

Received: 2005.02.02
Accepted: 2005.03.14
Published: 2005.10.15

Inflammation in periodontal tissues in response to mechanical forces

Masaru Yamaguchi and Kazutaka Kasai

Department of Orthodontics, Nihon University School of Dentistry at Matsudo, Japan

Source of support: This research was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (C:14571969, C: 14571970).

Summary

Orthodontic forces are known to produce mechanical damage and inflammatory reactions in the periodontium and dental pulp, as well as inflammatory mediators, e.g. prostaglandins, interleukin (IL)-1, IL-6, tumor necrosis factor α , and receptor activator of nuclear factor κ B ligand, in the periodontal ligament (PDL) and dental pulp. We have studied the effects of aging on the production of inflammatory mediators in the PDL using *in vitro* and *in vivo* methods and found that aging of PDL tissues may be an important factor in the severity of periodontal disease through a higher production of inflammatory mediators in response to mechanical forces. Further, the levels of inflammatory mediators in gingival crevicular fluid, an osmotically mediated inflammatory exudate found in the gingival sulcus, have been shown to be significantly elevated during orthodontic treatment. In order to reduce inflammation, low-level laser therapy has been recently studied *in vivo* and *in vitro* by many investigators as a substitute for anti-inflammatory drugs. Clinical and experimental studies have shown that low-level laser irradiation reduces orthodontic post-adjustment inflammation. We believe that orthodontic forces (mechanical forces) may play an important role in periodontal inflammation and that low-level laser therapy may be useful for its inhibition.

Key words: inflammation • mechanical forces • cytokines • orthodontics • periodontal disease

Full-text PDF: http://www.aite-online/pdf/vol_53/no_5/8147.pdf

Author's address: Masaru Yamaguchi, Department of Orthodontics, Nihon University School of Dentistry at Matsudo, 2-870-1 Sakaecho-Nishi, Matsudo City, Chiba 271-8587, Japan, tel.: +81 47-360-9414, fax: +81 47-364-6295, e-mail: dai@mascat.nihon-u.ac.jp

INTRODUCTION

Prostaglandins (PGs), interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α are key mediators involved in a variety of immune and acute-phase inflammatory response activities^{24, 26, 44, 112}. The RANK/RANKL (receptor activator of nuclear factor κ B and RANK ligand) pathway is also essential for osteoclast differentiation in inflammatory arthritis¹²⁷.

Orthodontic tooth movement is induced by mechanical stimuli and facilitated by remodeling of the periodontal ligament (PDL) and alveolar bone. A precondition for those remodeling activities, and ultimately tooth displacement, is the occurrence of an inflammatory process. Vascular and cellular changes were the first events to be recognized and described, and a number of inflammatory mediators, growth factors, and neuropeptides have been demonstrated in periodontal supporting tissues. Their increased levels during orthodontic tooth movement have led to the assumption that interactions between cells producing these substances, such as nerve, immune, and endocrine system cells, regulate the biological responses that occur following the application of orthodontic forces¹²³.

Mechanical stress evokes biomechanical and structural responses in a variety of cell types *in vivo* and *in vitro*. The overall objective of many investigations has been to further the understanding of the mechanisms involved with converting physical stress to the cellular responses that result in tooth movement. In sites where inflammation and tissue destruction have occurred, cells may communicate with one another through the interaction of cytokines and other related molecules. Thus it is important to elucidate completely the complex cytokine cascade flow associated with inflammation-mediated tissue destruction at the molecular level²¹.

Pain is one of the cardinal signs of inflammation, as well as a nearly inevitable and, for the patient, most unpleasant reaction to orthodontic therapy. The incidence of pain may be associated with the interactions of inflammatory mediators^{22, 36}. Therefore, control of inflammatory mediators may be important to relieve the pain that accompanies tooth movement. Recently, low-level laser therapy has been shown to inhibit inflammation^{2, 12, 46, 47} and is also thought capable of inhibiting that encountered during orthodontic treatment.

In this article we review current knowledge regarding the inflammatory changes (PGs, IL-1, IL-6, TNF- α , and, RANKL) in periodontal tissues associated with

orthodontic tooth movement. Further, we report findings showing the inhibitory effect of low-level laser irradiation on periodontal tissue inflammation.

