RESEARCH PAPER

Chemico-Biological Approach Accelerating Orthodontic Tooth Movement

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ABSTRACT

Orthodontics is a specialty of dentistry, work mainly using biomechanical principles of moving teeth that can correct dental malrelation and malformations of the jaws and face to correct and restore a functional, stableandaesthetic dentition. Orthodontic treatments are mainly to correct dental displacements, using either fixed or removable systems. Mostly the alveolar bone needs to be remodelled. Dentofacialorthopedics treatments also include the control and modification of jaw positions and facial growth by controlling the growth sites in the maxilla and mandible. An applied force to the crown of a tooth is transmitted through the root of the tooth to the periodontal ligament and alveolar bone. According to the applied force direction, there will be areas of pressure and tension on these supporting structures.

This increases the demand to find the best method to increase tooth movement with the least possible disadvantages. This article discusses the existing chemical and biological methods of enhancing tooth movement. Due to the advantages and disadvantages of each approach, further investigations should be done to determine the best method to accelerate tooth movement.

Keywords: Accelerating orthodontic tooth movement (OTM),chemical methods, biological methods, orthodontics.

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INTRODUCTION

Orthodontics is a specialty of dentistry, work mainly using biomechanical principles of moving teeth that can correct dental malrelation and malformations of the jaws and face to correct and restore a functional, stableand aesthetic dentition. Orthodontic treatments are mainly to correct dental displacements, using either fixed or removable systems. [1-7] Mostly the alveolar bone needs to be remodelled. Dentofacial orthopedics treatments also include the control and modification of jaw positions and facial growth by controlling the growth sites in the maxilla and mandible. An applied force to the crown of a tooth is transmitted through the root of the tooth to the periodontal ligament and alveolar bone. According to the applied force direction, there will be areas of pressure and tension on these supporting structures.[7-15]

For the movement of tooth, there must be resorption of alveolar bone in response to this stress, and deposition of bone in the opposite. [3,4]

It is generally accepted that the movement of the teeth with orthodontic forces depends on the bone remodeling rate, that are associated with the activity of inflammatory markers, quality and quantity of bone turnover, and the balance between osteoclastic and osteoblastic activity.[3,416] Osteoclastic activity is stimulated bychanges in tooth-supporting tissue biomarkers of receptor activator of nuclear factor kappa-light-chain-enhancer of activated B cells (RANK), RANK ligand (RANKL), andosteoprotegerin (OPG) during tooth movement. RANKL is a membrane-residing protein on osteoblasts and their precursors, which recognizes its receptor RANK on macrophages, promoting them to assume the osteoclast phenotype. [5,6,7,17]

The force applied on the teeth will cause changes in the microenvironment around the PDL due to alterations of blood flow, leading to the secretion of different inflammatory mediators such as cytokines, growth factors, neurotransmitters, colonystimulating factors, and arachidonic acid metabolites. As a result of these secretions, remodeling of the bone occurs.[18] Figure 1

Many experimental and clinical studies have worked towards many approaches for shortening the duration of

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orthodontic treatment including chemical, biological, surgical, pharmaceutical, laser, electromagnetic, or other procedures.

Regardless, none of these procedures have yet become a benchmark and an ideal solution to it.[3,4]

There are three phases of tooth movement: the initial phase which is characterized by rapid movement after the application of force; followed by a lag period, where little or no movement, and the last phase, where gradual or sudden increase of movement occurs.[1,2,9]

CHEMICAL APPROACH; EFFECT OF OSTEOCALCIN ON TOOTH MOVEMENT

Orthodontic tooth movement is achieved through the application of controlled therapeutic forces that elicit bone remodeling in the direction of the intended movement. These forces induce signaling pathways mediated by various osteogenic proteins, including OPN, bone sialoprotein, Osterix, and osteocalcin. Nonetheless, teeth subjected to orthodontic forces should have healthy periodontium to avoid any undesirable periodontal side effects. .[3**-9]**

Recently, the number of adult patients seeking orthodontic treatment has increased exponentially, and the number of patients is expected to increase in the upcoming years . Orthodontic treatment for adult patients has two challenges. The first challenge is age-related changes in the periodontium, which include a reduced number of fibroblasts, elastic fibers, and organic matrix production.

