

# Biological response at the cellular level within the periodontal ligament on application of orthodontic force – An update

Nazeer Ahmed Meeran

## ABSTRACT

Orthodontic force elicits a biological response in the tissues surrounding the teeth, resulting in remodeling of the periodontal ligament and the alveolar bone. The force-induced tissue strain result in reorganization of both cellular and extracellular matrix, besides producing changes in the local vascularity. This in turn leads to the synthesis and release of various neurotransmitters, arachidonic acid, growth factors, metabolites, cytokines, colony-stimulating factors, and enzymes like cathepsin K, matrix metalloproteinases, and aspartate aminotransferase. Despite the availability of many studies in the orthodontic and related scientific literature, a concise integration of all data is still lacking. Such a consolidation of the rapidly accumulating scientific information should help in understanding the biological processes that underlie the phenomenon of tooth movement in response to mechanical loading. Therefore, the aim of this review was to describe the biological processes taking place at the molecular level on application of orthodontic force and to provide an update of the current literature.

**Key words:** Interleukins, orthodontic force, periodontal ligament, prostaglandins

## INTRODUCTION

Teeth can be moved through the alveolar bone when appropriate orthodontic force is applied to them. This is mainly due to the fact that mechanical loading of a biological system results in strain, which subsequently leads to biological responses at the cellular and molecular level, aiming at adaptation of the system to the changed conditions.<sup>[1]</sup> As a result of this principle, remodeling of the periodontal ligament (PDL) and the alveolar bone takes place around teeth on application of orthodontic force.<sup>[2]</sup> Recent research in the biological basis of tooth movement has provided detailed insight into cellular, molecular, and tissue-level reactions to orthodontic forces.<sup>[3,4]</sup> There are many theories proposed regarding orthodontic tooth movement.<sup>[5-8]</sup> The pressure-tension theory proposed by Schwartz in 1932 is the simplest theory describing tooth movement on mechanical loading.<sup>[7]</sup> On the pressure side, the biological events are as follows: disturbance of blood flow in the compressed PDL, cell death in the compressed area of the PDL (hyalinization), resorption of the hyalinized tissue by

macrophages, and undermining bone resorption by osteoclasts beside the hyalinized tissue, which ultimately results in tooth movement. On the tension side, blood flow is activated where the PDL is stretched, which promote osteoblastic activity and osteoid deposition, which later mineralizes.<sup>[9,10]</sup>

The fluid flow hypothesis, describing a mechanism by which osteocytes respond to mechanical forces, states that locally evoked strain derived from the displacement of fluid in the canaliculi is very important.<sup>[11]</sup> When loading occurs, interstitial fluid is squeezed through the thin layer of the non-mineralized matrix surrounding the cell bodies and cell processes, resulting in local strain at the cell membrane and activation of the affected osteocytes.<sup>[12]</sup>

According to piezoelectric theory, there is production of piezoelectric signal on application of orthodontic force, which quickly reduces to zero. On removal of the mechanical force, the piezoelectric signal is again produced, but in the opposite direction. The possible sources of this electric current could be

Departments of Orthodontics and Dentofacial Orthopedics,  
Priyadarshini Dental College and Hospital,  
Tamil Nadu, India

**Address for correspondence:** Dr. Nazeer Ahmed Meeran,  
Old No 6, New No 11, NGO Colony First Street,  
Nanganallur, (Kendriya Vidyalaya School Road),  
Chennai – 600 114, Tamil Nadu, India.  
E-mail: nazeerortho@yahoo.co.in

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collagen, hydroxyapatite, or the mucopolysaccharide fraction of the ground substance.<sup>[13]</sup> On application of orthodontic force, the alveolar bone adjacent to the tooth bends and the area of concavity accumulates negative charges, resulting in bone deposition. Areas of convexity are associated with positive charges, resulting in bone resorption. These currents are affected by the nature of the fluid present within the canaliculi. The small voltages thus generated are called “Streaming Potentials.”<sup>[13]</sup>