INFLAMMATORY MEDIATORS IN PERIODONTUM

Prostaglandins

PGs, a product of arachidonic acid metabolism, are local hormone-like chemical agents produced by mammalian cells, including osteoblasts, that are synthesized within seconds following cell injury. One of the derivatives of the arachidonic acid cascade, PGE₂, acts as a vasodilator by causing increases in vascular permeability and chemotactic properties and it also stimulates the formation of osteoclasts and an increase in bone resorption.

The cyclooxygenase (COX) family of enzymes consists of two proteins that convert arachidonic acid, a 20-carbon polyunsaturated fatty comprising a portion of the plasma membrane phospholipids of most cells, to PGs^{79, 124}. The constitutive isoform (COX-1) is found in nearly 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 in inflammatory processes²⁹. There are several lines of evidence showing that COX is also closely associated with periodontitis, and that PGs are mediators of gingival inflammation and alveolar bone resorption^{48, 89}. In addition, numerous studies have confirmed that among lipid mediators, PGE₂ levels in periodontal tissues and crevicular fluid in particular are highly correlated with periodontal tissue destruction⁸⁹. Further, recent studies have suggested that COX-2 is induced by periodontitis and plays an important role in gingival inflammation and alveolar bone destruction⁷¹.

Cytokines

Some studies have suggested roles for the immune system in the regulation of bone remodeling through cytokine production by inflammatory cells that have migrated from dilated PDL capillaries after the application of orthodontic forces²¹. Cytokines are proteins that act as signals between the cells of the immune system, which are produced during the activation of immune cells and usually act locally, though some act systemically with overlapping functions. Previous studies have implicated the involvement of certain cytokines in bone remodeling *in vitro* and *in vivo*, including IL-1, IL-6, and TNF- α ^{62, 65}, which are key

mediators involved in a variety of immune and acute-phase inflammatory response activities^{24, 44}.

IL-1 exists in two forms, α and β ²³, of which IL-1 β is the form mainly involved in bone metabolism, stimulation of bone resorption^{32, 43}, and inhibition of bone formation¹¹⁵. IL-1 β also plays a central role in the inflammatory process. The staining of feline PDL cells for IL-1 β showed the presence of bound signal complexes in the plasma membrane, which was expected, as it is known that receptors for IL-1 β are present on fibroblasts²⁵. Lo et al.⁷⁰ suggested that large amounts of IL-1 β are present in inflamed gingival tissues and found that both macrophages and neutrophils are predominate in IL-1 β production in inflamed gingival tissues. Kanda-Nakamura et al.⁵⁴ also suggested that the response of gingival fibroblasts to IL-1 may represent a mechanism for amplification of gingival inflammation. Further, IL-1 β may act synergistically with TNF- α ²⁴ as a powerful inducer of IL-6^{68, 122}.

IL-6, a multifunctional cytokine previously referred to as B cell stimulatory factor 2, hepatocyte stimulating factor, or interferon- β_2 , is produced by both lymphoid and non-lymphoid cells⁴⁵ and can apparently induce osteoclastic bone resorption through an effect on osteoclastogenesis^{50, 59, 73}. IL-6 was found to be produced by the human foreskin fibroblast line FS-4 and its synthesis was stimulated by treatment with IL-1^{5, 76}. The identification of IL-6 in human gingival tissues and cells implicates this lymphokine as a participant in the molecular events associated with inflammatory periodontal diseases⁵. Irwin and Myrillas⁴⁹ reviewed the biological functions of IL-6 and found them to be specifically related to tissue destruction in the periodontal site. In addition, Yakovlev et al.¹²⁹ found that levels of IL-1 β and IL-6 were significantly higher in inflamed as compared with non-inflamed gingival tissues in young adults, while Shimizu et al.¹⁰⁴ demonstrated that IL-6 was produced by IL-1 β from PDL cells.

TNF- α is a pro-inflammatory cytokine that is often over-expressed in a number of disease states such as sepsis syndrome, rheumatoid arthritis, inflammatory bowel disease¹¹³, and periodontitis^{97, 98, 114}. Takeichi et al.¹¹⁹ found that human polymorphonuclear leukocytes derived from alveolar bone can spontaneously produce IL-1 α , IL-1 β , and TNF- α in sites of inflammation, and likely initiate inflammation and regulate augmentation of bone resorption *in vivo*, while Gaspersic et al.³¹ concluded that a subcutaneous administration of TNF- α accelerated the progression of experimental periodontitis in rats. The potential role of TNF- α in osteoclastogenesis is of significance in both tooth eruption and periodontitis. The PDL

becomes degraded in periodontitis along with excess resorption of the alveolar bone, and TNF- α has been implicated in this inflammatory condition⁶⁶.

