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Review Article

Orthodontic tooth movement: The biology and clinical implications

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Abstract Orthodontic tooth movement relies on coordinated tissue resorption and formation in the surrounding bone and periodontal ligament. Tooth loading causes local hypoxia and fluid flow, initiating an aseptic inflammatory cascade culminating in osteoclast resorption in areas of compression and osteoblast deposition in areas of tension. Compression and tension are associated with particular signaling factors, establishing local gradients to regulate remodeling of the bone and periodontal ligament for tooth displacement. Key regulators of inflammation and tissue turnover include secreted factors like RANK ligand and osteoprotegerin, transcription factors such as RUNX2 and hypoxia-inducible factor, cytokines, prostaglandins, tissue necrosis factors, and proteases, among others. Inflammation occurred during tooth movement needs to be well controlled, as dysregulated inflammation leads to tissue destruction manifested in orthodontic-induced root resorption and periodontal disease. Understanding the biology has profound clinical implications especially in the area of accelerating orthodontic tooth movement. Surgical, pharmacological, and physical interventions are being tested to move teeth faster to reduce treatment times and time-dependent adverse outcomes. Future developments in acceleratory technology and custom appliances will allow orthodontic tooth movement to occur more efficiently and safely.

Conflicts of interest: All authors declare no conflicts of interests.

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Introduction

Orthodontics is a special discipline dedicated to the investigation and practice of moving teeth through the bone. Moving teeth through the dentoalveolar complex is a synergistic sequence of physical phenomenon and biological tissue remodeling. The physical behavior of tooth movement due to orthodontic force relies on Newton's Laws. The tooth biological system reacts to variation in force magnitude, time of application and directionality through receptor cells and signaling cascades that ultimately produce bone remodeling and orthodontic tooth movement (OTM). This review focuses on the biology of tooth movement and its implication in clinical orthodontics.

Periodontium: the tooth supporting complex

Periodontium is the investing and supporting attachment of the teeth to alveolar bone. It includes both the soft tissues of periodontal ligament (PDL) and gingiva as well as the hard tissues of cementum and alveolar bone (Fig. 1).

The ability of teeth to move through the bone relies on the PDL, which attaches the tooth to the adjacent bone. The PDL is a dense fibrous connective tissue structure that consists of collagenous fiber bundles, cells, neural and vascular components and tissue fluids. Its primary function is to support the teeth in their sockets while allowing teeth to withstand considerable chewing forces. On average, the PDL occupies a space about 0.2 mm wide. Depending on its location along the root, PDL width can range from 0.15 to 0.38 mm, with its thinnest part located in the middle third of the root. PDL space also decreases progressively with age [1]. Most PDL space is taken up by bundles of collagen fibers (mainly Type I) that are embedded in the intercellular substance. The terminal portion of the fibers that insert in the cementum and alveolar bone is termed Sharpey's fibers. These fibers can be divided into the principal fibers, the accessory fibers and the oxytalan (elastic) fibers. According to their orientation and location along the tooth, the principal fibers can be further categorized into the transseptal fiber (or interdental ligament) and alveolodental ligament

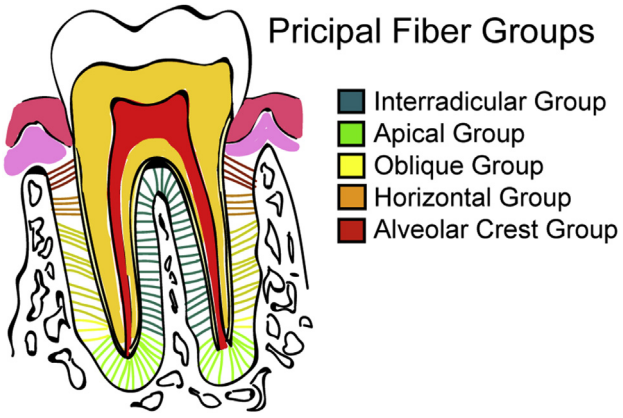

Figure 1. Components of the periodontium. Different types of principal fiber groups are indicated with different colors. Red: pulp. Yellow: dentin. White crown: enamel. Pink: Gingiva. Black outline: alveolar bone.