Osteocalcin (OC) is the most abundant non-collagenous matrixprotein in bone. Using this material to enhance the TM have beenexperimented by various scientists. It was found that pharmaceutical doses of OC had an additive effect on tooth movement .Since the effect was well correlated to the augmentation of osteoclasts on the alveolar bone in the pressure side, it was strongly suggested that the OC promoted the recruitment of osteoclasts into the local bone remodeling site. [18.19]

In fact, OC has been shown to significantly enhance the formationof TRAP-positive multi-nuclear osteoclast-like cells in the presence of macrophage colony-stimulation factor (M-CSF) and granulocyte-macrophage colony stimulating factor using the invitro murine bone marrow culture system, but not in the absence5 of these factors. .[3-9] Figure 2

EFFECTS OF DIAZEPAM

Increased levels of cAMP in the areas of bone resorption during orthodontic tooth movement have been suggested as correlates of cellular activity. Diazepam has been shown to increase the levels of cAMP in rat brain, cat heart muscle, and central nervous system cells by an inhibitory action on cAMP phosphodiesterase.[16,21]The data from this investigation indicate that administration of diazepam results in faster orthodontic tooth movement. [3 ,4,18]

Effect of Vitamin D3 on tooth movement Vitamin D3 has also attracted the attention of some scientist to its role in the acceleration of tooth movement; [17.31] 6dihydroxycholecalciferol is a hormonal form of vitamin D and plays an important role in calcium homeostasis with calcitonin and parathyroid hormone (PTH). Few nvestigators have made an experiment where they have injected vitamin D metabolite on the PDL of cats for several weeks; it was found that vitamin D had accelerated tooth movement at 60% more than the control group due to the increasement of osteoclasts on the pressure site as detected histologically. .[19]

PTH EFFECT ON TOOTH MOVEMENT

Parathyroid hormone (PTH) is known to accelerate orthodontic tooth movement (OTM) by increasing alveolar bone turnover, stimulating osteoclast-mediated bone resorption, and inducing a Regional Acceleratory Phenomenon (RAP). Studies indicate that local, chronic application of PTH(1-34) can significantly increase the rate of tooth movement, with some studies showing up to a 1.6-fold increase in movement rate. [3, 4,20] Figure 3

PTH influences gene transcription, cellular metabolic activity, and various protease secretion in osteoblasts. It affects osteoclasts by causing them to produce RANK-L, a protein that is essential for osteoclast activity and formation. The paradoxical effects of parathyroid hormone on the metabolism of the bones have drawn attention as one of the major regulators of calcium and phosphate homeostasis.[21] According to research, parathyroid hormone can increase both osteoblast-mediated bone formation and osteoclast-mediated resorption of the bones, speeding up the bone turnover rate. In clinical osteoporosis treatment, intermittent low-dosage parathyroid hormone analogs were majorly used. Previous research has looked into the effects of various parathyroid hormone administration patterns, and findings proposed that continuous systemic infusions or the local chronic applications of the parathyroid hormone can speed up tooth movement by increasing alveolar bone resorption. In contrast, long-term intermittent injection regarding parathyroid hormone facilitated periodontal bone or root resorption following orthodontic tooth movements by activating the osteoblastic cells. [8,9.22]

PTH has been shown to accelerate orthodontic tooth movement on rats, which was studied by continuous infusion of PTH (1 to 10 μg/100 g of body weight/day) implantation in the dorsocervical region, and the molars were moved 2- to 3-fold faster mesially by orthodontic coil spring. [3,24,25] Some studies have shown that locally injected PTH induces local bone resorption, and it is more advantageous to give PTH locally rather than systemically. [8,23]

EFFECT OF LEUKOTRIENES ON TOOTH MOVEMENT

Leukotrienes are a type of eicosanoid which is a product of arachidonic acid conversion and are the only eicosanoids that are formed independently from cyclooxygenase (COX). They are produced when arachidonic acid is metabolised by lipoxygenase enzymes[19,26].Leukotrienes also play an important role in Inflammation, allergies, and diseases such as asthma.