The possibility that TNF- α is involved in normal physiological processes is supported by its function in osteoclastogenesis. RANKL (RANK ligand, osteoclast differentiation factor, osteoprotegerin ligand) and its receptor RANK, which are present on osteoblasts and precursor osteoclasts, respectively, have been identified as the key factors that stimulate osteoclast formation^{63, 136}. It is now clear that RANKL, together with macrophage-colony stimulating factor, is required for osteoclast formation from precursor monocyte/macrophages⁴¹. The natural inhibitor of RANK-RANKL interactions is the soluble TNF receptor-like molecule osteoprotegerin (OPG)¹³⁷, which binds to RANKL and prevents its ligation, thereby preventing osteoclast differentiation and activation. The importance of these three molecules in regulating bone metabolism has been demonstrated by transgenic and gene knock-out studies in mice^{9, 58, 80}. It is considered that the relative levels of RANKL and OPG *in vivo* are likely to be important in determining where and when osteoclasts form. Considering the importance of RANK, RANKL, and OPG in physiologic osteoclast formation, it is reasonable to propose that they may also be key regulators of pathological bone resorption. Thus, inflammatory cytokines and the RANK/RANKL/OPG system may act together to trigger bone resorption via regulation of the RANKL/OPG ratio. Previous studies have shown that IL-1, IL-11, IL-17, TNF, PTHrp, and PGE₂ increased RANKL mRNA expression by T cells, while both PTHrp and PGE₂ decreased OPG expression^{28, 118}.

Recent studies have shown that several cell types may be important in the ectopic production of RANKL in tissues adjacent to bone^{17, 18, 19, 42}. RANKL protein was found to be predominant in inflammatory cells in inflamed tissues adjacent to areas of pathological bone loss in periodontal disease¹⁷. Further, a study by Liu et al.⁶⁹ suggested that up-regulation of RANKL mRNA in inflammatory cells may be associated with the activation of osteoclastic bone destruction in periodontitis. Furthermore, Ogasawara et al.⁹⁰ reported RANKL mRNA expression in macrophages and multinucleated cells in periodontal diseased tissues in an animal model of periodontitis. Together, the results of these studies suggest that RANKL is also involved in the progress of periodontal inflammation.

PDL RESPONSE TO MECHANICAL FORCES

The PDL lies between hard tissues such as the cementum and alveolar bone, where it functions as

a cushion to withstand mechanical forces applied to teeth; thus it receives and responds to external forces. 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.

Several experimental models for mechanical stress have been developed for cell-culture systems, such as application of compressive high pressure^{55, 56, 93, 131}, placement of a convex template on the bottom of a Petriperm dish (Heraeus Inc., South Plainfield, NJ, USA)^{37, 85, 100, 131}, and cyclic tension force controlled by a computer (Flexercell Strain Unit: Flex Corp., PA)^{4, 132, 133, 134} (Fig. 1). In addition, *in vitro* studies have shown that the expression and production of some inflammatory mediators (PGE_2 , $\text{IL-1}\beta$) are promoted by mechanical stimulation of the PDL^{106, 133}. COX-2 is induced in PDL cells by cyclic mechanical stimulation and is responsible for the augmentation of PGE_2 production *in vitro*¹⁰⁵. In addition, Kanzaki et al.⁵⁵ demonstrated that compressive force up-regulated RANKL expression and induction of COX-2 in human PDL cells *in vitro*. These results suggest that PDL cells under mechanical stress may induce osteoclastogenesis through up-regulation of RANKL expression via PGE_2 synthesis during orthodontic tooth movement.

In other *in vivo* studies, experimental tooth movement has been shown to lead significantly to an increased recruitment of cells that belong to the mononuclear phagocytic system (Fig. 2). Saito et al.¹⁰⁰ indicated that there is a local increase in PGs in the PDL and alveolar bone during orthodontic treatment, and other studies have shown an arrest in tooth movement in experimental animals when nonsteroidal anti-inflammatory drugs were administered¹⁴. Further, when PGE_1 was administered locally or systemically to rats, accelerated bone resorption and tooth movement were observed after the application of orthodontic forces¹³⁵. Therefore, PGs play an important role in orthodontic tooth movement.