Recently,<sup>[14]</sup> it has been proposed that the pressure-tension theory is not simple and might involve more complicated biological tissue response, suggesting that bone apposition could be induced by (1) the load exerted by stretched fibers of the PDL, which may also induce a slight bending of the alveolar wall; (2) direct resorption by unloading of the alveolar wall in the case of low forces; and (3) indirect resorption as repair due to ischemia following the application of high forces.<sup>[14]</sup> Schwarz proposed the classic concept of the optimal force.<sup>[15]</sup> He defined optimal continuous force as “the force leading to a change in tissue pressure that approximated the capillary vessels’ blood pressure, thus preventing their occlusion in the compressed periodontal ligament.” According to Schwarz,<sup>[15]</sup> forces well below the optimal level cause no reaction in the PDL. Forces exceeding the optimal level would lead to areas of tissue necrosis, thereby preventing frontal bone resorption. Tooth movement would thus be delayed until undermining resorption eliminates the necrotic tissue obstacle.

## INFLAMMATORY MEDIATORS IN THE PERIODONTAL LIGAMENT

### Prostaglandins

Prostaglandins (PGs) are a group of chemical messengers and are derivatives of arachidonic acid.<sup>[16]</sup> They are synthesized within seconds following physical injury to the cells and tissues.<sup>[16]</sup> Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) is a potent vasodilator and can increase the vascular permeability. It also has chemotactic properties and can stimulate the formation of osteoclasts, resulting in a subsequent increase in bone resorption. PGs are produced through two different pathways by the action of the enzyme cyclooxygenase on arachidonic acid: the constitutive isoform or cyclooxygenase-1 (COX-1) and the inducible isoform or cyclooxygenase-2 (COX-2). The PGs resulting after either pathway activation are different.<sup>[16]</sup>

The COX family of enzymes consists of two proteins that convert arachidonic acid, a 20-carbon polyunsaturated fatty acid comprising a portion of the plasma membrane phospholipids of most cells, to PGs.<sup>[17]</sup> The constitutive isoform (COX-1) is found in almost all tissues and is tissue protective. In contrast, COX-2, the inducible isoform of COX, appears to be limited in basal conditions within most tissues, and *de novo* synthesis is activated by cytokines, bacterial lipopolysaccharides, or growth factors to produce PGs in large amounts during inflammatory processes occurring due to cell injury.<sup>[18]</sup>

It has been found that PGs have an important role in promoting bone resorption. Although the exact role of PGs in bone resorption is not clear, it is thought to do so by stimulating cells to produce cyclic adenosine monophosphate, which is an important chemical messenger for bone resorption.<sup>[19,20]</sup>

Research proved that the application of orthodontic force increased the synthesis of PGs, which in turn stimulated osteoclastic bone resorption.<sup>[21]</sup> A similar study on cats by Davidovitch *et al*,<sup>[22]</sup> also showed increased levels of PGE<sub>2</sub> in the alveolar bone, as a result of application of orthodontic force. The histological data were supported by the finding of Chumbley *et al*,<sup>[23]</sup> that Indomethacin, an inhibitor of PG synthesis, also inhibited orthodontic tooth movement.

Leiker *et al*<sup>[24]</sup> studied the long-term effects of varying concentrations and frequencies of injectable, exogenous PGE<sub>2</sub> on the rate of tooth movement in rats and reported that injections of exogenous PGE<sub>2</sub> over an extended period of time in rats did enhance the amount of tooth movement. However, there was an increase in the amount of root resorption with increasing numbers and concentrations of the PGE<sub>2</sub> injections, which could be a potential concern.

Sekhvat *et al*,<sup>[25]</sup> reported that Misoprostol was effective in enhancing tooth movement in doses as low as 10–25 µg/kg, twice daily. It was also noticed that Misoprostol did not significantly increase the amount of root resorption. They suggested that oral Misoprostol could be used to enhance orthodontic tooth with minimal root resorption. However, long-term studies are needed to justify the use of PGs to accelerate orthodontic tooth movement in clinical practice.