These conditions can be cured by using leukotriene inhibitors which block leukotriene receptors hence counteracts their effects. Examples of medication are montelukast and zafirlukast. [9,27]

Leukotrienes play an important role in inflammation, allergic, and asthmatic reactions. Their effects can be counteracted by antagonists of leukotriene receptors, such as montelukast and zafirlukast, medication used for asthma, or by inhibition of leukotriene synthesis by a drug such as zileuton. Zileuton selectively blocks the essential enzyme lipoxygenase resulting in inhibition of bone resorption, as well as stimulation of bone deposition, thereby possibly influencing OTM. [25,28,29]

EFFECT OF PROSTACYCLINS ON TOOTH MOVEMENT

Prostaglandins (PGE) are a group of chemical messengers belonging to the family of hormones called eicosanoids. It acts by regulating the synthesis of cyclic AMP in many tissues. Cyclic AMP is responsible in controlling the action of various hormones. This allows prostaglandin to affect a wide range of cellular and tissue functions. Prostaglandins are responsible in stimulating contraction of the smooth muscles of the uterus, affects blood flow, sleepcycle and also response to hormones such as adrenaline and glucagon. It also plays a role in elevating body temperature, which leads to inflammation and pain. According to Klein and Raisz[25,30], Prostacyclins (PGI 2) act as vasodilators and prevent plateletaggregation. However, surprisingly, local iloprost administration at dosages from 2.10 −5 to 2.10 −3 μM/12 h significantly increased the rate of OTM evoked by a separation force of 20 cN between rat incisors. This indicates that the effects of prostacyclins and thromboxanes on OTM are comparable, although their effects on platelet aggregation and vasodilatation are contrary. An explanation can be found in in vitro findings showing that stimulation of either thromboxane receptors or prostacyclin receptors leads to an upregulation of COX-2 andsubsequently to a positive feedback loop that also includes prostaglandin synthesis. [26,32] Effect of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) on tooth movement NSAIDs form the most important class of prostanoid synthesis inhibitors. Almost all studies on the effects of NSAIDs during experimental OTM in animals evaluate the effects of a relatively short-lasting administration. They have shown a decrease in the number of osteoclasts, since prostaglandins are involved either directly or indirectly in osteoclast differentiation or in stimulating their activity. There are recommendations that the prostaglandin inhibitors during the orthodontic treatment should be avoided. [33,34] Acetaminophen was proposed as the analgesic of choice for the orthodontic patients.[27]Ketorolac is an analgesic that is used for the short-term relief of moderate to severe pain and should not be used for longer than 5 days and for mild pain or for pain from chronic (long-term) conditions.[28,35] However, OTM is a multifactorial process over a long period of time, and the effect of long-term use of ibuprofen therefore may differ. In patients with chronic illnesses like juvenile rheumatoid arthritis, osteoarthritis, or gout, where long-term analgesic consumption is needed, the inhibiting effects on OTM may become more evident.[29,36]

EFFECT OF OPIOIDS ON TOOTH MOVEMENT

Opioids, including morphine, codeine, and methadone, reduce the rate of orthodontic tooth movement (OTM) by inhibiting bone remodeling and reducing orthodontic force, with effects potentially dose-dependent. Studies indicate these drugs interfere with the biological response to force, although some, like tramadol, may have minimal impact at lower doses. [26,32,37] Figure 4