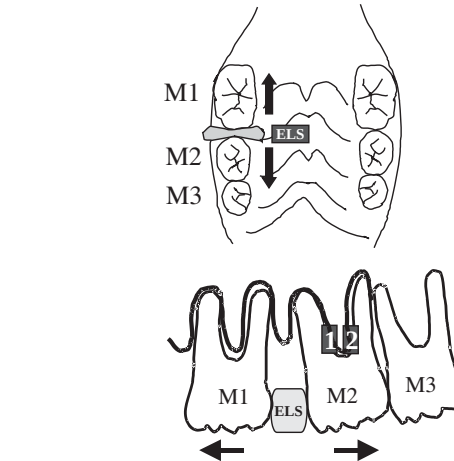


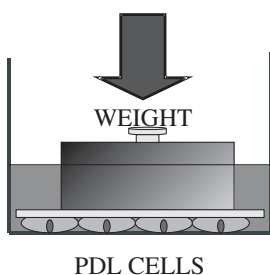
Figure 2. Diagram of the method used for experimental tooth movement. A piece of elastic band (ELS) is inserted between the upper first molar (M1) and the second molar (M2). Rectangles 1 and 2 indicate the observation area (1 – compression side; 2 – tension side; M3, the third molar).

Macrophages have the ability to produce cytokines, such as $\text{IL-1}\beta$ and IL-6 , the levels of which are known to increase during orthodontic tooth movement¹⁰⁰. The number and distribution patterns of RANKL- and RANK-expressing osteoclasts change when excessive orthodontic force is applied to periodontal tissue, and $\text{IL-1}\beta$ and $\text{TNF-}\alpha$ were shown to be expressed in osteoclasts in pathological status rat periodontal tissues⁹⁰. Shiotani et al.¹⁰⁹ also showed the presence of RANKL in periodontal tissues during experimental tooth movement of rat molars. Therefore it is suggested that RANKL is regulated by inflammatory cytokines in the PDL in response to mechanical stress.

RESPONSE OF DENTAL PULP TO MECHANICAL FORCES

A number of different neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P (SP), are known to be present in the nerve fibers that supply tooth pulp and the periodontium in rats, cats, monkeys, and humans^{11, 13, 75, 92, 110, 126}. Further, the morphology and distribution of CGRP and SP

(a) COMPRESSIVE APPARATUS



(b) STRETCH APPARATUS

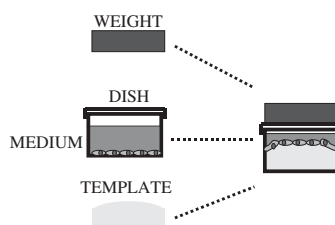


Figure 1. The method used to apply compressive force (a). Precultured PDL cells were compressed continuously using a glass cylinder containing different weights. A glass cylinder was placed over a confluent cell layer in one well of a 6-well plate. The number of lead granules placed in the cylinder controlled the compressive force. Diagrammatic representation of the apparatus used to stretch PDL cells (b). Cells are cultured on a flexible membrane of a Petriperm dish which is placed over a brass template with a convex surface. A brass weight placed on top of the dish forces the membrane and the tightly attached cells to be stretched.

through immunoreactive nerves have been shown to change their patterns as a result of local pulp trauma, which may indicate that CGRP- and SP-containing fibers take part in the inflammatory process in connection with tissue injury and repair⁶¹. Orthodontic forces are known to produce mechanical damage and inflammatory reactions in the periodontium⁹⁹, as well as cell damage, inflammatory changes, and circulatory disturbances in dental pulp⁸³. In addition, it was recently observed that the expression of CGRP and SP increased in dental pulp in response to buccally directed orthodontic tooth movement of the upper first molar in rats, and that these neuropeptides might be involved in inflammation of the dental pulp at the time of orthodontic tooth movement⁸⁷, while CGRP and SP in dental pulp have been implicated in the mediation of pulpal inflammation^{92, 110, 126}.

