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THE ROLE OF BIOMARKERS PGE2 AND IL-1β IN ORTHODONTIC TOOTH MOVEMENT - REVIEW PAPER

УЛОГАТА НА БИОМАРКЕРИТЕ PGE2 И IL-1β ВО ОРТОДОНТСКОТО ДВИЖЕЊЕ НА ЗАБИТЕ - РЕВИЈАЛЕН ТРУД

Amella Cana[1]

[1]University Dental Clinical Centre St. Panteleimon- Skopje, Republic of North Macedonia

Abstract

Introduction: Tooth movements caused iatrogenically by the application of orthodontic forces for therapeutic purposes are realized through remodeling of the alveoli, with facilitation of numerous biomarkers including inflammatory mediators. The mediators PGE2 and IL-1β have a particular role in these events. **Aim:** The aim of this review is to determine the role and effect of PGE2 and IL-1β in orthodontic tooth movement. **Material and Method:** A total of 39 articles were analyzed, including original articles and reviews published on PubMed and Google Scholar. Only articles published in English were included in the investigation. Key words used for collecting data were Orthodontic treatment, biomarkers, PGE2 and IL-1β, bone remodeling. **Conclusion.** In the treatment of malocclusions the highest values of PGE2 and IL-1β in gingival fluid have been detected in the early orthodontic phase. Both inflammatory mediators have osteoclastic activity, with IL-1β acting in the first hours of the action of mechanical force, and PGE2 activity is synergistic, with the final effect being tooth movement and alveolar remodeling. **Key words:** Orthodontic treatment, biomarkers, PGE2 and IL-1β, bone remodeling.

Апстракт

Вовед: Движењето на забите кое се јавува како резултат на примена на ортодонтските сили во терапевтски цели, се остварува преку ремоделација на алвеоларната коска потпомогнато од бројни биомаркери, во прв ред инфламаторните медијатори PGE2 и IL-1β, кои имаат посебна улога во целиот овој процес. **Цел:** Целта на овој ревијален труд е да се утврдат улогата и влијанието на инфламаторните медијатори PGE2 и IL-1β во ортодонтското движење на забите. **Методи:** За реализација на поставената цел беа анализирани вкупно 39 стручни статии, вклучувајќи ревијални трудови и трудови со оригинални резултати објавени на базите PubMed и Google Scholar. Во испитувањето беа вклучени само трудови објавени на англиски јазик. Клучни зборови користени за прибирање на податоците беа ортодонтски третман, биомаркери, PGE2 и IL-1β и ремоделирање на алвеоларната коска. **Заклучок:** При ортодонтскиот третман на малоклузиите највисоки вредности на медијаторите PGE2 и IL-1β во гингивалниот флуид беа констатирани во раната ортодонтска фаза. И двата инфламаторни медијатори имаат остеокластична активност, при што IL-1β делува во првите часови од дејството на механичката сила, а активноста на PGE2 е синергистичка, при што крајниот ефект е движење на забите и ремоделација на алвеоларната коска. **Клучни зборови:** ортодонтски третман, биомаркери, PGE2 и IL-1β и ремоделирање на алвеоларната коска.

Introduction

In everyday life, in physiological conditions the teeth are in constant motion which is slow, minor and invisible, and is accomplished by permanent remodeling of the alveoli in which they are placed. In healthy periodontitis, although they are constantly in discrete motion, they remain firmly fixed in the alveoli without luxation. In this case the forces are controlled. But throughout life, teeth are constantly exposed to the effects of various stressors (weaker or stronger) due to mastication, phonetics or may be the result of many other causes that are transmitted from the tooth to the alveoli and surrounding support apparatus. The forces are not always within the permissible force or direction. In many situations they overlap with the axial axis of the tooth, and are vertically oriented. But for a variety of reasons, in addition to the vertical direction, they can be more or less longitudinal, sloping, even horizontal.

In essence, the supportive tooth apparatus is the main harmonizing system that balances strength in physiological stresses, and during pathological stresses tolerance is limited, thus if compensatory mechanisms are unable to continue balancing alterations appear. The consequences depend on the strength, duration of the action of force, and the capacity of the tissues around the over-

loaded teeth. Of course, in these conditions the immune response of individuals that has a significant influence on the tissue response, should not be forgotten.

