ACCELERATED TOOTH MOVEMENT

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ABSTRACT

The primary goal of contemporary orthodontic treatment is to decrease the duration of orthodontic treatment time by maximizing the biological response. There is a general consensus that the rate of tooth movement is controlled by the rate of bone resorption in the direction of tooth movement, which in turn is determined by the rate of osteoclast differentiation and activation. Our research demonstrates that the rate of osteoclast formation is controlled by the activity of local inflammatory markers (cytokines). In response to orthodontic forces, there is a transient up-regulation of inflammatory markers that play a key role in recruitment of osteoclast precursors and their differentiation into active osteoclasts. Therefore, it is logical to assume that one way to accelerate the rate of tooth movement is to increase the expression of inflammatory markers and, therefore, the rate of osteoclastogenesis. In this paper, we report a new approach to accelerating orthodontic tooth movement, present evidence from animal and human studies, and discuss biological principles supporting our results.

KEY WORDS: orthodontics, tooth movement, cytokines, osteoperforations, translational research

INTRODUCTION

From the Lab to the Clinic

Five years ago, the Consortium for Translational Orthodontic Research (CTOR; www.orthodonticscientist.org) was created as a nucleus for the integration of basic science, clinical science and industrial resources in the field of orthodontics. One of its objectives is to promote the translation of research findings and biological principles into clinical applications contributing to the development of more efficient and safer orthodontic therapies. CTOR has developed and created a network of
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orthodontists and scientists around the world with a common goal of addressing many questions in orthodontics and craniofacial orthopedics. The focus of these collaborations is to establish a road map to elevate orthodontics from an art into a science. CTOR also offers a one- or two-year intensive, “hands on” research training for healthcare professionals with an interest in translational research in craniofacial biology. The work presented here on accelerated tooth movement is a successful example of this translational effort.

Biology of Tooth Movement

One of the main challenges in orthodontics today is decreasing treatment time without compromising treatment outcome. To address this challenge, we need to understand the three variables that can control the duration of treatment. First, there are practitioner-dependent factors, such as proper diagnosis and treatment planning, mechanotherapy, selection of appliances and delivery of treatment in a timely fashion. Second, we have patient-dependent factors, such as maintaining appointments, good oral hygiene, integrity of the appliances and following the practitioner’s instructions. The third factor is the individual’s biology, which is beyond the control of the practitioner and patient. Assuming the first two factors have been optimized, the rate of tooth movement will be determined by the body’s response to orthodontic forces. In this regard, understanding the biology of tooth movement is essential.

In response to the application of orthodontic forces, the periodontal ligament (PDL) will exhibit areas of compression and tension. Displacement of the tooth due to compression of the PDL causes immediate constriction of blood vessels and damage to the periodontal tissues, which results in an aseptic, acute inflammatory response with the early release of chemokines and several other members of the cytokine family. Many of these cytokines have pro-inflammatory roles that help to amplify or maintain the inflammatory response and activation of bone resorption machinery. In contrast, some proteins have anti-inflammatory roles, thereby preventing unrestrained progress of the inflammatory response. Cytokines are produced primarily by inflammatory cells and secondarily by non-inflammatory cells such as osteoblasts, fibroblasts and endothelial cells. Many cytokines and chemokines play a significant role in osteoclastogenesis, recruiting osteoclast precursors from the
microvasculature into the extravascular space of the periodontal ligament and stimulating the differentiation and activation of osteoclasts. These multinucleated giant cells are responsible for resorption of alveolar bone, thus allowing specific tooth movements in response to orthodontic forces.

The importance of cytokines in controlling the rate of tooth movement can be appreciated through the dramatic results obtained from studies that block their effects. For example, injections of interleukin-1 receptor antagonist or tumor necrosis factor alpha receptor antagonist (TNF-α-RI) results in a 50% reduction in the rate of tooth movement (Iwasaki et al., 2001; Kesavaluet al., 2002; Jager et al., 2005; Andrade et al., 2007). Similarly, tooth movement in TNF type II receptor-deficient mice is reduced compared to wild-type mice (Yoshimatsu et al., 2006). Animals that are deficient in chemokine receptor 2 (a receptor for chemokine ligand 2) or chemokine ligand 3 show a significant reduction in orthodontic tooth movement that may be due in part to a reduced number of osteoclasts (DeLaurier et al., 2002). Likewise, it is well known that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the rate of tooth movement by inhibiting prostaglandin synthesis (Chumbley and Tuncay, 1986; Knop et al., 2012). Inhibition of other derivatives of arachidonic acid, such as leukotrienes, also significantly decreases the rate of tooth movement (Mohammed et al., 1989).