### Cytokines

Orthodontic forces result in capillary vasodilatation in the PDL, resulting in migration of inflammatory cells as well as cytokine production by these cells. This in turn helps in the process of bone remodeling.<sup>[26]</sup> Cytokines are proteins acting as signals between the cells of the immune system, produced during the activation of immune cells and usually act locally although some act systemically with overlapping functions. Cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) have been proved to be associated with bone remodeling.<sup>[27]</sup>

IL-1 predominantly exists in two forms,  $\alpha$  and  $\beta$ , of which IL-1 $\beta$  is the form mainly involved in bone metabolism, stimulation of bone resorption, and inhibition of bone formation. IL-1 $\beta$  also plays a central role in the inflammatory process, and large amounts of IL-1 $\beta$  are present in inflamed gingival tissues. They are released within 12 to 24 h after orthodontic force application and play an important role in initiating bone resorption and tooth movement.<sup>[28]</sup>

It was found that both macrophages and neutrophils predominate in IL-1 $\beta$  production in inflamed gingival tissues.<sup>[29]</sup>

The staining of feline PDL cells for IL-1 $\beta$  showed the presence of bound signal complexes in the plasma membrane, which was expected, as it is known that receptors for IL-1 $\beta$  are present on fibroblasts.<sup>[30]</sup>

IL-6 is produced by both lymphoid and non-lymphoid cells and can induce osteoclastic bone resorption through an effect on osteoclastogenesis.<sup>[31,32]</sup> IL-6 has been identified in human gingival tissues and cells; and participates in the molecular events associated with inflammatory periodontal diseases<sup>[33]</sup> and tissue destruction in periodontitis.<sup>[34]</sup>

The levels of IL-6 increase significantly 24 h after mechanical loading and play an important role in initiating tooth movement. After the application of force, the induction of both IL-1 $\beta$  and IL-6 was observed to reach a maximum on day 3 and to decline thereafter.<sup>[35]</sup>

TNF- $\alpha$  is a pro-inflammatory cytokine that is often over-expressed in periodontitis and is responsible for alveolar bone resorption during periodontal breakdown.<sup>[36-38]</sup> The possibility that TNF- $\alpha$  is involved in normal physiological processes is supported by its function in osteoclastogenesis. Receptor activator of nuclear factor kappa-B ligand (RANKL) and its receptor receptor activator of nuclear factor k B (RANK), which are present on osteoblasts and precursor osteoclasts, respectively, have been identified as the key factors that stimulate osteoclast formation.<sup>[39]</sup>

Recent studies analyzing the cytokine expression pattern in compression and tension sides of the PDL during orthodontic tooth movement in humans, by means of real-time polymerase chain reaction, found that both the pressure and tension sides showed higher expression of all the cytokines when compared to the PDL of normal teeth which served as control. The compression side exhibited higher expression of TNF- $\alpha$ , RANKL, and matrix metalloproteinase I (MMP-1), whereas the tension side presented higher expression of IL-10, tissue inhibitor of MMP-I (TIMP-1), type I collagen, osteoprotegerin (OPG), and osteocalcin. The expression of transforming growth factor- $\beta$  was similar in both pressure and tension sides.<sup>[40]</sup> These findings strongly suggest that TNF- $\alpha$  plays a pivotal role in the bone resorption process, thus helping in orthodontic tooth movement.<sup>[36-40]</sup>

It is now clear that RANKL, together with macrophage-colony stimulating factor, is required for osteoclast formation from precursor monocytes and macrophages.<sup>[41]</sup> The natural inhibitor of RANK-RANKL interactions is the soluble TNF receptor-like molecule OPG, which binds to RANKL and prevents its ligation, thereby preventing osteoclast differentiation and activation. The RANKL protein was found to be predominant in inflammatory cells around inflamed tissues adjacent to areas of pathological bone loss in periodontal disease<sup>[42,43]</sup> and is associated with the progress

of periodontal disease. They have a major role in orthodontic tooth movement.