Orthodontic pain is an unavoidable consequence and one of the most common side effects of orthodontic treatment. Numerous modalities, including pharmacological and non-pharmacological approaches, have been developed to alleviate orthodontic pain and discomfort in clinical practice [1,2]. The most commonly used pain management drugs for relieving orthodontic pain are acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs (NSAIDs) [3]. Acetaminophen is a widely used analgesic, but despite its structural similarity to NSAIDs, it lacks anti-inflammatory effects in peripheral tissues [4]. NSAIDs have been widely shown to be effective in managing orthodontic pain [5,6]. However, there remains an ongoing debate about their potential to slow down the rate of tooth movement and their use in the orthodontic field has been generally discouraged [7–10]. There is no clear scientific recommendation for the best NSAIDs with minimal side effects in orthodontic treatment that allows achieving professional precision and ensuring patient well-being in orthodontic care. Considering this, our study explores the relationship between tooth movement and orthodontic pain, describes NSAIDs used for pain relief, and assesses their impact on tooth movement through a comprehensive literature review. [1,2]

Opioids are effective for the treatment of acute and chronicrelated pain, i.e., with degenerative conditions such as rheumatoid arthritis, or even during labor and cardiac infraction. Only a very few studies have been performed on the effects of opioids on OTM. The opioids tested were only morphine (INN) and tramadol. However, tramadol is under strict control in some countries. In one rat study, it is reported that daily morphine injections at a dose of 5 mg/kg/day over 14 days reduced the rate of OTM induced by a force of 60 cN.15 In another study from the same group, daily tramadol injections at a dose of 20 mg/kg/day during 14 days had no effect.[31] Figure 5

EFFECT OF BISPHOSPHONATES ON TOOTH MOVEMENT

Bisphosphonates (BPs) significantly inhibit orthodontic tooth movement (OTM) by reducing osteoclast activity and bone resorption, leading to slower, restricted tooth movement and longer treatment duration. While useful for enhancing anchorage, they carry risks of increased root resorption and, rarely, medication-related osteonecrosis of the jaw (MRONJ).

Bisphosphonates currently represent the therapy of choice for treating osteoporosis and are indicated for preventing and treating skeletal complications in cancer patients. Are a class of drugs highly effective in the treatment of various bone diseases, such as osteoporosis, Paget disease and bone metastasis [3,4]. Used for the treatment of several osseous disorders. The main subtypes of are alendronate, ibandronate, risedronate, pamidronate, clodronate, and zoledronic acid [5]. Studies have shown that these drugs may influence the amount of tooth movement and root resorption during orthodontic tooth movement. [3,4,7]

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As bisphosphonates have an action mode which interferes in the osteo-resorptive process, their use during dental treatment may occasionally have side effects, such as: inhibition of tooth movement, delayed bone healing, and osteonecrosis in the maxilla and mandible. Thus, authors have suggested that these drugs may alter bone physiology and potentially hinder orthodontic treatment[1,31].

They are used primarily for the prevention and therapy of osteoporosis, Paget's disease, bone metastases, and bone painsome types of cancer.They build in the extracellular bonematrix and inhibit bone resorption. Once built in, bisphosphonates have extremely long half-life of 10 years or moreTherefore, they may affect bone metabolism for many years after the patient has completed therapy. [32]

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a complication described in the long-term bisphosphonate treatment.This is caused by the suppressive and anti-angiogenic effects on epithelial cells and inhibitory effect on endothelial cell proliferation and wound healing. [32-36]

BIOLOGICAL APPROACH

Experiments have been done using these molecules exogenously to enhance tooth movement both in animal experiments and humans. Example of these molecules are prostaglandin E (PGE), cytokines that include lymphocytes and monocytes-derived factors, receptor activator of nuclear factor kappa B ligand (RANKL), and macrophage colony-stimulating factor (MCSF). [33]

EFFECT OF CYTOKINES ON TOOTH MOVEMENT

Cytokines are critical signaling proteins that mediate orthodontic tooth movement (OTM) by regulating alveolar bone remodeling. Proinflammatory cytokines (e.g., IL-1β, TNF-α, RANKL) are released under mechanical stress, accelerating osteoclast differentiation and bone resorption, while anti-inflammatory cytokines facilitate later tissue repair.[5]