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In general, there are two main methods of increasing the rate of tooth movement. One approach involves the application of physical and chemical stimulants to activate pathways that cause an increase in bone remodeling. Interestingly, these pathways are not the natural pathways the body utilizes during orthodontic tooth movement; examples are discussed in the following paragraphs. The second approach involves intensifying the same pathways that are activated naturally in response to orthodontic forces.

For physical stimulation of bone remodeling pathways, the use of light (Tafur and Mills, 2008; Huang et al., 2009), heat (Tweedle, 1965), electrical currents (Davidovitch et al., 1980, 1984), laser (Kawasaki and Shimizu, 2000; Cruz et al., 2004; Bjordal et al., 2003, 2008; Bjordal and Baxter, 2006; Limpanichkul et al., 2006; Tafur and Mills, 2008; Youssef et al., 2008; Doshi-Mehta and Bhad-Patil, 2012) and vibration (Oxlund et
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al., 2003; Nishimura et al., 2008) have been suggested. Unfortunately, the application of these physical stimuli suffers from a lack of evidence, poorly studied mechanisms or impracticality. In addition, the increase in the rate of tooth movement is not significant enough to justify the application. It is important to note that many of these approaches are in early stages of development. Thus, these adjunct therapies to accelerate tooth movement show great promise for future research and clinical application.

For chemical stimulation of bone remodeling pathways, injections of parathyroid hormone (Potts and Gardella, 2007), vitamin D₃ (1,25 dihydroxycholecalciferol; Collins and Sinclair, 1988; Suda et al., 2003), corticosteroids (Ashcraft et al., 1992; Ong et al., 2000; Angeli et al., 2002; Kalia et al., 2004), thyroxin (Verna et al., 2000), osteocalcin (Hashimoto et al., 2001) and relaxin (Madan et al., 2007) have been suggested. The application of chemicals to accelerate tooth movement has many drawbacks including root resorption. First, all chemical factors have systemic effects that raise questions about their safety during clinical application. Second, the majority of the factors have a short half-life; therefore, multiple applications of the chemical are required, which is not practical. In addition, administration of a chemical factor in a manner that allows an even distribution along the alveolar bone surface is a challenge. Uneven distribution can change the pattern of resorption and, therefore, the biomechanics of tooth movement.

Another approach to accelerate the rate of tooth movement is to intensify the same biological response activated naturally during application of orthodontic forces. In this regard, if expression of inflammatory makers plays a critical role in controlling the rate of tooth movement, it is logical to assume that increasing the activity of these factors should accelerate tooth movement significantly. Previous studies have attempted to increase local inflammation during orthodontic tooth movement by the injection of prostaglandins (Yamasaki, 1984; Lee, 1990; Leiker et al., 1995; Kale et al., 2004), thromboxanes and prostacyclin (Gurton et al., 2004) or by systemic application of misoprostol, a prostaglandin E1 analog (Sekhavat et al., 2002; Seifi et al., 2003) with mixed results. These methods produced a biological response, but they possess similar limitations as the injection of the chemical agents discussed above. For example, injection of prostaglandins requires multiple applications due to their very short half-life and has undesirable
side effects. It has been shown that local injection of prostaglandins can cause hyperalgesia due to release of histamine, bradykinin, serotonin, acetylcholine and substance P from nerve endings (Knop et al., 2012). In addition, because orthodontic tooth movement is a multi-factorial phenomenon with many up- and down-regulated factors, the application of one factor to achieve such a complex biological response may be an oversimplification.

Given the drawbacks and limitations of physical and chemical stimulants to increase the rate of orthodontic tooth movement, a better approach would be to increase all the required inflammatory markers to intensify osteoclast activity and bone resorption, thereby increasing the rate of tooth movement. However, the best approach to producing higher levels of inflammatory markers is not clear.