## TISSUE RESPONSE TO MECHANICAL FORCES

The PDL lies between the cementum and alveolar bone, acting as a cushion to withstand mechanical forces applied to teeth.<sup>[44]</sup> It receives the applied mechanical forces and responds to these external forces by remodeling. It is likely that PDL cells stimulated by forces of mastication, occlusal contact, and orthodontic treatment produce local factors that participate not only in the maintenance and remodeling of the ligament itself, but also in the metabolism of adjacent alveolar bone.

The most dramatic remodelling changes incident to orthodontic tooth movement occur in the PDL. Application of a continuous force on the crown of the tooth leads to tooth movement within the alveolus that is marked initially by narrowing of the periodontal membrane, particularly in the marginal area. If the duration of movement is divided into an initial and a secondary period, direct bone resorption is found notably in the secondary period, when the hyalinized tissue has disappeared after undermining bone resorption. During the crucial stage of initial application of force, the tissue reveals a glass like appearance in light microscopy, termed hyalinization. It represents a sterile necrotic area, generally limited to 1 or 2 mm in diameter. The process displays three main stages: degeneration, elimination of destroyed tissue, and establishment of a new tooth attachment.<sup>[45]</sup>

A clear relationship between force level, timing, and extent of hyalinization could not be found despite the availability of abundant research.<sup>[46,47]</sup> Even with a force as low as 5 cN, hyalinization occurred and the timing of the event seemed to be independent of the force level.<sup>[9]</sup> The assumption that higher forces lead to more hyalinization could not be confirmed. An interesting finding from a recent study, however, was that an initially light and gradually increasing force resulted in less hyalinization than a heavier initial force that increased to the same end force level.<sup>[48]</sup> It is prudent to use lighter forces for initiating orthodontic tooth movement and then gradually increasing the force levels, instead of using heavy force right at the start.

In the secondary period of tooth movement, the PDL is considerably widened. The osteoclasts attack the bone surface over a much wider area and, provided the force is kept within certain limits, further bone resorption will be predominantly of the direct type. The fibrous attachment apparatus is somewhat reorganized by the production of new periodontal fibrils. These are attached to the root surface and parts of the alveolar bone wall where direct resorption is not occurring by the deposition of new tissue, in which the fibrils become embedded.<sup>[48]</sup>

The main feature is the deposition of new bone on the alveolar

surface from which the tooth is moving away. Cell proliferation is usually seen after 30 to 40 h in young human beings. Shortly after cell proliferation has started, osteoid tissue is deposited on the tension side. The original periodontal fibres become embedded in the new layers of osteoid, which mineralizes in the deeper parts. New bone is deposited until the width of the membrane has returned to normal limits, and simultaneously fibrous system is remodelled. Concomitantly with bone apposition on the periodontal surface on the tension side, an accompanying resorption process occurs on the spongiosa surface of the alveolar bone. This tends to maintain the dimension of the supporting bone tissue.<sup>[9,48]</sup>

*In vitro* studies have proved that the expression and production of some inflammatory mediators (PGE<sub>2</sub>, IL-1 $\beta$ ) are promoted by mechanical stimulation of the PDL.<sup>[49,50]</sup> PGs of the E series play an important role in the pathogenesis of chronic periodontitis by regulating production of osteoclast activating factor in activated lymphocytes.<sup>[51]</sup> PGE<sub>2</sub> have an important role in orthodontic tooth movement, which has been conclusively proven in the literature.

The induction of both IL-1 $\beta$  and IL-6 was observed to reach a maximum on day 3 after mechanical loading and declines thereafter. This shows that they have an important role in initiating bone resorption and subsequent tooth movement during orthodontic treatment. It must be acknowledged that any interference in the signaling pathway resulting in reduced production of PGE<sub>2</sub>, IL-1 $\beta$ , and IL-6 would significantly delay tooth movement, which might be the reason for differences in the rate of initial tooth movement in different patients. The same could be the reason for the initial delay in orthodontic tooth movement seen in adults when compared to adolescent patients.<sup>[52]</sup>

