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Orthodontic force, tooth movement, and interleukin-1β

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ABSTRACT : This review presents the basic knowledge and understanding of the biological processes involved in the orthodontic force and tooth movement. It also explains one of the basic inflammatory markers that was the "interleukin-1β" (IL-1β). Because orthodontic mechanic has to be carefully used during treatment, traumatic effects on the periodontium and teeth may occur. Proper understanding of biological events will help design orthodontic force that will produce minimal tissue damage. In addition, inflammatory markers such as IL-1β play a critical role in bone remodeling and tooth movement. This may be of benefit in understanding how it works and the relevance of the concepts to clinical practice.

Key Words : orthodontic force, tooth movement, interleukin-1beta, biomarker, inflammatory

Introduction

Orthodontic tooth movement is the result from applying forces to teeth. This activation evokes cellular responses in the teeth and their surrounding tissues, including the periodontal ligament, alveolar bone, and gingiva. It is advantageous for the orthodontist to know the details of the biological events that unfold during tooth movement, because some of these details from one person may differ to another. This is due to variables such as gender, age, psychological status, nutritional habits, and drug consumption. These biological variations also cause the differences that are frequently observed in the outcomes of orthodontic treatment between patients with similar malocclusions, treated identically[1)].

The essence of orthodontic treatment is the movement of teeth through bone to obtain a more perfect dental occlusion. Accurate and precise control of tooth movement can be optimized with the proper use of mechanics and knowledge of the subsequent tissue response. Although the art of repositioning teeth has been practiced for centuries, the exact mechanism by which orthodontic forces orchestrate tooth movement is not thoroughly understood. However, despite recent advances, the molecular basis for the conversion of the orthodontic pressure stimulus into cell-mediated bone modeling followed with tooth movement is not completely resolved[2, 3)].

1. Optimal mechanical force for orthodontic tooth movement

Tissue remodeling that facilitates orthodontic tooth movement is performed by various cell types. Some of these cells are local, such as fibroblasts and bone surface lining cells. Other cells are migratory, like macrophages and lymphocytes, but evidently play a crucial role in modulating the effect of mechanical forces on paradental cells. Thus, an optimal orthodontic force is capable of evoking an inflammatory response in paradental tissues, leading to remodeling of these tissues and tooth movement in a desirable direction.

For the past decade, there were many studies about optimal force in orthodontic tooth movement conducted in animals and human[4-12)]. The current concept of optimal force is led based on the hypothesis that a force of a certain magnitude and temporal characteristics (continuous vs. intermittent, constant vs. declining, etc.)

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would be capable of producing a maximum rate of tooth movement without tissue damage and with maximum patient comfort[5]. The optimal force for tooth movement may differ for each tooth and for each individual patient.

Many authors have expressed the similar opinion that an optimal force is the least harmful to cells, leaving most or all of them unharmed. However, Storey[13] suggested that some tissue damage is unavoidable, and is actually beneficial, because it evokes inflammation. Schwarz[5] tried to equate this force with the capillary blood pressure, and recommended to use force magnitudes below this pressure level. To reach this goal, he suggested applying forces not greater than 15-30 g. per cm^2 through root surface. However, practically it is difficult to measure accurately these forces, and in most cases the force distribution in the periodontal ligament (PDL) is uneven, resulting in areas of great strain, as well as areas of little strain[10]. Reitan and Rygh[7, 14] favored interrupted forces, because such forces reduce the risk of dental pulp pathology, provide adequate time for tissue reorganization, reduce the degree of relapse after tooth rotation, and are particularly suitable for treatment of adults. They postulated that such forces allow the PDL fibers to maintain a functional arrangement, improve the circulation, and increase the number of PDL cells. Moreover, when these forces are light, they can cause only semi-hyalinization, or incomplete necrosis of PDL cells, with less disturbed resorption of the alveolar bone.

In 1998, Blechman[15] proposed that static magnets generate electromagnetic fields which stimulate bone formation in PDL tension sites, thereby reducing tooth mobility, pain, and discomfort. He stated that in routine orthodontic treatment, bone formation occurs after resorption, resulting in widening of the periodontal space and increasing tooth mobility. Re-examination of histological section of cat jaws in the combination of orthodontic force/ electric signals by Davidovitch *et al*[16] supported Blechman's proposition. These observations suggest that an optimal orthodontic force is accompanied by an additional signal, such as an electric current, which accelerates the rate of alveolar bone formation.