The role of cytokines in the orthodontic tooth movement is considered in the context of inflammation, which occurs at the very beginning of this process as a reaction to the mechanical pressure and represents necessary precondition for the realization of all its subsequent levels. In the conjunction of mechanical and biological mechanisms, which move the teeth during the orthodontic treatment, cytokines are given great importance for their feature of transmission of biochemical signals among numerous cells of various kinds reacting to orthodontic forces. Binding themselves to specific receptors at membranes of these cells, cytokines cause in them the biochemical changes responsible for the signal transmission to corresponding genes in these cells and, consequently, to the change of gene expression in them. This orthodontic tooth movement causes the features of unusually complex processes, whose different degrees—each individually and all together—are regulated by the network of positive and negative feedbacks, in which cytokine molecules act as mutual activators or inhibitors [3].

High concentration of cytokines such as interleukins IL-1, IL-2, IL-3 IL-6, IL-8, and tumor necrosis factor alpha (TNF) were found to play a major role in bone remodeling; moreover, interleukin-1 (IL-1) stimulates osteoclast function through its receptor on osteoclasts.3It was also found that mechanical stress due to Orthodontic treatment increased the production of prostaglandin PGE and IL-1 beta in the periodontal ligaments.[3-8] Using biological molecules in the acceleration of tooth movement19has been shown in two unique experiments in which it was demonstrated that the transfer of RANKL gene to the periodontal tissue induced prolonged gene expression for the enhancement of osteoclastogenesis and acceleration of tooth movements in rats. On the other hand, the transfer of OPG gene inhibited orthodontic tooth movements.[3]

RELAXIN EFFECT ON TOOTH MOVEMENT

Orthodontic treatment is the rearrangement of skeletal or dental tissues. The clinician’s ability to do so is facilitated by an extensive network of sutures and soft tissues within the orofacial complex: facial and cranial sutures, periodon tal ligament, and the gingiva. Unfortunately, as much as they allow movement of dental or skeletal units, they are also thought to be responsible for the relapse of corrected relationships. Movement and relapse both require remod eling of these soft tissue systems. At the microscopic level, they are highly organized. Mechanical forces evoke a remodeling response, and remodeling involves either syn thesis or degradation of collagen, or both (1–3). Arguably, if an agent or stimulus could break down the structural organization or interfere with collagen metabolism, then the orthopedic or orthodontic corrections might be easier and more stable.[5,9]

One such phenomenon is physiologically present in the body: the relaxin-induced widening of the pubic symphysis during childbirth. This hormone is also present

in the male, but its role remains obscure. In the pregnant female, it interferes with the collagen types I and III gene expression, reduces total collagen, and increases the collagenase activ ity. Currently, there are no reports of its effect on cranio facial sutures, but it was suggested as the responsible element in the degradation of the temperomandibular joint (TMJ) disc (4). Actually, the scope of relaxin's effect outside the reproductive system is largely unknown (5, 6). The potential is exciting for an application of this hormone in dentofacial orthopedics or orthodontics. Accordingly, this study was designed to 1) demonstrate the presence and effects of relaxin in the connective tissue and 2) show relaxin's effects on the proteinase activity.

Relaxin is a hormone that helps during childbirth by widening of the pubic ligaments in females and is suggested to be present in cranial suture and PDL.[35] The role of relaxin is known in the remodeling of soft tissue rather than remodeling of bone. It has been shown that it increases collagen in the tension site and decreases it in compression site during orthodontic movement.Figure 6

Also, the administration of human relaxin may accelerate the early stages of orthodontic tooth movement in rat experiments.[3-8]

However, another study showed that human relaxin does not accelerate orthodontic tooth movement in rats, but can reduce the level of PDL organ/ization and mechanical strength of PDL and increase tooth mobility. [36-38]