(Fig. 1). Transseptal fibers extend interproximally connecting the cementum of adjacent teeth to maintain tooth alignment, and the alveolodental ligament group of fibers helps teeth withstand compression forces during mastication. In addition to principal fibers, accessory fibers run from alveolar bone to cementum in different planes, more tangentially to prevent rotation of the tooth. Besides PDL fibers, paradental cells of different functions reside in the PDL space, including: 1) synthetic cells like fibroblasts which make up 50–60% of total PDL cellularity, osteoblasts, and cementoblasts; 2) resorptive cells such as osteoclasts, fibroblasts, cementoclasts; 3) progenitor cells including undifferentiated mesenchymal cells; 4) defense cells such as macrophages, mast cells and lymphocytes; and 5) epithelial cells, i.e. remnants of the epithelial root sheath of Hertwig [1]. Together, these various cells participate in the homeostasis of the periodontium. Finally, the PDL space is filled with tissue fluid known as interstitial fluid that is ultimately derived from the vascular system. This fluid-filled chamber allows the PDL space to evenly distribute forces loaded onto teeth, serving as a shock absorber.

The alveolar bone is a mineralized connective tissue that consists of mineralized tissue (60 w%), organic matrix (25 w %) and water (15 w%) [2]. While the majority of alveolar bone is trabecular, a plate of compact bone called the lamina dura lies adjacent to the PDL space. PDL fibers anchor to the alveolar bone by piercing through the lamina dura, while the other ends connect to the cementum (Fig. 1). Multiple cell types, namely osteoblasts, osteoclasts and osteocytes, play critical roles in the homeostasis and function of the alveolar bone. In addition, macrophages, endothelial cells and adipocytes can also be found within the alveolar bone. Osteoblasts are mononucleated and specialized "bone forming" cells. Both osteoblasts and fibroblasts can synthesize Type I collagen matrix. Osteoblasts differ from fibroblasts because they can express Runx2 (aka. Cbfa1), a master switch for osteoblast differentiation from mesenchymal progenitor cells [3]. The number of osteoblasts decreases with age, leading to an imbalance of bone deposition and resorption [4]. Osteocytes are derived from osteoblasts that are embedded in mineralized bone during bone apposition. During this process, minerals such as hydroxyapatite, calcium carbonate and calcium phosphate get deposited around the osteocyte, forming lacuna, the space that an osteocyte occupies during its entire lifespan. Lacunae are connected via narrow channels known as cannaliculi, where dendrites of osteocytes contact and communicate via gap junctions. While the "bone forming" osteoblasts and osteocytes arise from the mesenchymal cell lineage, the "bone resorbing" osteoclasts originate from a different progenitor population, the hematopoietic/monocyte lineage, and are formed by the fusion of multiple monocytes becoming "multinucleated". Osteoclasts are characterized by their high expression of Tartrate Resistant Acid Phosphatase (TRAP), Cathepsin K, Chloride channel 7 (ClCN7), and Osteoprotegerin (OPG). Cathepsin K is a protease capable of catabolizing bone matrix proteins such as elastin, collagen and gelatin. ClCN7 shuffles chloride ions through the cell membrane, thereby maintaining osteoclast neutrality. OPG (aka osteoclastogenesis inhibitory factor or tumor necrosis factor receptor superfamily member 11B) is an osteoblast expressed decoy receptor for the receptor activator of

nuclear factor kappa B ligand (RANKL), thus inhibiting osteoclast differentiation by blocking RANK and RANKL docking. RANKL is expressed on osteoblasts, and it promotes osteoclast differentiation by binding to RANK on osteoclast precursors [5,6].

