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## Prostaglandin E2, an orthodontic point of view

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### Abstract

**Introduction.** Chemical, biological, physical stimulants and surgical procedures are used to accelerate orthodontic treatment.

**Objective.** Analyze the literature about Prostaglandin E2 (PGE2) from an orthodontic perspective. **Methods:** Review of available literature in scientific articles indexed in PubMed, Cochrane Library and EBSCO about the effector mechanism of PGE2, its participation during orthodontic movements, as well as its beneficial and adverse effects.

**Results:** PGE2 acts in bone resorption through osteoclast activation and acts on osteoblasts to facilitate osteoclast genesis by increasing the secretion of the RANKL activator. It has been shown that osteoblasts and gingival fibroblasts respond to mechanical stress with increased production of PGE2, rapid movement of the teeth is possible without causing root resorption, because they reduce tissue resistance during orthodontic movement. It has both anti-inflammatory and pro-inflammatory effects, its role is fundamental in the improvement of immunosuppressive functions, promotes the healing of peptide ulcers, angiogenesis and re-endothelization as well as the proliferation of stem cells and positive effect on gene therapies. Its acceleration of the G1-S cycle during mitosis can cause several types of cancer, including Kaposi's sarcoma.

**Conclusion.** Promoting therapy to accelerate orthodontic movement with this mediator should be carefully evaluated, taking into account the risk / benefit that PGE2 can cause.

**Keywords:** Prostaglandin E2, accelerated orthodontics, RANKL, EP4, dental movement

### 1. Introduction

In orthodontics, there is no consensus on the most competent manual methods for dental movements [1]. Which are complex phenomena that according to the theory of pressure-tension occurs in three stages: obstruction in blood flow after the application of pressure to the periodontal ligament, release of chemical messengers, and activation of bone resorption [2]. During the last decade, several strategies have been proposed to accelerate orthodontic treatment, these include chemical agents, physical stimulants and surgical procedures [3]. They can help meet the demands of patients. Taking into account the risk factors related to treatment [4, 5]. Periodontal ligament fibroblasts perform regulatory functions in the innate immune response, respond to compressive and tensile forces during orthodontic treatment with the release of prostaglandins [6], which are cytokines involved in inflammation caused by such movements. Among the subclasses of prostaglandins, PGE2 is strongly related to bone resorption [7], inhibits osteoprotegerin and stimulates the activator of the nuclear factor receptor kappa-B ligand (RANKL), which regulates the increase in COX- 1 and COX-2 [8]. One of the factors that are being investigated for their effects on tooth movement are prostaglandins (PG), especially E2, which are potent multifunctional regulators of bone metabolism [9]. Brudvik was the first author to investigate the effects of PE2 injections [10]. Currently animal studies have reported that the rate of orthodontic dental movement, as well as some growth of the mandibular condyle increases significantly after the administration of exogenous, intraligamentous and submucosal injections of PGE2 because they substantially increased the osteoblastic and osteoclastic populations in the alveolar bone, greatly accelerating orthodontic dental movement [4, 11, 12]. There is currently a greater desire to implement less invasive methods to achieve rapid movements during orthodontic treatment. Therefore, the objective of this study is to review the available literature,

about the effector mechanism of prostaglandins specifically PGE2, their participation during orthodontic movements, the beneficial effects they cause in humans and their adverse effects.

## 2. Materials and methods

Major headings are to be column centered in a bold font without underline. They need be numbered. "2. Headings and Footnotes" at the top of this paragraph is a major heading. A bibliographic search of scientific articles indexed in pages such as PubMed, Cochrane Library and EBSCO was carried out, taking into account the most relevant for the realization of this article. 109 bibliographies were analyzed, of which 50 articles were selected that met the inclusion criteria which were articles that talked about the effector mechanism of prostaglandins, their participation during orthodontic movements, positive or beneficial effects for humans, as well as adverse effects. Articles that talked about the use of other cytokines with therapeutic effects were excluded.