**Simpler and Safer Approach**

Here we suggest a simple and safe approach to stimulate the body to respond to orthodontic forces at a higher level. This approach is based on a natural response by the body when it encounters any physical trauma. Specifically, we hypothesize that introducing controlled micro-trauma without affecting the integrity and architecture of hard and soft tissue will stimulate the inflammatory defense mechanism in the body, which then synergizes with the effects of orthodontic forces to accelerate the bone remodeling response. Our group first examined this hypothesis using an animal model of tooth movement before completing the human clinical trials. Since the objective of this translational research was establishing a therapeutic modality, the practicality and versatility of the technique was the focus of these studies. Results of this translational effort are presented here.

**MATERIALS AND METHODS**

**Animal Study**

Thirty-six adult male Sprague-Dawley rats were divided into three groups. In the experimental group (MOP), animals received a spring connecting the first maxillary molar to the incisors to apply a force to move the first maxillary molar mesially, and three shallow micro-osteoperforations (MOP) in the cortical bone 5 mm mesial to the first maxillary molar (Fig. 1A). In the sham group (O), animals
received the exact same force without the MOP. In the control group (C), animals received passive springs without any force application. All animals were anesthetized and Sentalloy closing coil springs (Dentsply GAC International, Bohemia, NY) exerting a force of 50 cN were placed between the first maxillary molar and incisors as described by Teixeira and colleagues (2010). For micro-computed tomography (mCT) analysis, hemimaxillae were scanned using Scanco Micro CT to evaluate changes in bone density. For histological analysis and immunohistochemistry studies, the hemimaxillae were collected, fixed in 10% phosphate buffered formalin, decalcified and embedded in paraffin blocks that were sectioned at 5-μm thickness. Hematoxylin and eosin staining was used to evaluate cell and tissue morphology and areas of bone resorption. Tartrate-resistant acid phosphatase (TRAP) immunostaining was used to locate and quantify osteoclast numbers and activity. For fluorescent microscopy, hemimaxillae were collected and embedded in polymethyl methacrylate. Blocks were sectioned with 7-μm thickness and viewed under fluorescent microscopy to evaluate bone formation and mineral deposition. Cytokine gene expression was evaluated by reverse transcription polymerase chain reaction analysis (RT-PCR). The hemimaxillae were collected and immediately frozen in liquid nitrogen for mRNA extraction and analysis. All methods are described in detail in Teixeira and associates’ study (2010).

**Human Clinical Trial**

A randomized, single-center, single-blinded study was approved by the Institutional Review Board of New York University. Participants were recruited from the patient pool that sought comprehensive orthodontic treatment at the Department of Orthodontics at New York University College of Dentistry. Twenty patients randomly were divided into control and experimental groups. Patients’ ages ranged from 19.5 to 33.1, with a mean age of 24.7 years for the control group and 26.8 for the experimental group. The control group consisted of three men and