Orthodontic tooth movement: the biological response to sustained force

Orthodontic tooth movement is a process that combines physiologic alveolar bone adaptation to mechanical strains with minor reversible injury to the periodontium [7]. Under normal/healthy conditions, such movement is carried out by highly coordinated and efficient bone remodeling, which requires coupling of bone formation following bone resorption. The classic pressure-tension theory proposes chemical, rather than electric, signals as the stimulus for cellular differentiation and ultimately tooth movement. This theory proposes that, within a few seconds upon force loading, the tooth shifts its position within the PDL space, resulting in PDL compression in some areas and PDL stretch or tension in others (Fig. 2). While blood flow is decreased on the compression side, it is maintained or increased on the tension side. If the loading force is sustained, the alteration in blood flow quickly (in minutes) changes the oxygen tension (O_2:CO_2 level) and the chemical environment by releasing biologically active agents such as prostaglandins and cytokines (e.g. Interleukin (IL)-1β). These chemical mediators differentially affect cellular activities in the compression vs. tension areas within the PDL promoting a net outcome of bone resorption at the compression side and bone formation at the tension side. Force magnitude is associated with varied cellular responses on the compression side. Heavy force cuts off blood flow, resulting in cell death under compression (hyalinization). As a result, no osteoclast differentiation occurs within the compressed PDL space; instead, a delayed recruitment/differentiation of osteoclasts from adjacent bone marrow space is responsible for the "undermining resorption" that removes the lamina dura next to the compressed PDL. Tooth movement follows completion of these processes on the compression side, but not before. Therefore, it usually takes 7—14 days for tooth movement to occur when heavy force is applied. By contrast, light force only reduces blood flow, allowing quick recruitment of osteoclasts either locally within the PDL or via blood flow. These osteoclasts remove the lamina dura in the process of "frontal resorption." Tooth movement begins soon thereafter, usually within 2 days after light force application. Clinically, it is almost impossible to avoid blood vessel occlusion completely, thus hyalinization always occurs to a certain degree and tooth movement is a result of combined undermining and frontal resorption [8].

As discussed, orthodontic loading alters blood flow in the PDL and regional hypoxia develops. The reduction in O_2 tension stabilizes hypoxia inducible factor-1 (HIF-1), a transcription factor that activates vascular endothelial growth factor (VEGF) and RANKL expression in PDL fibroblasts and osteoblasts; osteoclast differentiation is also increased, favoring resorption in areas of compression [9—11]. With mild hypoxia, HIF-1 stimulates cell proliferation and angiogenesis downstream of VEGF, promoting regeneration of the PDL and its blood supply [12]. Hypoxia is a critical initiator for orthodontic tissue remodeling that acts in concert with loading-induced fluid flow, another activator of signaling. The fluid flow hypothesis focuses on osteocyte and fibroblast response to strain due to fluid displacement in canaliculi [13]. Force application initiates a sequence of events including: 1) matrix strain and fluid flow; 2) cell strain; 3) cell activation and differentiation; and 4) tissue remodeling [14]. Mechanoreceptor cells that detect strain are present in the bone, as osteocytes, and in the PDL, as fibroblasts. Loading causes remodeling of mineralized tissue (bone) and non-mineralized paradental tissues (the PDL, gingiva and neurovascular supply) [15]. When teeth are loaded, interstitial fluid is forced through the canaliculi and around osteocytes, causing strain on the cell surface and extracellular matrix. The extracellular matrix (ECM) of bone is a hydroxyapatite-collagen composite and the ECM of PDL is a network of fibrous structural proteins embedded in a polysaccharide gel surrounding cells. Fluid flow applies shear stress to the bone ECM and cell membrane, perturbing Integrins and activating signaling cascades in osteocytes [13,16] (Fig. 3). Integrins are a transmembrane protein that tether a cell's external ECM to its internal cytoskeleton. Integrin stimulation on the cell surface causes release of intracellular molecules that alter osteocyte gene expression, promoting differentiation of osteoblasts and osteoclasts to form and resorb bone. Intracellular calcium rises, increasing phospholipase A activity which releases arachidonic acid, the precursor to prostaglandins; cyclooxygenase (COX) enzymes then convert arachidonic acid to prostaglandins, key inflammatory mediators [7,13,16]. Second messengers cAMP and cGMP are elevated downstream of calcium, prompting phosphorylation events and subsequent gene expression change with release of autocrine and paracrine signals initiating bone turnover (discussed below) [16,17]. Osteocytes are mechanosensors that couple strain from orthodontic loading to tissue remodeling [15]. Fibroblasts serve a similar mechanosensor function in the PDL and gingiva. Strain perturbs the ECM in the PDL and gingiva. Like osteocytes, fibroblasts express transmembrane Integrin receptors. Stress from mechanical loading is transmitted intracellularly from the ECM via integrins, which induce a signaling cascade through focal adhesion kinases (FAK) to alter gene expression, cytoskeletal organization, proliferation and differentiation, and ultimately tissue remodeling [18—20].