## 3. Results & Discussion

### 3.1 Role of PGE2

PGs are synthesized in almost all body tissues in response to physical, chemical, mechanical, immunological or neurohormonal stimuli [12]. They are eicosanoids formed from unsaturated fatty acid of 20 carbons and arachidonic acid, which is released from membrane phospholipids through phospholipase A2. Subsequently, specific labile PGH2 isomerases and synthases are converted to active prostanoids, including prostaglandins [13]. PGE2 which is one of the most typical lipid mediators produced from arachidonic acid by cyclooxygenase (COX) [14] exerts its biological function through actions including pyrexia, pain sensation and inflammation through four subtypes other than receptors (E-prostanoid (EP) 1-4) [15]. Of which EP2 and EP4 have been identified *in vivo* and *in vitro* as the receptors responsible for the mediation of bone formation or prevention of bone loss, they are expressed in the membrane of human CD34 + cells [16]. In addition, EP4 is known for its diverse and sometimes paradoxical activities in different cells of the immune system during the different stages of the immune response [17] as it is by imposing a general suppressive effect on activation and production of T cells, differentially regulates the lineage specification of CD4 + effector T cells, shifting the type 1 balance towards other forms of immunity, such as Th2, Th17 and Treg [18]. The concentration of PGE2 increases rapidly in acute inflammatory processes, promoting local vasodilation, increasing microvascular permeability and promoting extravasation of blood granulocytes and mast cell activation [19], plays an important role in the regulation of various cell lines, works both in physiological and pathological conditions, such as bone resorption through osteoclast activation, acts on osteoblasts to facilitate osteoclastogenesis by increasing the secretion of the RANKL activator in response to mechanical stress *in vitro* and *in vivo* [20] which is a key molecule in the differentiation and activation of osteoclasts. The increase in the level of this molecule is detected in periodontal disease and orthodontic tooth movement [21]. The effector mechanism of PGE2 is a phenomenon that is related especially during inflammatory processes, which among its actions within this reaction a very important one is to promote the activation of several cell lineages, including osteoblasts and osteoclasts, these cells having the activity of creating and reabsorbing bone.

### 3.2 PGE2 during orthodontic movements

Bone tissue is constantly renewed and bone homeostasis is finely regulated by a balance between bone apposition, carried out by osteoblasts, and bone resorption, for which osteoclasts are responsible [22]. Orthodontic dental movement is based on the resorption and coordinated formation of tissue in the surrounding bone and the periodontal ligament. Compression and tension are associated with particular signaling factors, which establish local gradients to regulate bone remodeling and the periodontal ligament for tooth displacement. Facilitating osteoclastic resorption in the alveolar bone exposed to continuous compressive force is an important factor for tooth movement [23]. Various types of immune system cells, vascular elements and bone cells participate in tissue remodeling during orthodontic dental movement [24]. Key regulators of inflammation and tissue turnover include secreted factors such as RANKL and osteoprotegerin, transcription factors such as RUNX2 and hypoxia-inducible factor, cytokines such as IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, [25], prostaglandins, TNF- $\alpha$  and proteases, among others [26]. Osteoblasts and gingival fibroblasts have been shown to respond to mechanical stress with increased PGE2 production [27]. Experimental studies using prostaglandins, cytokines, neuropeptides and leukotrienes have shown that rapid movement of the teeth is possible without causing root resorption, because they reduce tissue resistance during orthodontic movement [12]. It has long been suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen [28] and Meloxicam [29] can slow down orthodontic tooth movement due to inhibition of synthesis of prostaglandins [30]. Orthodontic movements cause in the alveolar bone a place where a pressure and tension occurs that in turn this mechanical stress will be translated as bone resorption and apposition, where the synthesis of PGE2 for the activation of osteoblasts will have an important role. Osteoclasts, allowing dental movement to the place desired by the operator, taking into account that there are NSAIDs commonly prescribed to the patient when he suffers post-operative pain that causes delayed orthodontic movements.