The peripheral sensory nervous system contributes to the development of acute and chronic inflammatory processes through local release of neuropeptides. SP, a sensory neuropeptide released from the peripheral endings of sensory nerves during inflammation, can modify the secretion of pro-inflammation cytokines from immunocompetent cells, and has also been reported to induce the secretion of IL-1 β , IL-6, and TNF- α from monocytes^{72, 95}. CGRP, another major sensory neuropeptide, has also been found to evoke the release of IL-6 and IL-8 from synovial fibroblasts in patients with rheumatoid arthritis⁹⁴. In another study, SP and CGRP both stimulated the release of IL-6 and TNF- α from a human bronchial epithelial cell line¹²⁵. Further, we recently reported that CGRP and SP significantly stimulated the production of PGE₂, IL-1 β , IL-6, TNF- α , and RANKL in HDP cells^{57, 130}. Based on these results, we consider that CGRP and SP may be involved in pulpal inflammation that occurs during orthodontic tooth movement.

AGING AND INFLAMMATION

In general, aging is defined as a decline in the ability to adapt to environmental stress. This decline has often been attributed to a decrease of each cellular function or to an excessive response to stimuli thought to be involved in diseases of the aged. For example, it is well known that the severity of periodontal disease is affected by host age^{6, 51}. It is important to define how the aging of periodontal tissue at the cellular level affects the severity of periodontal diseases associated with the aging process, therefore, *in vitro* and *in vivo* studies of aging have been conducted.

Fibroblasts have been frequently used as a model for studying the process of cellular senescence *in vitro*^{16, 40}. When fibroblasts are allowed to passage in cultures

over many generations, they eventually reach a stage where they remain viable but permanently unable to replicate³⁹ and are generally considered to be senescent. Norwood and Pendergrass⁸⁸ expressed the view that though the causes of the loss of proliferative activity of cultured human diploid fibroblasts are unknown, the system is useful as a model for the study of cellular aging *in vitro*. As a result, methods utilizing increasing population doubling have been used for cellular aging studies. An *in vitro* model of aging in human PDL cells can be prepared by sequential sub-cultivation (5 to 6 passages for young, 18 to 20 passages for old). Utilizing such models, cyclic tension force-stimulated PGE₂ and IL-1 β were found to be increased in old human PDL cells compared with younger cells^{91, 103}.

Although an *in vitro* aging experimental system that utilizes an increasing population doubling method is a useful model for cellular aging studies, some points require attention. The changes seen with increasing time in culture might represent either a phenotypic instability of the cells in the culture or the selection of a specific subpopulation of cells rather than true age-related change. However, it remains a useful model that has provided abundant information regarding cell behavior under stressful conditions. Overall, the obtained evidence indicates that *in vivo* cells accumulate damage over their life-span that results in a gradual loss of differentiated function. Hayek et al.³⁸ studied *in vivo* aging using an animal model and suggested that it was useful. In our *in vivo* aging method, aged PDL cells are obtained from the incisors of 6-week-old (young) and 60-week-old (old) rats and cyclic tension forces are applied. Results have shown that stimulation of PGE₂ and IL-1 β by tension forces was enhanced by aging *in vivo*¹⁰⁸.

These findings suggest that aging of the PDL may be an important factor in the severity of periodontal disease through a higher production of inflammatory mediators in response to mechanical stress.

GINGIVAL CREVICULAR FLUID DURING ORTHODONTIC TOOTH MOVEMENT

Gingival crevicular fluid (GCF) is an osmotically mediated inflammatory exudate found in the gingival sulcus, where it tends to increase in volume with inflammation and capillary permeability. Serum is the primary source of the aqueous component of GCF; however, the gingival tissue through which the fluid passes, along with bacteria present in the tissue and gingival crevice, can modify its composition¹⁵. 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. In general, cells, immunoglobulins, microorganisms, toxins, and lysosomal enzymes can all 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 diseases⁶⁴, though only a few studies have focused on those involved in bone remodeling during orthodontic tooth movement. Mogi et al.⁸¹ found that GCF concentrations of IL-1 β and IL-6 were significantly higher in a group with severe periodontal disease compared with controls, and Yavuzylmaz et al.¹³⁸ demonstrated the GCF IL-1 β and TNF- α levels had a positive correlation to mean pocket depths, and suggested that those cytokines may be involved in the pathogenesis of periodontal diseases. Further, Mogi et al.⁸² reported that an increased concentration of RANKL and decreased concentration of OPG were detected in GCF from patients with periodontitis, while the ratio of RANKL concentration to that of OPG in GCF samples was significantly higher for periodontal disease patients than for healthy subjects. Taken together, these data suggest that RANKL and OPG contribute to osteoclastic bone destruction in periodontal disease.