Role of inflammation in orthodontic tooth movement

Fluid-induced strain and hypoxia synergistically promote bone and PDL remodeling, by inducing an aseptic inflammatory response devoid of bacteria. Tooth loading causes areas of tension and compression of the PDL and its associated nerve endings and blood vessels. PDL nerve endings are tightly associated with blood vessels. When nerve endings are distorted, they release vasoactive neurotransmitters, like substance P and CGRP, which interact with vascular endothelial cells causing vasodilation and increased permeability with plasma leakage [7,16]. The activated endothelium binds and recruits circulating

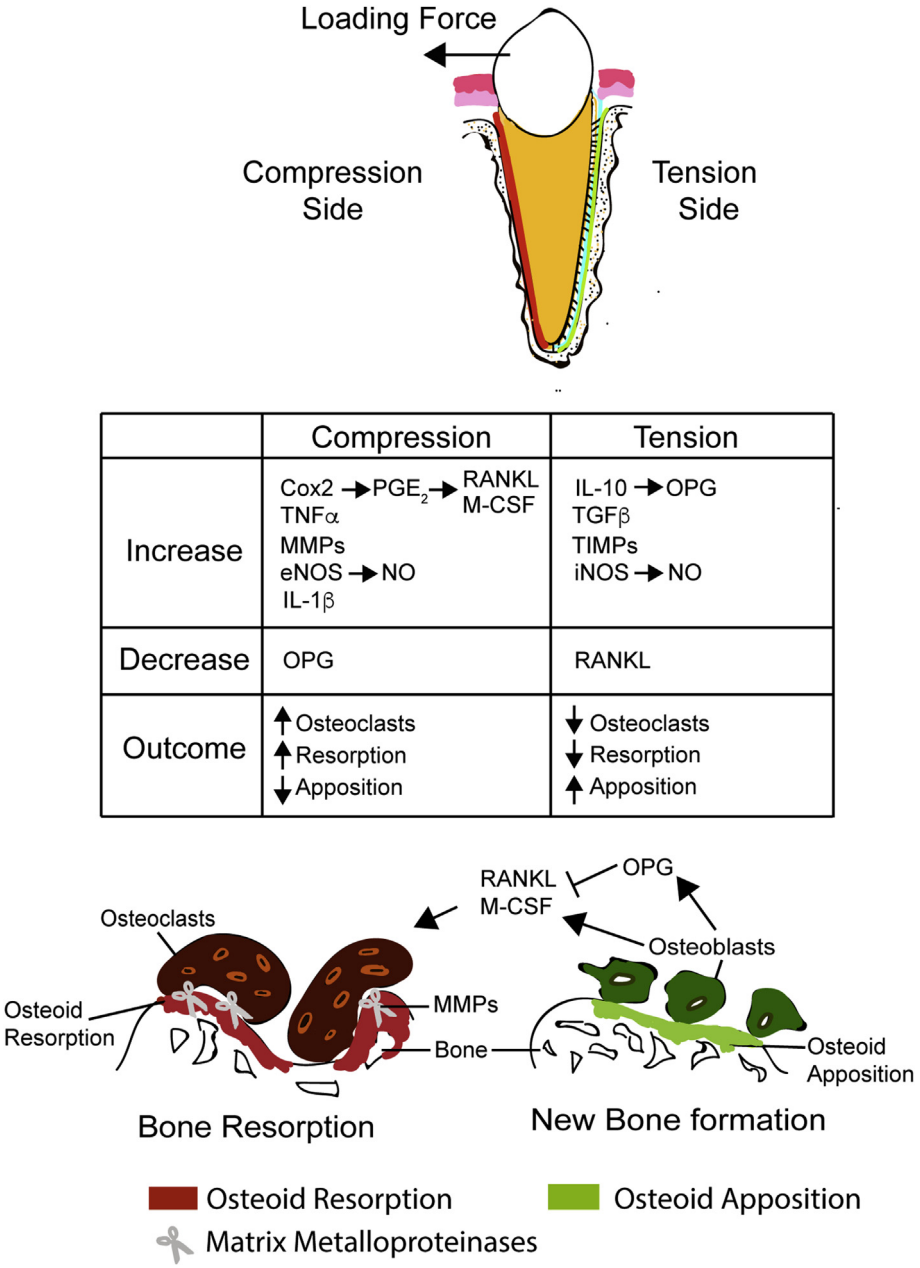

Figure 2. Signaling pathways associated with compression and tension due to orthodontic loading. Distinct signaling factors are upregulated and downregulated associated with compressive and tensile strain, as summarized in the table, with the net outcome of resorption in compression and bone apposition in tension.

leukocytes, monocytes, and macrophages to the PDL, signifying the onset of acute inflammation [15,21]. Leukocytes elaborate cytokines, prostaglandins, growth factors and colony-stimulating factors that promote tissue remodeling [22,23]. After several days, inflammation transitions from acute to a chronic and proliferative process involving fibroblasts, endothelial cells, osteoblasts and osteoclasts.