### 3.3 Benefit effects of PGE2

PGE2 plays a fundamental role in tissue maintenance and regeneration; It has been found to induce cell differentiation of some neuronal cells [31], has a substantial influence on bone, bone remodeling and healing, but its effects are still controversial and discussed [32]. However, it has been reported that it has anti-inflammatory effects because it increases the synthesis of IL-10 and decreases the production of proinflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$  and IL-12 [33]. In addition, it inhibits the proliferation of activated T cells, the cytotoxicity of NK cells and the maturation of dendritic cells, so their role is essential in improving immunosuppressive functions [34, 35]. It also plays an important role in stem cells. A previous study showed that it promotes the proliferation of progenitor cells in cell cultures *in vitro* and in trials of a spleen transplant [36]. Through its subtype EP4, it stimulates anti-inflammation in the lung and provides a new clinical perspective for chronic inflammatory conditions of the respiratory tract [37]. It has also been shown that PGE2 promotes the proliferation of primary myoblasts by accelerating the transition of the G1-S phase in the cell cycle [38]. It has an intestinal cytoprotective action [39], shows a healing effect on gastric ulcers and lesions of the small intestine [40] stimulation of angiogenesis and reendothelialization through the activation of EP4 receptors

[41]. It has recently been shown to be useful in clinical applications of gene therapy because the synthesis of PGE2 improves lentiviral transduction and increases the number of copies of the vector, resulting in increased transgene expression [42]. It seems that PGE2 has multiple beneficial effects for humans that are in a state of immunosuppression, chronic respiratory disease and intestinal diseases because it has anti-inflammatory, pro-inflammatory effects, promotes angiogenesis and repair of the endothelium of blood vessels. As well as its synthesis promises to be a factor with positive effect in more innovative therapies with stem cells and gene therapy.

### 3.4 Adverse effects of PGE2

In general, it has been shown that prostaglandins interfere with cytokines and amplify their actions in various types of inflammatory cells, and drive the pathogenic conversion of cells by critically regulating their gene expression [43]. PGE2 is involved in numerous physiological processes, which include the development of stem cells, inflammation and cancer [44] because it promotes the progression of the cell cycle, by accelerating the transition of the G1-S phase [38]. Therefore, its inhibition is considered one of the approaches to limit the growth and spread of several types of cancers [45]. Its subtype EP4 has been shown to be the key receptor in endometrial cancer [46]. It has also been reported that PGE2 plays a role in the development of ovarian, breast, colorectal cancer [47] and pancreas [48]. In addition, the secretion of PGE2 and its autocrine and paracrine interactions with EP receptors (EP1-4) has been involved, signaling of the COX-2 / PGE2 / EP receptor regulates the pathogenesis and latency of Kaposi's Sarcoma [49]. Recently, it has been shown that PGE2 can have serious effects on humans, such as the progression of several types of cancer, including Kaposi's Sarcoma, which can be detected in the oral cavity, with EP4 being the subclass most related to tumor development.

### 4. Conclusions

PGE2 is a lipid mediator that plays an extremely important role during orthodontic movements, promoting bone resorption and apposition through the activation of osteoblasts and osteoclasts. There are certain types of NSAIDs that inhibit the synthesis of PGE2 caused the delay of dental movement. In general, its synthesis has multiple beneficial effects on the body that include an intestinal cytoprotective action and improvement in patients who are in a state of immunosuppression and with chronic respiratory disease, is also a mediator that demonstrates positive effects on gene therapies and with stem cells. However, it has been observed that due to its acceleration of the G1-S cycle during mitosis, several types of cancer can occur in the female reproductive tract, pancreas and orally Kaposi's Sarcoma. Because of this, promoting therapy to accelerate orthodontic movement with this mediator should be thoroughly studied taking into account the risk / benefit that PGE2 can cause.

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