In an experiment with avian long bones, Lanyon and Rubin[17-19] observed that the most efficient force was dynamic (intermittent) rather than static (continuous). A short duration of 5-10 minutes a day was adequate time to stimulate a potent periosteal and endosteal osteogenic reaction. The force magnitude found to be important and defined as optimal was in range of 2,000-4,000 microstrain. However, this magnitude could be much lower if the frequency of force application was increased.

Gibson *et al* had performed experiments in rats and reported that only 1 hour of force application was sufficient to cause maxillary molars to move mesially for 2 weeks[20]. However, to achieve this movement required the extraction of the mandibular molars, to prevent occlusal contacts. Unfortunately, this approach is not a viable option in human orthodontic practice.

A meta-analysis of the literature concerning the optimal force or range of forces for orthodontic tooth movement was performed by Ren *et al*[4]. This indicated that there are several studies on human maxillary canines with force ranges from 18 to 450 gm. and there are variations in several factors in each experiment. The study of Lee[10] found that optimal force should be between 150 to 200 gm. And in a few years later, he studied in moving human maxillary canines for 7 weeks and found that the highest rate of tipping movement was 0.78-1.34 mm./wk., the force ranged from 337 to 388 gm. For the bodily tooth movement, the highest rate was 0.86-1.37 mm./wk., the force ranged from 354 to 375 gm[14]. However, a threshold for force could not be defined. It was concluded that a wide range of forces can be identified, all of which lead to maximum rate of tooth movement.

2. The effects of mechanical force on tissues and cells

In 1911-1912, Oppenheim reported that tooth movement in one pre-adolescent baboon resulted in complete remodeling of the entire alveolar process[21]. This result indicated that orthodontic force effects spread beyond the constraints of the PDL. The effects of orthodontic force magnitude on the dog's paradental tissue responses was examined by Schwarz[5]. He concluded that an optimal force is smaller in magnitude than that capable of occluding PDL capillaries. Furthermore, he suggested that occlusion of the blood vessels would lead to necrosis of surrounding tissues, which could harm the tissues and slow down the rate of tooth movement.

These are consistent with Reitan's opinion. He conducted comprehensive histological examinations of paradental tissues incidental to tooth movement. These studies were conducted on a variety of species, including rodents, canines, primates, and humans. Reitan preferred the use of light intermittent forces, because they cause minimal amounts of tissue damage and cell death. He noted that the nature

tissue response differs from species to species, limitting the value of extrapolations. Experimenting in rabbits, Storey reported in observing migration of leukocytes out of PDL capillaries 20 minutes after orthodontic force application to incisors[13]. He concluded that inflammation is an integral part of the tissue response in orthodontics. In the view of participation of blood-borne cells in the remodeling of the mechanically stressed PDL was confirmed by Rygh. He detected macrophages at the edge of the hyalinized zone during the early phases of treatment[22].

Teeth can be induced to move from one location in the oral cavity to another, by the remodeling of tissues in response to the applied forces. The agents responsible for this biological response are the various cell types that populate the affected tissues. In orthodontics, the effect of applied mechanical forces may be assessed on basis of the response of single cells, and of groups of interconnected, neighboring cells. Such cell-to-cell interactions in the PDL and alveolar bone may not be limited to cells of the same type, but rather to cells derived from different systems, such as osteoblasts and macrophages.

Although the effects of mechanical stimulation have been studied in many tissues, especially for the orthodontic treatment, the effects of forces derivatives on bone and paradental tissues are of particular importance[23]. It is known that bone cells (osteoblasts and osteoclasts) respond to orthodontic force by proliferation and increased activity; however, the mechanisms for conversion of orthodontic force into biologic activity are not completely understood[2]. Since the decade 1960s, there had been demonstrated that orthodontic force produced the alveolar bone deflection accompanied with changes in periodontal ligament[24, 25]. These events initiate the mechanical stress and induced an electrical charge polarization referred to a piezoelectric response. In electronegative regions, bone formation occurs, whereas bone resorption predominates in electropositive areas. Both in vitro and in vivo studies indicate that areas that have been described as predominantly osteoblastic were routinely electronegative and areas of positivity or electrical neutrality were characterized be elevated osteoclast activity.

Mostafa et al. represented an interesting flow chart of the events that may influence tooth movement response to orthodontic force application (Fig. 1). This separated into 2 pathways[2].