PDL cells, under mechanical stress, may induce secretion of osteoclasts through up-regulation of RANKL expression via PGE<sub>2</sub> synthesis during orthodontic tooth movement. It has been shown that compressive force up-regulated RANKL expression and induction of COX-2 in human PDL cells *in vitro*.<sup>[53]</sup> It is a well-known fact that there is a local increase in PGs in the PDL and alveolar bone during orthodontic treatment.<sup>[54]</sup> Several studies have shown an arrest in tooth movement in experimental animals when non-steroidal anti-inflammatory drugs were administered.<sup>[54,55]</sup> Macrophages have the ability to produce cytokines, such as IL-1 $\beta$  and IL-6, the levels of which are known to increase during orthodontic tooth movement.<sup>[56]</sup> Non-steroidal anti-inflammatory drugs must be avoided in orthodontic patients, as they would delay tooth movement and prolong the treatment duration.

The number and distribution patterns of RANKL- and RANK-expressing osteoclasts change when excessive orthodontic force is applied to periodontal tissue, and IL-1 $\beta$  and TNF- $\alpha$  are expressed in osteoclasts in inflamed rat periodontal tissues. The presence of RANKL in periodontal tissues, during

experimental tooth movement of rat molars, shows that RANKL is regulated by inflammatory cytokines in the PDL in response to mechanical stress.<sup>[57]</sup> The RANKL levels increase 24 h after mechanical loading and play an important role in initiating orthodontic tooth movement. Compressive forces are more important for an increase in RANKL levels compared to tensile forces. This indicates that the biomechanics used to initiate tooth movement could play a role in the increase in RANKL levels and subsequent rate of tooth movement.

Kanzaki *et al.*<sup>[58]</sup> showed that the local RANKL gene transfer into the periodontal tissue significantly enhanced RANKL expression and secretion of osteoclast in periodontal tissue without any systemic effects. The rate of tooth movement was significantly increased in the RANKL gene transfer side. It was conclusively proved that the transfer of RANKL gene to the periodontal-tissue, activated osteoclast secretion and accelerated the amount of experimental tooth movement. They proposed that local RANKL gene transfer might be a useful tool not only for shortening the duration of orthodontic treatment, but also for moving ankylosed teeth.

Long-term studies are needed to validate the effectiveness of the local RANKL gene transfer as an useful tool to reduce the treatment time, by accelerating the rate of tooth movement in orthodontic patients undergoing fixed appliance treatment. The potential use of the local RANKL gene transfer in moving ankylosed teeth has to be further evaluated to justify its use.

## PULP TISSUE RESPONSE TO MECHANICAL FORCES

Dental pulp is the soft connective tissue that supports the dentine. It consist of the odontoblastic zone, cell free zone of Weil, cell-rich zone, and the pulp core, which can be seen in a histological slide preparation. The principal cells of the pulp are odontoblast, fibroblast, undifferentiated ectomesenchymal cells, macrophages, and dendritic cells. The innervation is from the sensory afferent from trigeminal nerve and sympathetic branches from superior cervical ganglion. Pulp consists of both myelinated and unmyelinated nerves. An extensive plexus of nerves in the cell-free zone is seen called the subodontoid plexus of Rushkov.

Orthodontic forces not only tend to produce mechanical damage and inflammatory reactions in the periodontium<sup>[59]</sup> but also cause cell damage, inflammatory changes, and circulatory disturbances in dental pulp.<sup>[60]</sup> Calcitonin gene-related peptide (CGRP) and substance P present in the dental pulp have been associated with the mediation of pulpal inflammation.<sup>[61]</sup> CGRP is a major sensory neuropeptide which has been found to evoke the release of IL-6 and IL-8 from synovial fibroblasts in patients with rheumatoid arthritis.<sup>[62]</sup> Substance P is another sensory neuropeptide released from the peripheral endings of sensory nerves during inflammation, capable of modifying the secretion of pro-inflammation cytokines from immunocompetent

cells, and has also been reported to induce the secretion of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  from monocytes.<sup>[63,64]</sup> The fact that the expression of CGRP and substance P is increased in dental pulp in response to buccally directed orthodontic tooth movement of the upper first molar in rats positively reinforces the fact that these neuropeptides might be involved in inflammation of the dental pulp at the time of orthodontic tooth movement.<sup>[65]</sup>