Native paradental cells, leukocytes, and platelets release a milieu of inflammatory factors initiating functional units to remodel bone and paradental tissues; factors include cytokine IL-1β, IL-6, IL-10, Nitric Oxide (NO), Tissue necrosis factor-α (TNF-α), tissue growth factor β (TGF-β), macrophage colony-stimulating factor (M-CSF), Prostaglandins, OPG, and RANKL. Compression and tension zones are associated with specific mediators regulating resorption and deposition, respectively (Fig. 2). Compression is associated with elevated Cycloxygenase-2 (COX-2) which catalyzes production of prostaglandins, including PGE2, from arachidonic acid [10]. Prostaglandins act on osteoclasts, increasing intracellular cAMP concentrations and boosting their resorptive activity [16]. PGE2 stimulates osteoblast differentiation and expression of RANKL and OPG [10,16]. An increase in RANKL and M-CSF and a decrease in OPG release by osteoblasts collectively favors osteoclast differentiation and bone resorption. Release of cytokines IL-1β and TNF-α induces osteoclast differentiation, function

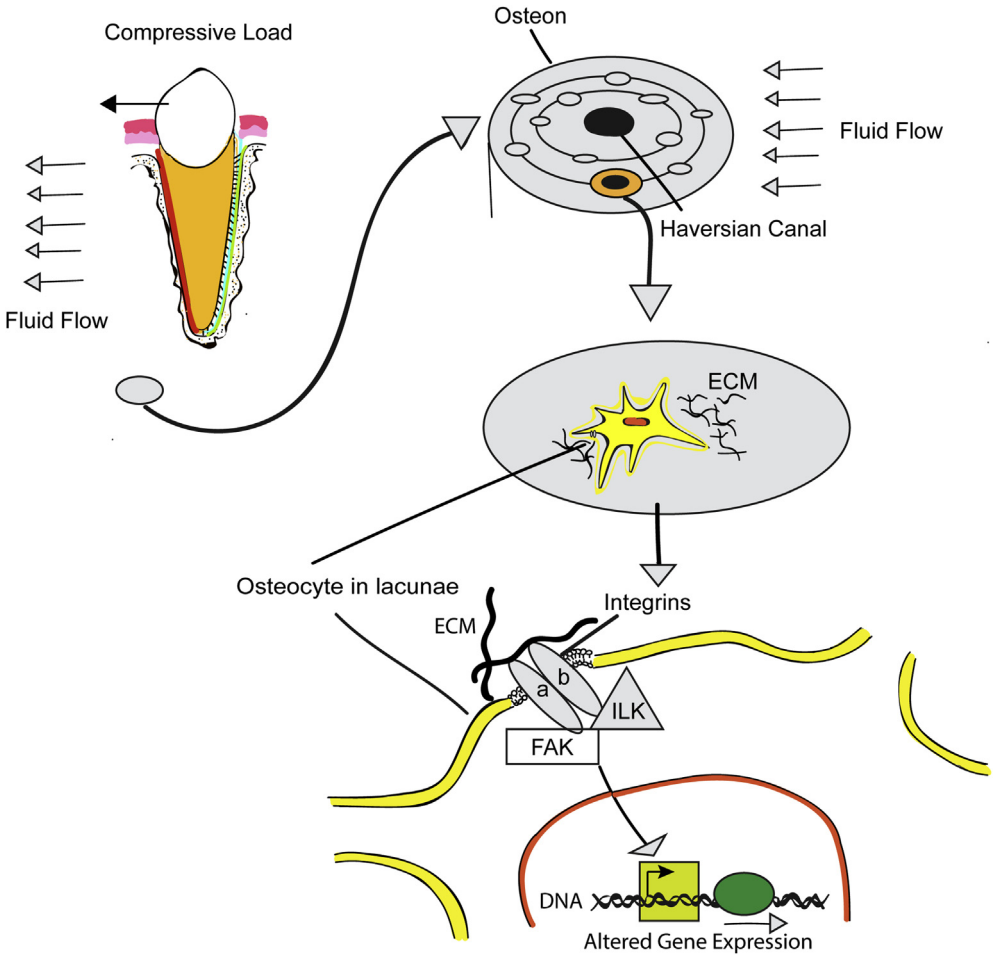

Figure 3. Role of fluid flow in orthodontic tooth movement. Tooth loading causes flow of interstitial fluid around osteocytes, resulting in strain on the extracellular matrix (ECM) perturbing membrane-bound Integrins. Integrins activate focal adhesion kinase (FAK) and an intracellular signaling cascade culminating in altered gene expression and tissue remodeling.