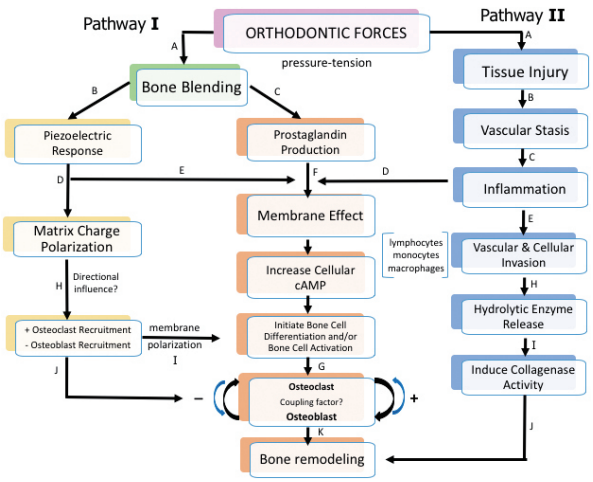

Fig. 1 Two possible biologic pathways generated by orthodontic forces. Pathway I shows the possibility of the major biologic response to orthodontic force ; pathway II shows the possibility of a secondary effect (modified from Mostafa *et al*, 1983)[2].

Pathway I

Orthodontic force creates vectors of pressure and tension, then generation of tissue bioelectric polarization in response to bone bending occurs, accompany with prostaglandin synthesis by bone cells or the piezoelectric effects themselves (I, C, E). After that both prostaglandin synthesis and membrane electrical polarization by the piezoelectric process act on changes in the levels of cAMP (I, F)

Changes in cAMP levels have been correlated with alteration in cell proliferation, differentiation, and activation. The results of these changes are increasing in the number of the cells involved in bone formation and resorption. It has recently been suggested that bone formation and resorption are synchronized by a diffusible product produced by the osteoblast, "*Coupling factor*"[26]. This would provide for a mechanism in which net bone formation equaled net bone resorption. The coupling factor could then explain the observation that both bone resorption and formation occur in area of pressure and tension, so maintaining the alveolar bone plate thickness.

Pathway II

The tissue injury generated by orthodontic force elicits a classic inflammatory response (II, C). Inflammatory processes are triggered along with the classic vascular and cellular infiltration (II, E). Lymphocytes, monocytes, and macrophages invade the inflamed tissue and, in all likelihood, contribute to prostaglandin release (II, D) and hydrolytic enzyme secretion (II, H).

It has been reported that local inflammatory responses stimulate osteoclast activity. This increase in osteoclast activity is believed to be generated by local elevation of prostaglandin (II, F) and the subsequent increase in cellular cAMP (II, G). The inflammatory response is also characterized by hydrolytic enzyme secretion (II, I). It is believed that collagenase exists in an inactive form and may be activated by hydrolytic action, so it is probable that increased collagenase activity contributes to increased bone remodeling (II, J). It appears that the inflammatory response is a component of responses to orthodontic force and that this mechanism most likely plays a contribution role during bone remodeling[2].

3. Effects on nervous and immune systems

In the view of nervous and immune systems in relation of bone remodeling process, Davidovitch *et al*[27] demonstrated that these systems were influenced by neuropeptides and cytokines in the PDL and alveolar bone. Furthermore, the response of the paradental tissues to orthodontic forces is physical and chemical in nature. When applying orthodontic force, the extracellular fluids of the PDL must be displaced to permit distortion of fibers and cells[28]. Movement of fluids causes

1. Change in physical and chemical of PDL and bone cells
2. Change in nervous system : peripheral nerve fiber
3. Change in the cells of immune system

Change in physical and chemical of PDL and bone cells

When applying orthodontic force, tooth moves within the PDL space and increasing compression of blood vessels as pressure increases in the PDL. The extracellular fluid is displaced, then the movement of tissue fluid will happen and follow with translocation of ion and molecules, leading to interactions with cell surface charges[28]. These charges presumably to interact with osteocytes' cell membrane, reflects in alterations in contents of intracellular "*second messengers*" such as Ca^{2+}, adenosine 3', 5'-monophosphate (cAMP), and guonosine 3', 5'-monophosphate (cGMP). These second messengers will change in synthesis and secretion of cell products, cell proliferation, motility, etc.

Change in nervous system : peripheral nerve fiber

Stress from orthodontic force causes in distortion of nerve ending follow with releasing of stored neurotransmitter, react centrally by stream toward the ganglion, and peripherally by interact with adjacent target cells, primarily in the walls of blood vessels.

Change in the cells of immune system

Neuropeptides from activated peripheral nerve ending such as substance P(SP), vasoactive intestinal polypeptides (VIP), calcitonin gene related peptide (CGRP) have shown to effect on vascular system.

