment time. Various risk factors such as morphology of root (thin, tapered, dilacerated roots), trauma to anterior teeth, various habits such as thumb sucking habit, occlusal trauma, history of chronic bruxism etc. predisposes the patient to root resorption. (Talic, 2011)
2) **Pain:** It is the most common adverse effect associated with orthodontic treatment it is due to pressure, tension and soreness associated with teeth caused due to orthodontic forces applied during the treatment. Anterior teeth are said to experience more pain than the posterior teeth. Pain usually begins after *4 hours* from the start of the treatment and may last for seven days. Worst pain is experienced during the second day of the treatment. It is recommended to the orthodontist to prescribe analgesics like *ibuprofen* and *acetaminophen* preoperatively and for shorter duration after the start of the treatment. (Talic, 2011)
3) **Pulpal changes:** The reaction of the pulp to orthodontic forces is in the form of *mild transient inflammatory reaction.* However, the loss of vitality of pulp does exist during the treatment. The risk factor includes the history of previous trauma to the teeth undergoing treatment. Thus, preoperative radiograph of the teeth prior to the treatment becomes important for comparative purposes. In addition to these, use of heavy, uncontrolled forces by the orthodontist for longer duration can lead to loss of vitality of pulp. Therefore, orthodontist must use *optimal light forces* to bring about the changes in the teeth. (Talic, 2011)
4) **Periodontal disease:** Orthodontic treatment can give rise to various periodontal disease like gingivitis, periodontitis and loss of attached gingival margin. Multiple factors like host resistance, presence of systemic disease, amount and composition of dental plaque, smoking etc. may compromise the periodontal health during the treatment. Orthodontic treatment is contraindicated in patients with active periodontal disease and also in patients with uncontrolled diabetes. Complete evaluation of the periodontium is required prior to the treatment. Oral hygiene instructions should be given priorly and reinforced during every visit. Brushing with electrical, ultrasonic or manual brushes should be made mandatory to the patient. Various studies have shown that use of electric and ultrasonic brushes show superior results in reducing bacterial plaque and gingival inflammation than manual brushes. Fluoride concentration of the toothpaste should not be less than 0.1 %. (Talic, 2011)
5) **Decalcification:** Decalcification of enamel occurs in approximately 50% of the patients undergoing orthodontic treatment. Teeth commonly affected by decalcification are maxillary anterior teeth. Preventive protocol includes brushing of teeth with fluoridated toothpaste. Also, use of fluoride mouth-rinses (0.02% or 0.05% sodium fluoride daily) can be prescribed to the patient. In addition to these, application of fluoride varnish twice a year may be helpful in reducing the incidence of decalcification. (Talic, 2011)

Conclusion

Orthodontic tooth movement is intricate interplay among cellular, molecular as well as physiological constituents of bone. An understanding of biological mechanisms and associated factors can assist in deciding the biomechanics of orthodontic therapy in a subject.

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