Storey¹¹⁷ proposed that the early phase of tooth movement involves an acute inflammatory response characterized by periodontal vasodilation and migration of leukocytes out of the capillaries. Recent research has led to the hypothesis that inflammatory mediators are released following mechanical stimulus, triggering the biologic processes associated with alveolar bone resorption and apposition²¹. Among the local biochemical mediators are 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, including PGs and growth factors, thus interacting directly or indirectly with bone cells²¹. Uematsu et al.¹²⁰ found that the levels of inflammatory mediators (IL-1 β , IL-6, TNF- α , epidermal growth factor, and β_2 microglobulin) in GCF were elevated during orthodontic treatment, and Grieve et al.³³ reported similar results for PGE and IL-1 β . Further, Lowney et al.⁷⁴ described an increase in TNF- α in GCF from teeth undergoing orthodontic forces. As noted above, inflammatory mediators have been detected in GCF samples during orthodontic tooth movement in the early phase. Our laboratory found an increased concentration of RANKL in GCF during orthodontic tooth movement, and the ratio of concentration of RANKL to that of OPG in the GCF was significantly higher than

in control sites in another study⁸⁶. Consequently, analysis of GCF samples may provide a better understanding of the biochemical processes associated with tooth movement and can help clinicians make therapeutic choices based on qualitative and quantitative information.

PAIN DURING ORTHODONTIC TOOTH MOVEMENT

Vandevska-Radunovic¹²³ summarized pain during orthodontic tooth movement as follows. Pain is one of the cardinal signs of inflammation, as well as a nearly inevitable and, for the patient, most unpleasant reaction to orthodontic therapy. Furstman and Bernick³⁰ suggested that periodontal pain is caused by a process of pressure, ischemia, inflammation, and edema. Burststone¹⁰ identified both immediate and delayed pain responses, which begin a few hours after application of an orthodontic force and then last for approximately 5 days^{52, 60, 84, 101}. Pain results, in part, from the stretching and distortion of tissues¹¹⁶ due to mechanical forces, as well as from interactions of multiple inflammatory mediators with local pain receptors^{22, 35}. PGs have been shown to cause hyperalgesia, which is an increased sensitivity to noxious agents such as histamine, bradykinin, serotonin, acetylcholine, and substance P. There are indications that perceptions of pain in the PDL are due to changes in blood flow^{10, 60, 84, 128}. Since pain leads to impaired function, biting and chewing are reported to be the source of the most intense discomfort during fixed orthodontic therapy¹⁰¹. Burststone¹⁰ noted a wide range of individual responses when similar forces were applied to the teeth. Further, a recent study of patients with fixed orthodontic appliances showed that the initial pain was perceived at 2 h, peaked at 24 h, and decreased by day 3²⁷. Therefore, control of inflammatory mediators may be important in relieving the pain that accompanies tooth movement (Fig. 3).

ANTI-INFLAMMATORY EFFECTS OF LASER IRRADIATION

The use of modulating agents, including antiproteinase to inhibit matrix metalloproteinases, anti-inflammatory drugs to block the production of pro-inflammatory cytokines and PGs, and bone-sparing agents to inhibit activation of osteoclasts, has been postulated to be of therapeutic value as adjunctive therapy for the management of periodontitis. Non-steroidal anti-inflammatory drugs (NSAIDs) and bisphosphonate drugs may also have an adjunctive role in periodontal therapy⁹⁶, as NSAIDs have been shown to have a role in postoperative pain management, though they can cause gastrointestinal ulceration, renal injury, and disruption of platelet function and hemostasis³⁴.