As a result of changing in nervous system, cells of immune system and interaction on vascular endothelial cells, there will be the extravascular migration of macrophages and lymphocytes, follow with synthesis and secrete various types of mediators (Fig. 2). These responses are likely to the parts of inflammatory processes that complex, continuously changing series of responses by the body to injury. It is an effort to counteract noxious stimuli and repair or replace damaged tissue. These inflammatory-liked processes effect on PDL and bone cells such as change in synthesis and secretion of cell products, cell proliferation, motility, etc. resulted in alveolar bone remodeling. Recent studies of mechanisms regulating bone remodeling have concentrated on the role of cytokines (cyto = cell , kines = kinesis) since these factors appear to have crucial roles in both normal and pathologic bone cell function[29-31].

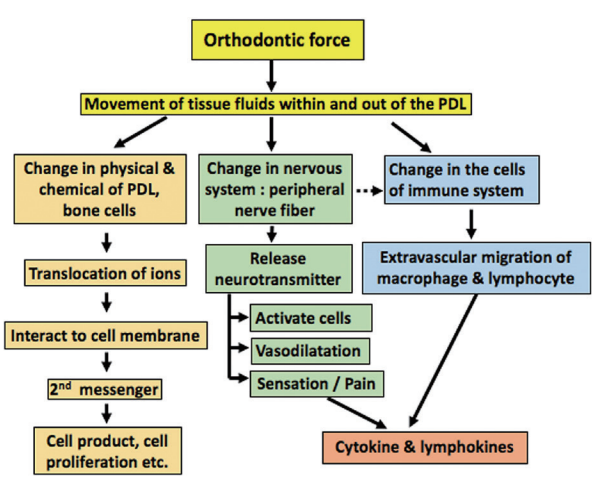

Fig. 2 A schematic model for the possible involvement of the nervous system, immune system and interaction between physical and chemical factors. (Modified from Davidovitch *et. al*, 1988)[27]

In essence, the above steps represent the development of an acute inflammatory reaction in orthodontically strained paradental tissues. These processes induce the exposing these tissues to systemic factors, such as

immune cells, drugs, and nutritional components. Directed evidence for modified or enhanced cellular activities during tooth movement can be found in oral fluids, particularly in gingival crevicular fluid (GCF) of treated teeth.

The GCF is an osmotically mediated inflammatory exudate found in the gingival sulcus. As an exudate, it tends to increase in volume with inflammation and capillary permeability. The GCF flow rate has been shown to be a reliable indicator of gingivitis development during experimental induction of gingivitis[32]. Furthermore, Glycosaminoglycan (GAG) components have been detected in GCF samples from sites around teeth affected by such conditions as chronic gingivitis, chronic periodontitis, and juvenile periodontitis. The presence of sulfated GAG chondroitin sulfate (CS) in GCF has been associated with those clinical situations in which degradative changes were occurring in the deeper periodontal tissues of alveolar bone and the PDL. Consequently, GCF analysis may derive from the basis of a special test for the assessment of various clinical conditions, such as the active phases destructive periodontal disease.

4. Effects of orthodontic treatment on GCF

During orthodontic treatment, the forces exerted produce a distortion of the PDL extracellular matrix, resulting in alterations in cellular shape and cytoskeletal configuration and creating short-lived piezoelectric spikes that can lead to cellular activation by changing membrane polarity and ion channel activity. This distortion of the periodontal tissues also induces neuropeptide release from afferent nerve endings. Some of these molecules are vasoactive, causing vasodilatation and migration of leukocytes into the extravascular space. These migratory cells synthesize and secrete a wide variety of cytokines and growth factors. In addition, as the capillaries are stretched or compress excessively, tissue damage may occur. Such events and interactions lead to the synthesis and secretion of extracellular matrix components, tissue-degrading enzymes, acid, and local factors ; induces cellular proliferation and differentiation ; and promote wound healing and tissue remodeling. In vivo studies suggest that as biologic reactions progress at varying rates and intensities during different periods of treatment, alternate combinations of biochemical molecules come into play. These combinations are dependent on alveolar remodeling dynamics, the cycles of injury and healing, and the composition of the PDL cell population at each period[33]. Such changes in the deeper periodontal tissues may modify both the GCF flow rate and its components. Thus, analysis of GCF samples may help in assessing tissue status around teeth undergoing orthodontic movement and provide a useful instrument for the modification of orthodontic treatment procedures.

5. Effects of orthodontic treatment on GCF composition

After exposure to orthodontic forces, periodontal cells are stimulated to produce cytokines, growth factors, and colony-stimulating factors that may function as autocrines or paracrines. This process is reflected in the synthesis and secretion of extracellular matrix components and tissue-degrading enzymes and acids, resulting in modification of GCF composition[34].