## GINGIVAL CREVICULAR FLUID DURING ORTHODONTIC TOOTH MOVEMENT

Gingival crevicular fluid (GCF) is an inflammatory exudate present in the gingival sulcus. The aqueous component of GCF is primarily derived from the serum; however, the gingival tissue through which the fluid passes, along with bacteria present in the tissue and gingival crevice, can modify its composition.<sup>[66]</sup> Therefore, its constituents, which are derived from a variety of sources, including microbial dental plaque, host inflammatory cells, host tissue, and serum, vary according to the condition of the periodontal tissues and the predominant bacterial flora present. In general, cells, immunoglobulins, lysosomal enzymes, microorganisms, and toxins can be detected in GCF, while the mechanism of bone resorption might also be related to the release of inflammatory mediators present in GCF.

Recently, a number of GCF constituents have been shown to be diagnostic markers of active tissue destruction in periodontal diseases<sup>[67]</sup> although only a few studies have focused on those involved in bone remodeling during orthodontic tooth movement.

During the course of orthodontic treatment, the forces exerted produce a distortion of the PDL extracellular matrix, resulting in alterations in cellular shape and cytoskeletal configuration. Such events lead to the synthesis and presence in the deeper periodontal tissues of extracellular matrix components, tissue-degrading enzymes, acids, and inflammatory mediators; induce cellular proliferation and differentiation; and promote wound healing and tissue remodeling. These produce an alteration in the GCF flow rate and its components.<sup>[68]</sup>

Glycosaminoglycans (GAG) have been detected in GCF samples from sites around teeth affected by such conditions as chronic gingivitis, chronic periodontitis, and juvenile periodontitis.<sup>[69,70]</sup> GCF collected from around the canine tooth subjected to orthodontic force showed an increase in the GAG components particularly hyaluronic acid and chondroitin sulfate.<sup>[47]</sup> The cytokine levels in the GCF peaked 24 h after application of orthodontic forces.

The GCF concentrations of IL-1 $\beta$  and IL-6 were found to be significantly higher in a group with severe periodontal disease compared with controls.<sup>[71]</sup> It was demonstrated that the GCF IL-1 $\beta$  and TNF- $\alpha$  levels had a positive correlation to mean pocket depths, which led to the suggestion that those cytokines may be involved in the pathogenesis of periodontal diseases.<sup>[72]</sup>

The GCF isolated from tooth, 24 h after being subjected to orthodontic forces, showed an increase in the levels of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , epidermal growth factor and  $\beta_2$ -microglobulin, when compared to controls.<sup>[73]</sup> IL-8 was found to be associated with the bone remodeling process in orthodontic patients.<sup>[74]</sup> The level of pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  reached a significant level at 24 h after application of orthodontic forces. IL-8 reached a significant elevation after 1 month.<sup>[75]</sup> It was also found that force induced IL-8 secretion from the PDL cells required the presence of IL-1 $\beta$  in sufficient quantity.<sup>[76]</sup>

The lysosomal cysteine protease cathepsin B is known to play an important role in the resolution of organic matrix, a final step in bone resorption. During human orthodontic tooth movement, mechanically stimulated Cathepsin B levels were analyzed with the help of fluorospectrometry and western blot analysis. The Cathepsin B levels were found to be significantly increased when compared to the control teeth, which may be involved in extracellular matrix degradation in response to mechanical stress.<sup>[77]</sup> Immunocytochemical studies demonstrated that cathepsin B and cathepsin L were localized in the PDL of the rat molar and were expressed in compressed sites during experimental tooth movement. There was a three-fold increase in cathepsin B and four-fold increase in cathepsin L when compared to the control.<sup>[78]</sup> This proves that Cathepsin B and Cathepsin L play an important role in initial orthodontic tooth movement by initiating bone resorption.