In physiological conditions there is a balance between osteoclastic resorption and osteoblastic bone formation; hence, in the absence of excessive forces these two processes are in equilibrium. The resorption on one side of the tooth is balanced by the deposition of newly created bone on the opposite side. At the same time, these processes are aided by the continuous deposition of cement which throughout life manages to maintain, more or less, a constant relationship between the root surface and the alveolar cup.

For therapeutic purposes in certain situations, tooth movement during orthodontic treatment (OTM) is desirable, predictable and expected. In orthodontic dosing, tooth movement is a consequence of a series of biological events in the teeth, periodontal ligament (PDL) and alveolar bone that causes microscopic, macroscopic, biochemical and other changes in and around the tooth[1,2].

Concerning these processes that occur in the tooth environment, it is well known and understood that orthodontically conditioned tooth loading causes cell changes in the alveolar bone initiating processes of cell differentiation, reparation, migration, vascular changes and inflammation. Bone remodeling facilitates tooth movement to the desired position. On the pressure side during OTM, the blood perfusion is reduced and is associated with hypoxia. This vascular condition creates conditions for the disrupted process of cell proliferation, which in certain situations can cause apoptosis-cell death[3].

In essence, OTM is not a simple activity, it is rather a complex dynamic movement that causes a series of sequential events that are dominated by vascular tissue changes, synthesis and release of molecules, biomarkers, cytokines or neurotransmitters[2]. Each of the released molecules has activity that in the tissue around and in the tooth has an effect on the alveolar wall or in PDL whose ultimate effect is compression (pressure) on one side and the opposite tension (traction)[4], or more precisely, certain biomarkers stimulate resorption processes, and others the opposite[2].

During orthodontic treatment, biomarkers that are released play a key role in biological changes in and around the tooth and are divided into three major groups: inflammatory mediators, metabolic products and enzymes[5]. Each group contains several substances that act as indicators for the events in and around the tooth. They all have different powers of specificity and sensitivity, but one thing is important - each of them has a field of action and informs about the biological status of PDL and alveolar bone at a particular stage of OTM[6].

Beside the periodontiumthat has an important role in the movement of teeth in OTM, the gingival fluid (GCF) plays the auxiliary role. It is an exudate and an indicator of biochemical events in the tooth[5].

In the GCF besides the largest percentage of water, immunoglobulins, bacteria, enzymes, toxins and many inflammatory mediators are present as well[7]. Some of them play the role of markers responsible for the active destruction of tissues in most periodontal diseases[8]. During orthodontic treatment the cytoskeletal configuration and shape of cells in the PDL are changed[9].

Biological tissue changes under the influence of orthodontic forces

The forces applied to tooth movement have different effects on and around the teeth depending on the duration of action[10]. Initially the force exerted causes thinning of the periodontal ligament followed in parallel by certain metabolic tissue changes that intensify several hours later. But these changes are not identical on both sides; on the contrary, metabolic deviations differ on the side where the tooth is directed, i.e. the compression side, as opposed to the side where the correction occurs, i.e. tension[11].

The forces affect all structures of the periodontal tissues (alveolar bone, periodontium, cementum and gingiva), but the dominant effects are observed on the alveolar bone, where the primary effect is related to the cells. They differentiate, migrate, collapse or heal not only as a result of orthodontic forces but also as a consequence of some other factors including obligatory inflammation and vascular disorders[12]. Thanks to these activities remodeling takes place in the alveolar cup which facilitates movement.

The alveolar bone is not only involved in the movement of teeth, the PDL is also subject to force-induced changes. Thus, in the pressure side of the PDL there is hypoxia-induced blood perfusion, which is believed to either influence cell proliferation or cause apoptosis. Definitely, the effects depend on the degree of oxygen present[12].

In the PDL besides the extracellular matrix and collagen fibers there is also a rich cell population composed of fibroblasts, osteoblasts, osteoclasts, cementoblasts, cementocytes, fibrocytes and other cells that contribute to the specific design of PDL, and each has its own role. Together they have the ability of renewal, so PDL can be easily adapted to the action of orthodontic forces if they are moderate and controlled[13]. Referring to all these developments, periodontal tissues allow the teeth to be moved to new positions, thus changing, what for the patients seems important, aesthetics as well as the function[14].

Given the changes in periodontal tissues, it can be concluded that orthodontic tooth movement is a fairly serious and complex procedure resulting from numerous and varied biomechanical changes that, according to Proffit[15], are primarily due to changes in PDL.