and survival while increasing inflammation and matrix metalloprotease (MMP) levels [10,16,24]. Cathepsins and MMPs including collagenase, degrade PDL ECM and the boney organic matrix, allowing osteoclast attachment for resorption [14]. Compression also activates inducible Nitric Oxide Synthase (iNOS) to produce nitric oxide (NO), which mediates inflammation-induced bone resorption [25]. These factors recruit and activate osteoclasts to form resorptive lacunae in the compressive zone [25]. Tooth movement begins once necrotic tissue is removed by osteoclasts, followed by osteoblasts creating osteoid with new periodontal fibrils embedded in the alveolar bone wall and root cementum (Fig. 2). Compression-induced bone morphogenic protein (BMPs) and Runx2 expression potentiate osteoblast differentiation and bone mineralization, while proliferating and active fibroblasts upregulate ECM fiber production [7,10,26]. The compressed bone and PDL are disassembled and then rebuilt.

Under tension, alveolar bone deposition predominates, with an increase in osteoblast numbers and activity. Tensile strain stimulates osteoblast progenitor proliferation in the PDL and activates endothelial Nitric Oxide Synthase (eNOS) to elaborate NO to mediate bone formation [25]. Cytokine IL-10 increases in areas of tension, boosting OPG and reducing RANKL production by osteoblasts; there is an overall reduction in RANK signaling, favoring bone deposition through inhibition of osteoclast formation, activity and survival [10]. TGF-β is also enriched under tension, and induces proliferation and chemotaxis of PDL cells, upregulates COL-I (collagen gene), recruits osteoblast precursors, induces their differentiation, down-regulates MMPs and upregulates tissue inhibitors of metalloproteases (TIMPs) [15,27]. MMPs and their inhibitors, TIMPs, act in concert to regulate remodeling and have localized expression patterns, suggesting careful coordination of turnover [7,26]. The cumulative result is increased osteoblast and reduced osteoclast activity, with production of bone and remodeled PDL fibers on the side opposite tooth movement (Fig. 2).

Inflammatory factors are central to tissue remodeling for tooth movement, yet many orthodontic patients take nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief that inhibit COX enzymes and their production of PGs, slowing rates of tooth movement. Acetaminophen (Tylenol), on the other hand, acts centrally rather than peripherally and is the preferred pain reliever for orthodontics. In rabbit studies, the rate of orthodontic tooth movement was unaffected by Acetaminophen, while Ibuprofen and Aspirin

resolve pain but slow tooth movement [28,29]. Pharmacological inhibition of inflammation is associated with retarded tooth movement, underlying the importance of inflammation in orthodontic tissue remodeling.

While the inflammatory cascade is critical for orthodontic tooth movement, unregulated or excessive inflammation is problematic. Orthodontic-induced root resorption (OIRR) and remodeling of tissue should be limited to the bone and paradental tissues, excluding the cementum and tooth. However, in 1—5% of orthodontic patients, excessive root resorption is observed, with loss of greater than 4 mm or a third of the original root length [17,30]. Reducing root length diminishes the crown-to-root ratio of affected teeth, with potentially great clinical significance. The cellular mechanism of OIRR is similar to osteoclastic bone resorption and correlates with elevated concentrations of RANKL and reduced OPG in the PDL [16,31,32]. Regulation of bone remodeling is compromised due to excess elaboration of cytokines and pro-resorptive ligands [33]. Inflammation is necessary for orthodontic tooth movement, but if uncontrolled, it leads to tooth destruction, similar to uncontrolled periodontal disease serving as an anti-bacterial defense while causing tissue damage [33]. Orthodontic treatment in patients suffering from periodontal disease is particularly dangerous, as the combination of aseptic inflammation and periodontal-related inflammation cause accelerated attachment loss and disease progression. Orthodontists must carefully screen for periodontal disease to avoid worsening periodontal status via braces due to excessive inflammation, particularly in adult patients.