→ Figure 1. MOPs accelerate tooth movement in rats. A: Experimental model. Rat hemimaxilla showing the location of three MOPs placed 5 mm mesial to the first molar. B: Comparison of the magnitude of tooth movement after 28 days of orthodontic force application (C = control; O = orthodontic force only; MOP =
orthodontic force + MOP). MOPs show greater magnitude of movement. C: Reverse transcription polymerase chain reaction analysis of cytokine gene expression. Data is presented as fold increase in cytokine expression in the O and MOP groups in comparison to C group. Data shown is mean ± SEM of three experiments. D: Histological sections stained with hematoxylin and eosin (top panels) show increase of periodontal space (p) thickness around the mesiopalatal root (r) of the first molar and increase in bone (b) resorption both in the O and MOP groups. Immunohistochemical staining (bottom panels) shows an increase in osteoclast activity represented by the increased number of tartrate-resistant acid phosphatase-positive osteoclasts (arrowhead) in both the O and MOP groups.
seven women whereas five men and five women participated in the experimental group. All participants had similar malocclusions; for inclusion criteria, refer to Alikhani and coworkers (2012). Both groups received similar treatment until the initiation of canine retraction. At that time, the experimental group received three MOP between the canine and the second premolar on one side only, while the contralateral side served as additional control (CL; Fig. 2A). The control group (C) did not receive MOP on either side. Clinical examination after 24 hours of placing the MOP in the experimental group showed no signs or symptoms of trauma. Canine retraction was accomplished using a calibrated 100-g cN nickel titanium (NiTi) closing spring that connected the canine via a custom-made power arm extending from the vertical slot of the canine bracket to the level of the center of resistance, to a temporary anchorage device (TAD) that was placed between the second premolar and the first molar. Evaluation of the rate of canine retraction was achieved through dental cast analysis from impressions taken immediately before the initiation of canine retraction and 28 days after the retraction. The distance between the canine and the lateral incisors was measured at three points: incisal, middle and cervical thirds of the crown using a digital caliper with an accuracy of 0.01 mm. The inflammatory response was evaluated by studying the cytokine level in the gingival crevicular fluid (GCF). Samples were collected from the distobuccal cervices of the canine before treatment, immediately before canine retraction and at every subsequent visit. Patient pain and discomfort were assessed using a numerical scale. Patients were asked to choose a number from 0 to 10, 0 meaning “no pain” and 10 meaning “worst possible pain”—on the day of appliance placement, the day of...
28 days of retraction in comparison to the C group and the contralateral side of the experimental group. D: Expression of inflammatory marker in the gingival crevicular fluid (GCF)—as measured by enzyme-linked immunosorbent–based assay before retraction and 24 hours, 7 days and 28 days after force application—shows significantly higher levels in the MOP group than in the C group. Data is presented as pg/uL. * = Significantly higher than control ($p < 0.05$).
canine retraction, and 24 hours, 7 days and 28 days after retraction. For method details, refer to Alikhani and colleagues (2013).

RESULTS

In the rat study, application of MOP significantly increased tooth movement by two-fold ($p < 0.05$) in the MOP group (0.62 mm) in comparison to the O group (Fig. 1B). At the molecular level, the expression of cytokines/cytokine receptors increased significantly 24 hours after force application in the MOP and O groups in comparison to the C group. In addition, 21 cytokines were significantly higher ($p < 0.05$) in the MOP group than the O group (refer to Teixeira et al., 2010 for a complete list of cytokines/cytokine receptors). Figure 1C shows the results for eight of these important markers. Histological analysis revealed increased alveolar bone resorption in both the MOP and O groups when compared to the C group. However, the MOP group showed a significantly greater rate of alveolar bone resorption than noted in the O group and a subsequent increase in PDL thickness (Fig. 1D). Immunohistochemical staining of TRAP-positive osteoclasts (Fig. 1D) revealed a three-fold increase in the number of osteoclasts in the MOP group in comparison with the O group (22 osteoclasts compared to eight osteoclasts per mm$^3$).

Using a canine retraction model in humans, we were able to mirror the results of our animal study. In our clinical trial, 28 days after initiation of canine retraction, we observed a significant increase in the space between the canine and lateral incisor in the MOP group when compared to both C group and CL side, where movement was diminutive (Fig. 2B). Dental cast measurements showed a 2.3-fold increase in canine retraction in comparison to both C group and CL side ($p < 0.05$; Fig. 2C). Protein analysis of the GCF showed an increase in cytokine expression after 24 hours of force application when compared to the pre-retraction levels for the same patients. However, in the MOP group, cytokines were significantly higher than in the C group ($p < 0.05$; Fig. 2D). After 28 days, all cytokine levels were decreased back to pre-retraction levels with the exception of interleukin-1-beta (IL1-β; for a complete list of cytokines and changes, refer to Alikhani et al., 2013). In the experimental groups, IL1-β levels still were significantly higher (5.0- and 3.6-fold, respectively) than their levels before retraction.
DISCUSSION

Our animal studies have shown that introducing small holes in alveolar bone (MOP) during orthodontic tooth movement can stimulate the expression of inflammatory markers significantly. This was accompanied by a significant increase in the number of osteoclasts and bone resorption (Fig. 3) as anticipated (Teixeira et al., 2010). We observed that the increase in bone remodeling was not limited to the area of the moving tooth, but extended to the tissues surrounding the adjacent teeth (data not shown). The increase in the number of osteoclasts and, therefore, increase in bone resorption and osteoporosity in response to bone perforations may explain the increase in the rate and magnitude of tooth movement observed in this study, thereby suggesting that the perforations do not need to be close to the tooth to be moved to accelerate the rate of tooth movement.