The expression of cathepsin K, a novel collagenolytic enzyme specifically expressed in osteoclasts, was investigated in the rat maxillary teeth during experimental tooth movement by *in situ* hybridization histochemistry with a non-radioisotopic complementary ribonucleic acid (cRNA) probe for rat cathepsin K. Cathepsin K messenger ribonucleic acid (mRNA) expression was detected in the mono- and multi-nuclear osteoclasts on the pressure side of the alveolar bone at 12 h after force application, and the distribution and number of cathepsin K mRNA-positive osteoclasts increased time-dependently on the pressure side. At 3-4 days, there was a marked increase in cathepsin K mRNA-positive osteoclasts on both pressure and tension side of the alveolar bone in response to tooth movement. At 7-12 days, the cathepsin K mRNA-positive osteoclasts on both sides had disappeared. These suggest that the recruitment of osteoclasts on the pressure side begins during the initial stage of orthodontic tooth movement and the site-specific early induction of cathepsin K mRNA may cause an imbalance in the relative resorption activities on the pressure and tension side incident to such movement.<sup>[79]</sup> The role of cathepsin K in orthodontic tooth movement and its mechanism of action could be made further clear by controlled experimental studies.

MMPs are enzymes that play a central role in PDL remodeling, both in physiological and in pathological conditions. Collagenase-1 (MMP-1) and collagenase-2 (MMP-8), because they share a unique ability to cleave native triple-helical

interstitial collagens, can initiate this tissue remodeling. MMP-8 degranulation by polymorphonuclear leukocytes is among the pivotal factors in pathological collagen destruction during periodontal diseases. Study done by Apajalahti<sup>[80]</sup> showed that MMP-2 levels significantly increased in the GCF 4-8 h after force application, while MMP-1 level failed to show any significant increase. Ingman<sup>[81]</sup> too found similar results when conducting the study by the immunofluorometric assay over a period of 1 month. There was a 12-fold increase in the orthodontic GCF when compared to the control GCF. The MMP-8 levels in orthodontic GCF were lower than those detected in gingivitis and periodontitis GCF, but significantly higher than in control GCF. This proves that MMPs, particularly MMP-2, play an important role in orthodontic tooth movement and tissue remodeling.

Cantarella<sup>[82]</sup> found that compression force induced a significant increase of MMP-1 protein after 1 h; the increase lasted until the third hour of force application and disappeared thereafter. The tension force induced significantly increased levels of the MMP-1 protein after just 1 h of force application. MMP-2 protein was induced by compression and increased significantly in a time-dependent fashion, reaching a peak after 8 h of force application. On the tension side, MMP-2 was significantly increased after 1 h, but gradually returned to basal levels within 8 h. Immunolocalization of collagenase-3 (MMP-13) done by Leonardi<sup>[83]</sup> showed that there was an increase in MMP-13 very early following the application of an orthodontic force in both PDL and alveolar bone. This indicates that MMP-13 also plays an important role during orthodontic tooth movement.

Analysis of the GCF in patients with periodontal disease<sup>[84]</sup> revealed that there was an increase in RANKL and a decrease in the OPG levels; and subsequently the ratio of RANKL concentration to that of OPG in GCF samples was significantly higher for periodontal disease patients than for healthy subjects. This shows that both RANKL and OPG contribute to osteoclastic bone destruction in periodontal disease. Experimental compressive forces on the PDL resulted in a 16.7-fold increase in RANKL secretion and a 2.9-fold decrease in OPG secretion when compared to the control.<sup>[85,86]</sup> This confirms that the RANKL/RANK/OPG system plays an important role in orthodontic tooth movement.

Alkaline phosphatase activity in the GCF is known to decrease during active tooth movement. This decrease was found to be significant during the first month of active tooth movement and started to stabilize later.<sup>[87,88]</sup> Batra<sup>[89]</sup> found that the alkaline phosphatase activity in the GCF showed an increase during canine retraction which peaked during the 14th day of retraction followed by a significant fall in activity in the 21st day. It is one of the important enzymes required in initiating orthodontic tooth movement and sustaining it for a 2 week period. Any defect in the production of this enzyme could interfere and delay orthodontic tooth movement.