Acceleration of the orthodontic tooth movement

Understanding the biology underlying orthodontic tooth movement has great clinical implication. The average active orthodontic treatment takes 18—24 months, which is a lengthy commitment. As a result, there has been strong interest in accelerating tooth movement to shorten treatment time, dating back to the 1890s [34]. Technological advancement in areas such as customized brackets and wires has greatly improved treatment efficiency; however, such improvements cannot indefinitely shorten treatment as we are ultimately limited by the biological response during OTM. Another trend in orthodontics is an increase in adult patients seeking treatment. According to the 2015 AAO Economics of Orthodontics Survey, an average orthodontist treated 125 adult patients in 2014, vs. 41 adult patients in 1989, a dramatic increase in recent years [35]. Adult patients can particularly benefit from accelerated orthodontic treatment, since they are not growing and local tissue metabolism and regeneration rates are much slower compared to adolescents. In addition, adult patients are more prone to periodontal complications and other time-dependent side effects (e.g. oral hygiene related problems, root resorption etc). Therefore, there is additional practical benefit to accelerate treatment in adults. Because remodeling of the alveolar bone is the key component of orthodontic tooth movement, a number of techniques, either surgical or nonsurgical, have been exploited to expedite tooth movement by interfering with biological pathways affecting activity of bone cells (osteoclasts, osteoblasts, and osteocytes).

Surgical techniques to accelerate orthodontic treatment have been tested for over 100 years in clinical practice [36]. The initial approaches involve alveolar osteotomy alone (defined as a surgical cut through both the cortical and trabecular bones) or combined with corticotomy (defined as a surgical cut where only the cortical bone is involved) to create a movable "bony block", and it was believed then teeth were moved faster by reducing the resistance exerted by the surround cortical bone. These approaches have been extremely invasive and associated with increased tooth morbidity and risk of periodontal damage (mainly in cases in which the interradicular space is less than 2 mm) [36—38]. Modern approaches have abandoned the concept of the bony block, and selective alveolar corticotomy has become a reproducible gold standard. Wilcko et al. were first to suggest that rapid tooth movement after corticotomy may be due to a demineralization-remineralization process that produces a regional acceleratory phenomenon (RAP) of bone remodeling, rather than movement of a bony block that contains a tooth [39]. In addition to bone density, RAP is also negatively influenced by the degree of hyalinization of PDLs. Corticotomy leads to increased chemoattraction of macrophages. The early disappearance of the hyaline zone by these macrophages contributes to the acceleration of tooth movement around the corticated alveolar area [40—42]. The duration of RAP usually lasts about 4—6 months in human bone [39]. The amount of movement during RAP period was doubled, at the rate of ~1 mm/month in animal studies [43—45]. More recent techniques include further refinement with minimally invasive procedures that require no flap, such as piezoelectricity and corticision [46,47]; these become more attractive due to the decrease in possible side effects.

While acceleration of orthodontic tooth movement by surgical techniques has been shown to be effective, nonsurgical approaches have always been preferred by clinicians and patients for their noninvasiveness. Such techniques range from systemic/local administration of biological molecules to innovative physical stimulation technologies such as resonance vibration, magnetic filed forces, cyclic forces, light electrical currents, low-intensity laser irradiation and photobiomodulation. All these methods have shown favorable outcomes with varying success. In particular, exogenous application of compounds (e.g. Prostaglandins) that are endogenously produced and affect bone remodeling have been tested for accelerating tooth movement; however, the results were disappointing as local administration of these agents was linked to increased risk for root resorption and pain [48,49]. New agents, such as Epidermal Growth Factor (EGF) [50], Parathyroid Hormone (PTH) [51,52], 1,25-Dihydroxyvitamin D3 [53], Osteocalcin [54,55] etc. are currently tested in animal studies and some have shown promising acceleratory effects; however, their safety and efficacy in humans remains to be further investigated. Physical stimulation techniques have becoming more attractive to patients and orthodontists as they are noninvasive and pain free. However, their clinical efficiency remains to be determined and more scientific evidence from randomized studies is needed before broad clinical adoption occurs.

Conclusions/Future directions

Improving the quality, rate and stability of orthodontic tooth movement is the goal of the practice. A better understanding of biological mechanisms underlying tooth movement helps guide our efforts towards new approaches to solve current challenges of orthodontic treatment. In particular, a mechanistic understanding of tooth movement could help in developing acceleratory techniques for orthodontics. This is needed now, more than ever, due to our growing adult patient base that requires more efficient, lower risk, interdisciplinary care. Future research is needed to enable the translation of biological concepts into clinical practice.

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