The results of our human clinical trial were similar to the rat study (2.3-fold increase in humans, 2-fold increase in rats). Canine retraction in the presence of MOP resulted in twice as much distalization as the one observed with the orthodontic forces alone. This increase in tooth movement was accompanied by an increase in the level of inflammatory markers. In addition, we recorded pain and discomfort levels using a numerical rating scale from 1 to 10, which showed patients that received canine retraction in presence or absence of microperforations reported an increase in discomfort levels when compared to pre-retraction levels (data not shown). However, no significant difference was noted between the MOP and the C group (orthodontic force alone group). Moreover, after the placement of the MOP, patients reported only moderate discomfort that was bearable and did not require any medication (data not shown).

When compared to other surgical approaches to accelerate tooth movement, it is obvious that MOP offers a number of advantages. This procedure is minimally invasive and flapless, allowing treatment to take place in the orthodontic chair. Corticotomies, on the other hand, require the reflection of a full-thickness flap to expose the buccal and lingual alveolar bone, followed by interdental cuts through the cortical bone. A modification of this technique recently has been introduced where, after selective decortication in the form of lines and points, a resorbable bone graft is placed over the surgical site. The effect of this...
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Figure 3. Schematic of the effect of cytokines and MOPs on osteoclastogenesis and bone resorption. Left side: Inflammatory cells that migrate to the periodontal ligaments from the bloodstream in response to orthodontic forces, as well as local cells such as osteoblasts, express nuclear factor κB ligand (RANKL) that binds to the receptor (RANK) on the surface of osteoclast precursor cells such as monocytes. This binding initiates the adhesion of these cells to each other to form osteoclasts that start the bone resorption. Right side: Adding MOPs increases the expression of inflammatory cytokines and chemokines, which, in turn, will increase the recruitment of osteoclasts and, therefore, the rate of bone resorption.

Technique has been attributed incorrectly to the shape of the cuts made into the bone (block concept) and to the bone grafts (Wilcko et al., 2001, 2005, 2009; Fischer, 2007; Nowzari et al., 2008). As previously discussed, the rate of tooth movement is controlled by osteoclast recruitment and activation. Therefore, regardless of the shape or the extent of the cut, bone resorption will not occur unless osteoclasts are activated. This means that, similar to microperforation, the effectiveness of corticotomy can be related to the activation of cytokines that are released in response to the trauma induced during the cuts. The release of cytokines is expected to be significantly higher in corticotomy in comparison with microperforation due to the extensive trauma to the bone. Unfortunately, similar to microperforation, the increased level of cytokines will not be sustained for a long period of time and eventually will return to normal levels. Corticotomies cannot be repeated as often as needed to maintain the desired level of cytokine activity due to the side effects of surgery and high cost. MOP offers a practical and minimally invasive procedure that can be repeated as needed. In addition, MOP can be incorporated into daily mechanics and at different stages of treatment. MOPs can be placed...
selectively in the areas where tooth movement is desired and away from teeth or segments used as anchorage.

REMAINING QUESTIONS

Although many of the approaches described above show promise, more studies are necessary to evaluate their efficiency and safety. Does faster tooth movement result in less tipping and more bodily movement of teeth, since change in bone density can affect the center of resistance? What are the adverse effects for the teeth and surrounding supporting tissues? Is there an increase in root resorption as teeth move faster or decrease in root resorption, since bone density significantly decreases? Does an increase in osteoclasts and bone remodeling during tooth movement result in less alveolar bone after treatment or more alveolar bone due to periosteal stimulation? Is accelerated tooth movement and faster alignment of teeth less stable or more stable in terms of retention?

Certainly, the CTOR studies discussed here advance our understanding of the biology that controls the rate of tooth movement and the molecular players in a race to shorter treatment time. Current investigations in the CTOR laboratories are attempting to answer some of these remaining questions in the field of orthodontics.

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