According to another group of researchers, tooth movement during orthodontic treatment may be the result of a series of consecutive reactions in the periodontal tissues including alveolar bone, not just in PDL[10].

Zainal Ariffin[10] confirms that these processes release numerous substances from the tooth and surrounding structures called biomarkers that can be identified in different media.

The remodeling process i.e. compression and stretching, alter the vascularization that causes the synthesis of different signaling molecules that generate a cellular response providing resorption or apoptosis processes[2]. Initiate activation processes on various cellular signaling pathways that promote resorption and apoptosis processes[16]. These signals are responsible for changing of the cytoskeletal structure. Some authors describe this process as a series of orchestrated cellular and molecular events in the alveolar bone and in PDL initiated from the application of orthodontic force[17]. Signals are responsible for the changes that initiate alterations in the cytoskeletal structure[7,18].

In addition to the macroscopic and morphological changes that occur during orthodontic treatment, changes are also evident at biomolecular level, where growth factors, prostaglandins, and cytokines in general are released as one segment of the large biomarker group[19].

The role of biomarkers in orthodontic tooth movement

Biomarkers are identified as important mediators during orthodontic therapy. They are the cause of inflammatory disorders, bone resorption and apoptosis, changes in the periodontal ligament, and vascular and neural tissue changes[20-21]. In essence, biomarkers are substances that are objectively measured and evaluated as indicators of normal biological, pathological processes or as pharmacological response status following applied therapeutic procedures in tissue, and most commonly in GCF.

Numerous studies in the 1990s have reported that biomarkers have been linked to alveolar bone destruction and the progression of periodontal disease. Macrophages and neutrophils, in response to bacteria, produce important inflammatory mediators such as TNF-α, IL-6, IL-1, and other cytokines that are associated with bone and tissue destruction[23, 24].

Thanks to studies[25, 26] concerning the orthodontic tooth movement, it is concluded that the inflammatory interleukins of IL-1β, IL-6, TNF-α and low molecular protein molecules are found in the inflamed periodontal pockets[27].

Therefore, it can be concluded that biomarkers can be indicators for other conditions of the periodontal tissues, and not only related to orthodontic tooth movement. They have a particularly important role in the processes of bone homeostasis and bone destruction. Specific inflammatory mediators such as ICTP, RANKL, osteoprotegerin (OPG), and osteocalcin are pointed out for this role. Bostanci[28] measuring the amounts of RANKL and OPG and their ratio showed that in bone destruction, RANKL increased in the gingival fluid and OPG decreased. This condition is reversed in healthy gingiva or gingivitis where other periodontal tissues including bone are not involved in resorption processes.

In addition to the metabolic substances and enzymes in the group of biomarkers that participate in bone shaping during orthodontic tooth movement, an important site belongs to the group of inflammatory mediators. This group includes the following biological substances: prostaglandin E, neuropeptides (calcitonin related gene peptide and substance p), transforming growth factor-α1, epidermal growth factor, α2 microglobulin and insulin-like growth factor-1, interleukin-1 (receptor antagonist) 1β, 2, 6, 8, tumor necrosis factor, macrophages colony stimulating factors, receptor activator of nuclear factor-kappa / receptor activator of nuclear factor-kappa ligand / osteoprotegerin system, myeloperoxidase, markers of root resorption[5].

Prostaglandins are one of the most important group of inflammatory mediators involved in bone loss and bone formation processes.

Prostaglandin E(PGE2)

Prostaglandins are lipid compounds that are derived enzymatically from fatty acids and have important functions in human and animal organisms. Each prostaglandin contains 20 carbon atoms, five of which form a ring. One of them is Prostaglandin E. Specifically, PGE2 is a major mediator of inflammatory and vascular events. It plays a major role in the destructive and absorptive processes that are based on increased osteoclast activity in the body[29].

Dosage of orthodontic force supplemented with PGE2 injection in animal models (monkeys and rats) resulted in advanced alveolar bone resorption which caused increased tooth mobility[31, 32].

Increased levels of PGE2 in GCF by 24-48 hours of application have been reported in the human population

where orthodontic controlled forces have been applied. However, the study reported a decrease in values after 168 hours of research[32].

Studies on the values of PGE2 and IL-1β in GCF indicate that ovarian activity has an influence on inflammatory mediators during the orthodontic tooth movement stage[33].