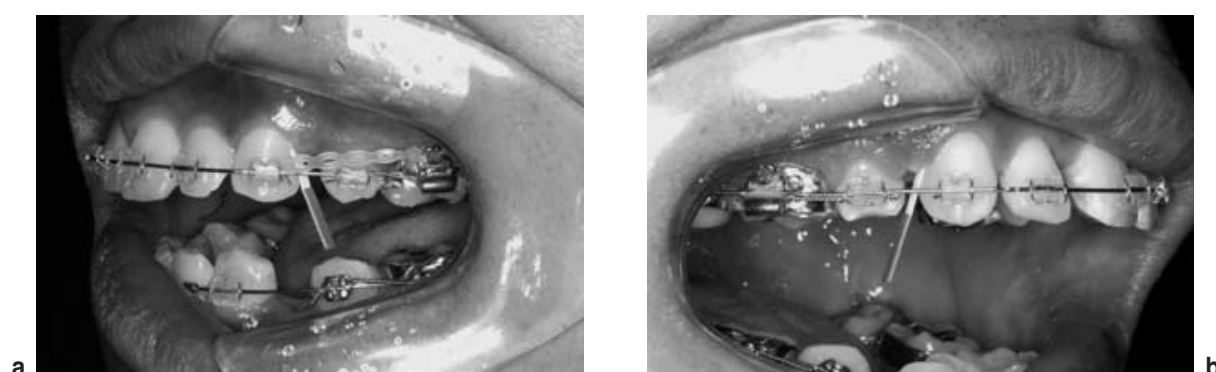


Figure 3. Collection of GCF. Within each patient, GCF was sampled at the distofacial angles of the tooth being retracted and at the contralateral and opposing control teeth. (a) Experimental side; (b) Contralateral side.

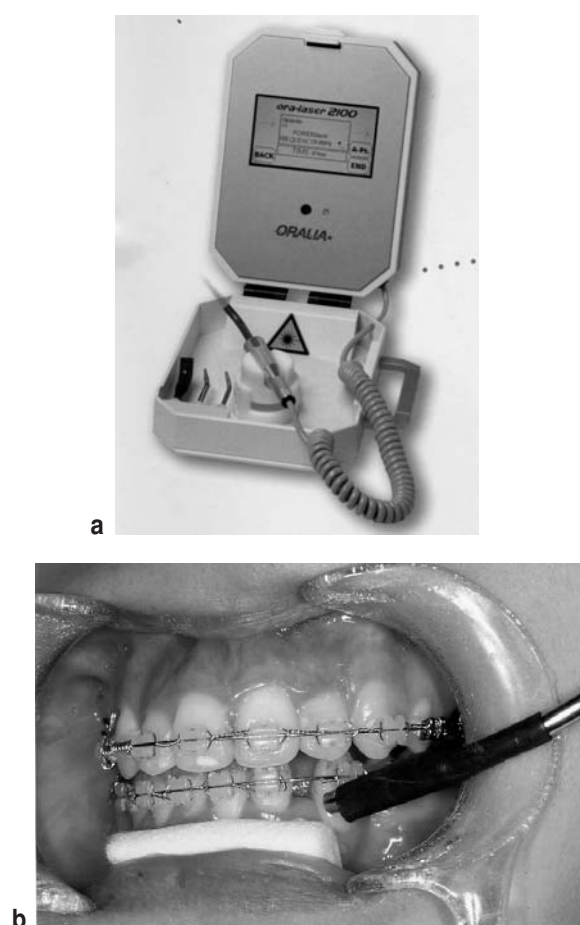


Figure 4. Diagram of Ga-Al-As diode laser (a; ora-laser 2100, ORALIA Dentalprodukte GmbH, Konstanz, Germany). Low-power laser irradiation during orthodontic tooth movement (b).

Various bio-stimulatory effects of low-energy laser irradiation have been reported, including wound healing^{53, 78}, fibroblast proliferation^{8, 111, 121}, chondral proliferation¹⁰², collagen synthesis^{1, 7}, and nerve regeneration³. Some anti-inflammatory effects of low-energy laser irradiation have been shown *in vivo*, including the inhibition of carrageenin inflammation in rats^{46, 47}, inflammatory cellular infiltration in the synovial membrane of patients with rheumatoid arthritis², and PGE₂ in the synovial fluid of a patient with rheumatoid arthritis¹².

A clinical investigation showed that low-level laser therapy reduced orthodontic post-adjustment pain⁶⁷, and we reported that low-energy laser irradiation inhibited the incidence of open gingival embrasure space following orthodontic treatment⁷⁷ and that PGE₂ and IL-1 β production in stretched human PDL cells was inhibited by laser irradiation *in vitro*¹⁰⁷. Further, a recent study showed that low-energy laser irradiation accelerated orthodontic tooth movement²⁰. Therefore, low-energy laser irradiation may be useful in inhibiting inflammation and pain as well as decreasing orthodontic treatment time without side effects (Fig. 4).

CONCLUSIONS

In summary, mechanical stimulus causes an inflammatory reaction within periodontal tissues, which in turn may trigger the biological processes associated with bone remodeling. Further, low-energy laser irradiation may be useful in inhibiting inflammation and stimulating bone remodeling.

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