PLATELET RICH PLASMA (PRP) AND DERIVATIVES

Platelet-Rich Plasma (PRP) is an autologous, injectable, growth-factor-rich serum used in orthodontics to accelerate tooth movement, primarily by enhancing bone remodeling. Clinical studies indicate it can significantly increase the rate of tooth movement during the first 1–2 months, particularly in canine retraction, by stimulating osteoclastic activity.[13]

latelet-rich plasma (PRP) was defined as an "autologous concentration of platelets in a small volume of plasma" by Marx in 2004.[1] Peripheral blood contains 94% of red blood cells (RBCs), 6% of platelets, and <1% of white blood cells (WBCs), while PRP contains 5% of RBCs, 1% of WBC, and 94% of platelets. There are many systems available for the preparation of PRP and different protocols have been used by different authors for synthesis of PRP. It is produced through a 2-phase centrifugation process of patient's whole blood, first centrifugation separates patients whole blood components and the second centrifugation produces the final PRP,[3] which is a rich source of autologous growth factors. The high concentration of various growth factors present in PRP is responsible for its different clinical applications in the field of dentistry. The GFs reported to be present in PRP are as follows: Platelet-derived growth factor (PDGF), transforming growth factors-β (TGF-β), vascular endothelial growth factor, epithelial growth factor, insulin growth factor-1, and fibroblast growth factor.[13,14]

Along with GFs, PRP also contains cytokines, adhesive proteins, proteases, antiproteases, and leukocytes. .[1 -9]

PRP made its first impression in dentistry when Marx in 1998, used it in combination with autogenous bone grafts for reconstruction of mandibular defects,[1] and concluded radiographically that PRP in addition with bone grafts revealed a higher bone density and maturation rate than bone grafts. However, controversies existed regarding these effects of PRP, some authors found that PRP favored bone formation and maturation while others were of the thought that PRP had an inhibitory effect on bone metabolism. .[13,14]

Since then, a large number trials and reviews have been conducted and published on the use of PRP in different dental procedures such as regenerative dentistry, endodontic healing, periodontal regeneration, wound healing in oral and maxillofacial surgery, implant dentistry, sinus floor augmentation, and bone remodeling.

Recently, PRP has also been utilized in the field of orthodontics mainly to see its effects on rate of orthodontic tooth movement (OTM), response of local application of PRP on the surrounding bone, and histological changes accompanying them.

One of the paramount problems of PRP is understanding its biology and mode of action in orthodontics. PRP contents have multiple and overlapping biological effects. .[13,14]

For example, PDGF is a powerful chemoattractant and stimulator of cell proliferation which stimulates osteoprogenitor cells and also stimulates resorption by increasing the number of osteoclasts Another growth factor TGFβ is known to be critical for initiation or progression of tissue repair but, can actually function to increase inflammation and retard wound healing which makes it role complicated to understand in healing . .[13,14]

PRP is defined as an autologous concentration of platelets in a small volume of plasma and is considered to be a rich source of autologous growth factors (GFs). [37]]PRP was first introduced to the dental literature in 1998 in combination with autogenous bone grafts for the reconstruction of mandibular defects, reporting that the addition of PRP to bone grafts resulted in a faster radiographic maturation rate and a higher bone density than bone grafts alone however controversies regarding this potential benefits exists.[13,14] .

Although their long-term effectiveness was debatable, this acceleratory impact was momentary and appeared to diminish at nearly stage

CLINICAL APPLICATIONS FOR THE FUTURE

The administration of exogenous biological molecules to accelerate tooth movement during orthodontic treatments has been intensively tested on animal experiments. However, clinical trials on humans are limited since they must be administered occasionally by local injections that can be painful and cause discomfort to the patients

avoiding systemic applications, plus their side effect was not tested for long [periods of time.[13,14]

CONCLUSION

As more and more chemical analogues are being used in the form of new drugs to avoid resistance, today's orthodontist should have updated knowledge about the clinical efficacy of the new drugs as well as the mechanism of action of these drugs on human tissues. It is always advisable for a dentist to confirm with the general physician for fitness of those patients who seek orthodontic treatment involving tooth movement.Orthodontists should assume that many patients are taking prescription or over-the counter medications regularly. The orthodontist must identify these patients by taking a proper history of medication and their consumption of food supplements; should be considered as a part of orthodontic diagnosis.

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