A comparison of PGE2 values in GCF during orthodontic force application revealed different findings. Namely, the young population has increased levels of PGE2 in the GCF, which increased to 21 days. From 21 to 28 days the concentration of this biomarker has been decreased. No difference was observed in adults before and after the study. Variations of PGE2 in GCF were not detected. In fact the results do not indicate that PGE2 levels vary with age and period of orthodontic activation. This may explain why orthodontic treatment is more successful in younger versus older populations[34].

PGE2 and IL-1β are considered to be strong stimulants of bone resorption and apoptosis and are a type of response to mechanical stress. In fact, the dynamics of this activity is dependent on their concentration, which in turn is reflected in the clinical finding in orthodontic loading conditions[34]. A study concerning the concentration of PGE2 and IL-1β in GCF confirms the recent findings. Values increase at the early stage of orthodontic treatment, and then normalize, i.e. are returned to their initial values in 7 days[35].

A research by Saito[36] showed that periodontal ligament cells responded to mechanical stress with increased production of PGE while IL-1β enriched the tissue response.

A well-known fact among orthodontists and periodontists is that orthodontic load on a periodontally compromised teeth is not very desirable as it leads to additional lesions of the already damaged tissues. To some extent this connection is also a limit for planning and implementing orthodontic appliances. But the adverse impact of whether and how advanced periodontal disease would affect tooth movement during orthodontic dosing, including the ultimate effect, is an issue that has yet to be elucidated. Okamoto[37] investigated the effect of experimentally induced periodontal inflammation on orthodontic tooth movement in mice. Special

Table 1. Relationship between PGE2 and IL-1β with orthodontic tooth movement

Mediator	Model	Medium	Sample	Important findings	References
PGE2	animal	GCF	rats	Tooth movement	[30]
PGE2	animal	GCF	rats	Tooth movement	[31]
PGE2	human	GCF	humans	Increasing from 24-48 hours	[32]
PGE2	animal	GCF	cats	Influence of ovaries	[33]
PGE2	human	GCF	Young population	Increase till the 21 day	[34]
PGE2	human	GCF	adult	No changes	[34]
PGE	human	GCF	humans	Increasing first 24-48 hours. Normalizing after 7 days	[35]
PGE	animal	tissue	cats	Marked staining of the tension side	[36]
PGE2	In vitro		rats	In vitro treatment with PGE2 decreases the extracellular signal- regulated kinase phosphorylation and RANKL expression	[37]
PGE2	Review	PGE 2		use of light continuous forces	[38]
PGE2	humans	GCF	children	Increase in the tension side	[21]
PGE2	humans	GCF	humans	Increase after 24 hours	[39]

staining has shown that during orthodontic treatment the number of osteoclasts was reduced in the pressure zone under conditions of induced periodontal disease.

The expression level of the receptor activator of nuclear factor kappa-B ligand (RANKL) in the pressure zone was reduced in the group where ligatures were applied. In contrast, experimental periodontitis increased the levels of cyclooxygenase-2 mRNA in periodontal tissues, whereas in vitro treatment with PGE2 reduced extracellular signal-regulated kinase phosphorylation and RANKL expression induced by mechanical stress in osteoblasts. These results suggest that force-induced orthodontic osteoclastogenesis in the alveolar bone was inhibited by concomitant periodontal inflammation, at least in part through PGE2 resulting in reduced tooth movement[37].

The activity of PGE2 and IL-1β is known, but their role in bone remodeling is confirmed in Ren's review[38]. The relationships of these two inflammatory mediators has been confirmed, revealing different patterns of regulation. Namely, PGE 2 and IL-1 beta jointly participate in orthodontic tooth movement. IL-1 beta responds primarily to mechanical stress, and PGE 2 is more responsive to the synergistic regulation of IL-1 beta. The results of the analysis suggest the application of light continuous forces in the orthodontic treatment of patients.

Studies have been conducted comparing PGE2 and IL-1β values on the side of compression and tension in patients undergoing orthodontic forces during the early phase of orthodontic tooth movement. Increases of basic values have in most cases been on the tension side. In control teeth throughout the study values of PGE2 and IL-1β remained at baseline. Results suggest that PGE2 and IL-1β in GCF reflect biological activity in the periodontium[21].

Conclusion

During orthodontic tooth movement, the highest values of PGE2 and IL-1β in gingival fluid have been detected in the early orthodontic phase. IL-1β exhibits osteoclastic activity and PGE2 acts synergistically. Both inflammatory mediators have osteoclastic activity with the final effect being tooth movement and alveolar remodeling.

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