6. Mineralized tissue components and other markers of bone turnover

Already seen GAGs : The substances in this group are CS, dermatan sulfate, heparan sulfate (HS), and the non-sulfated GAG, hyyaluronic acid (HA). They are found in the extracellular matrix of mineralized and other connective tissues, and are negatively charged complex carbohydrates, linked covalently, in the native state, to a core protein to form proteoglycans[35].

7. Other mineralized tissue components

This group is used routinely to provide information on bone resorption and formation in the evaluation of bone disorders such as Paget's disease, hyperparathyroidism, and osteoporosis. There had been reported the used of marker of this group such as "osteocalcin" to examine in relation to orthodontic tooth movement[36].

8. Mediators of the inflammatory processes

Storey proposed that the early phase of tooth movement involves an acute inflammatory response characterized by periodontal vasodilatation and migration of leucocytes out of the capillaries[13]. Recent study has led to the hypothesis that after mechanical stimulus, inflammatory mediators are released, triggering the biologic processes associated with alveolar bone

resorption and apposition[34]. Among the local biochemical mediators are the cytokines, which are secreted by mononuclear cells and leukocytes. Cytokines can provoke the synthesis and secretion of numerous substances that form the molecular basis for cell-to-cell communication, thus interacting directly or indirectly with bone cells[27, 34]

9. Tissue-degrading enzymes

Based on the cycles of injury and healing, several combinations of tissue-degrading or tissue-repairing enzymes come into play, following the mechanical perturbation induced by orthodontic forces. For example,

1) Interstitial collagenases were suggested to initiate the degradation procedures in periodontal tissues during orthodontic tooth movement
2) β-glucuronidase, the lysosomal enzyme that is a marker of primary granule release from polymorphonuclear leukocytes. It takes part in the degradation processes of mucopolysaccharides of connective tissues.
3) Acid and alkaline phosphatase
4) Matrix metalloproteinase
5) Proteinases : serine, cysteine proteinases

10. Chemical mediators and IL-1ß

The early phase of orthodontic tooth movement involves an acute inflammatory response characterized by periodontal vasodilation and the migration of leucocytes out of periodontal ligament capillaries. Inflammatory mediators may trigger the biological processes associated with alveolar bone resorption and apposition[35]. Previous research has suggested that local mediators such as prostaglandins, interleukins and growth factors play an important role in bone remodeling induced by orthodontic forces[37-39]. Some of these cytokines, particularly interleukin 1α (IL-1α) and IL-1β, tumor necrosis factor-α (TNF-α), and gamma interferon (γ-IFN), have been implicated in the mediation of bone remodeling process in vitro. IL-1 is distinguished from the others because there are many reviews and studies about it, indicating that IL-1 is the first polypeptides mediator of immune cell function and regulates bone resorption and formation[40-42].

IL-1β has been shown to be the most potent cytokine to stimulate osteoclast activity and attract leukocytes and other cell mediators to process bone remodeling. It is the first polypeptide mediator of immune cell function to regulate bone resorption and bone formation by mechanical stress[27, 43]. Moreover, IL-1β is one of the inflammatory chemical mediators which induce the secretion of pain producing substances[44]. Importantly, IL-1β is produced by the PDL in sufficient quantities to diffuse into the GCF, and could be identified as biomarkers of orthodontic tooth movement[45, 46]. Luppanapornlarp *et al*[47] studied the optimum orthodontic force, IL-1β levels, pain due to orthodontic tooth movement using different magnitudes of continuous forces from a broader point of view. The data of this study confirmed that IL-1β was expressed in GCF both from a healthy control canine with no force and the experimental teeth subjected to continuous forces of either light or heavier forces. Moreover at 24 hours, IL-1β concentration from a heavier force showed the highest data than the lighter one.

Nowadays there are many reports on cytokine production in alveolar bone and in PDL during tooth movement. More studies report effect of orthodontic forces on levels of inflammatory markers of cytokines, chemokines, receptors and their antagonists, which have been widely documented in GCF. The association of cytokine and receptor levels or activity index in GCF with velocity of tooth movement, nature of force applied, pain intensity, and growth status/age of the subjects, are concluded that application of orthodontic forces causes an immediate release of inflammatory bone-resorptive mediators (IL-1β, TNF-α) in 1 hour that reach peak in 24 hours, thus supporting the role of inflammation in initial orthodontic tooth movement. Moreover, the levels of cytokines decrease after attaining peak values, mostly at 24 hours in continuous forces but repeated activations in interrupted force upregulate their secretion. It was also concluded that a rise in GCF levels of IL-1β with higher force levels (150 vs 50 g) has been linked to increased pain intensity during orthodontic tooth movement. In addition, increased velocity of tooth movement has been correlated with a greater activity index in GCF[48].

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