Aspartate aminotransferase (AST) is a soluble enzyme that is normally confined to the cytoplasm of cells, but is released to the extra-cellular environment upon cell death. The activity levels of AST in the GCF are considered to be important in regulating alveolar bone resorption during orthodontic tooth movement.

Ever since the presence of AST enzyme in GCF has been demonstrated,<sup>[89]</sup> several studies have observed that the levels of AST activity in GCF may reflect the magnitude of periodontal tissue destruction in periodontitis.<sup>[90,91]</sup> However, there are only few studies which have investigated a possible role of AST activity levels in tissue remodeling incidental to orthodontic forces. AST activity in the GCF was found to be highest in the first week of orthodontic force application and there was a gradual reduction in the activity during the next 3 weeks.<sup>[92]</sup> Thus, it has the potential to serve as a biological marker to monitor orthodontic tooth movement. Similarly, lactate dehydrogenase activity in the GCF can be used as a diagnostic tool for monitoring orthodontic tooth movement in clinical practice.<sup>[93-95]</sup>

Leptin,<sup>[96,97]</sup> a polypeptide hormone, has been classified as a cytokine and is mainly secreted from the adipose tissue in humans. Leptin and its receptor share structural and functional similarities with members of the long-chain helical cytokines: IL-6, IL-11, IL-12, leukemia inhibitory factor, granulocyte-colony-stimulating factor, and oncostatin M.

It has been suggested that leptin orchestrates the host response to inflammatory and infectious stimuli; as it stimulates the immune system by enhancing cytokine production and phagocytosis by macrophages.<sup>[98]</sup> Thus, the overall increase in leptin during inflammation and infection indicates that leptin is part of the immune response and host defense mechanisms. Previous studies have suggested a relationship between periodontal disease and leptin levels. Since the presence of leptin within healthy and marginally inflamed gingiva has been demonstrated,<sup>[97]</sup> several studies have observed that the levels of GCF leptin activity may play an important role in the development of periodontal disease. Karthikeyan<sup>[99]</sup> reported that leptin levels decreased progressively in GCF as periodontal disease progressed.

Recently, it has been suggested that leptin plays a significant role in bone formation by virtue of its direct effect on osteoblast proliferation and differentiation, and in prolonging the life span of human primary osteoblasts by inhibiting apoptosis.<sup>[100]</sup> Leptin is also involved in anti-osteogenic effects by acting centrally on the hypothalamus.<sup>[101]</sup> Thus, leptin at high local concentrations protects the host from inflammation and infection. They also play an important role in maintaining marginal bone levels.

It was recently found that the concentration of leptin in GCF is decreased by orthodontic tooth movement and this conclusively

proved that leptin may have been one of the mediators responsible for orthodontic tooth movement.<sup>[102]</sup>

IL-17 has been found to be increased in patients with periodontitis, while it was barely detectable in sera from periodontally healthy individuals.<sup>[103]</sup> The role of IL-17 in orthodontic tooth movement and its potential to serve as a marker for validating the tooth movement remains a potential area for future research.

## CONCLUSION

The orthodontic displacement of a tooth is the result of a mechanical stimulus, generated by a force applied to the crown of a tooth, which results in an acute inflammatory response in periodontal tissues, which in turn may trigger the cascade of biological events associated with bone remodeling.<sup>[103]</sup> This leads to the synthesis and release of various neurotransmitters, arachidonic acid, growth factors, metabolites, cytokines, colony-stimulating factors, and enzymes like cathepsin K, MMPs, and AST, which are ultimately responsible for initiating bone remodeling and subsequent tooth movement. Any interference with the release of these neurotransmitters and enzymes could delay or hamper orthodontic tooth movement. With the increased scope of gene therapy, the possibility that the rate of tooth movement could be increased by local gene transfer is very much real and could go a long way in reducing the treatment duration of orthodontic patients. However, well-designed experimental studies are needed for the same in order to evaluate their clinical efficiency and validate their use, as this is an era of evidence-based dentistry.

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