International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 11 November 2023

Page No: 2636-2640

DOI: https://doi.org/10.47191/ijmscrs/v3-i11-18, Impact Factor: 6.597

The Role of Periodontal Ligament Remodeling on Orthodontic Tooth Movement

Hafiedz Maulana[1], Nuzulul Hikmah[2]

[1,2]Department of Biomedic and Oral Maxcillofacial Pathology, Faculty of Dentistry Universitas Jember, Indonesia

ABSTRACT

The periodontal ligament is a connective tissue located between the cementum that covers the roots of the tooth and alveolar bone, which is composed of large amounts of fibers, cells, and blood vessels. Orthodontic tooth movements are obtained through periodontal ligament remodeling and alveolar bone in response to orthodontic forces. When the orthodontic force is applied to the teeth, an injury will occur in the periodontal ligament, and the pressure and tension side in the periodontal ligament is formed. Furthermore, vasoconstriction occurs in blood vessels and hypoxia in the periodontal ligament, triggering inflammation, angiogenesis, cell proliferation, degradation, and synthesis of extracellular matrix, bone resorption, and alveolar bone deposition. The purpose of this article is to study the mechanism of periodontal ligament remodeling on orthodontic tooth movement to obtain optimal tooth movements.

KEYWORDS: periodontal ligament, remodeling, orthodontic tooth movement

ARTICLE DETAILS

Published On:
07 November 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Orthodontic tooth movement is a process that combines the physiological adaptation of the alveolar bone with reversible injury of aseptic periodontal tissue.[1] An essential mechanism for orthodontic tooth movement is the remodeling of the periodontal ligament and alveolar bone in response to orthodontic forces. During orthodontic tooth movement, the periodontal ligament undergoes dynamic remodeling, which requires adequate blood supply for its regeneration.[2]

The application of orthodontic force causes pressure on the periodontal ligament, vasoconstriction of blood vessels, and decreased blood flow, which causes a decrease in nutrient and oxygen levels (hypoxia).[3] Hypoxia can cause cellular damage and vascular changes in the periodontal ligament that include vascular occlusion in pressure side and vasodilation in tension side. Furthermore, hypoxia induces an increase in hypoxia-inducible factor 1 (HIF-1) in the periodontal ligament, which triggers angiogenesis, proliferation of periodontal ligament cells, periodontal ligament remodeling, osteogenesis, and osteoclastogenesis.[4,5,6,7,8]

The orthodontic force will directly affect the periodontal ligament so that the cells in this ligament will change in morphology and function and remodeling of the periodontal ligament, which is the process of active degradation and the synthesis of extracellular matrix. Type I and III collagen produced by fibroblasts will respond to mechanical forces affecting periodontal ligaments. Therefore, periodontal ligaments play an essential role in the mediation of orthodontic forces, trigger alveolar bone modeling and remodeling, and maintain a physiological balance of periodontal tissue.[9] Therefore, this article studies the periodontal ligament remodeling mechanism in the orthodontic tooth movement.

DISCUSSION

Orthodontic Tooth Movement

Orthodontic tooth movements are obtained through periodontal ligament remodeling and alveolar bone in response to orthodontic forces. When the orthodontic force is applied to the teeth, the injury occurs in the periodontal ligament, and pressure and tension sides are formed. It triggers the remodeling of periodontal ligaments and alveolar bones. The pressure side is an area in the periodontal ligament suppressed by the orthodontic device towards the force. The pressure results in the deformation of blood vessels and tissue damage around the teeth. Conversely, the tension side is an area opposite to the direction of force, and there is a stretch of periodontal ligaments.[10]

Transduction of orthodontic forces will trigger biological responses characterized by bone resorption on the pressure side and bone formation on the tension side. This

process is contrary to the mechanism of the bone, where the pressure will stimulate bone formation. There are two explanations why pressure on the teeth causes bone resorption while the pressure on the bone causes bone formation. First, applying pressure on the teeth reduces the tension between periodontal ligaments and side-by-side bones. Thus, orthodontic tooth movements are considered to reduce mechanical strength on the surface of the bone on the pressure side. Second, aseptic injury due to the orthodontic force in the periodontal ligament on the pressure side is an inflammatory process.[11]

Periodontal Ligament Remodeling Mechanism on Orthodontic Tooth Movement

The orthodontic forces cause vasoconstriction and decreased blood flow, which results in a decrease in nutritional and oxygen levels (hypoxia).[3] The hypoxia will cause an increase in Hypoxia Inducible Factor 1α (HIF-1α) in the periodontal ligament, which in turn will trigger angiogenesis, cell proliferation, and periodontal tissue reconstruction.[4,8] Increased HIF-1α expression due to induction of mechanical force can also cause osteogenic differentiation through increased ALP activity in osteoblast cell culture and increase the expression of the Receptor Activator of nuclear factor Kappa-B Ligand (rank), Cyclooxigenase-2 (COX-2), Interleukin-1β (IL-1β), Vascular Endothelial Growth Factor (VEGF), Prostaglandin E2 (PGE2), Collagen-I (Col1), Tartrate-Resistant Acid Phosphatase (Trap), Osteopontin (OPN), Runt-Related Transcription Factor (Runx-2), alkaline phosphatase (ALP) and decreased OPG expression in periodontal ligament cell culture.[7,5,6,8] Therefore, applying orthodontic forces also causes cellular and vascular changes in the periodontal tissue.

The mechanism of hypoxia in the angiogenesis process is the activation of the transduction signal, nuclear factor-κB (NF-κB), which is the family of mitogen-activated protein kinase (MAPK).[12] Phosphorylation and activation of the MAPK can further stimulate the expenditure of growth factors such as fibroblast growth factor-2 (FGF-2) and tumor necrosis factor-α (TNF-α) for the angiogenesis process. In hypoxia, HIF 1α and FGF-2 have a reciprocal relationship in releasing their expressions for the angiogenesis process.[13] In addition, HIF-1α dan HIF-1β can increase VEGF, which is an angiogenesis regulator.[14] FGF-2 induces VEGF's expression on the periodontal ligament and synergistically stimulates angiogenesis.[15] Increased expression of FGF-2 and VEGF also occurs in periodontal ligaments in orthodontic tooth movements.[16,17] VEGF was detected in vascular endothelial cells, osteoblasts, osteoclasts in resorptive lacuna, fibroblasts, local necrotic areas in pressure sides, and mononuclear cells in periodontal tissue during orthodontic tooth movements.[18] At the same time, FGF target cells include fibroblasts, endothel, myoblast, chondrocytes, and osteoblasts.[19]

Hypoxia also causes the release of several other growth factors, platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β).[20] PDGF itself comes from platelets and functions to determine the activation of phospholipase-A2 and the release of arachidonic acid through cyclooxygenase and lipoxygenase, which leads to the formation of prostaglandins and leukotrienes.[19] Alveolar bone contains a large amount of TGF-β produced by fibroblasts and osteoblasts deposited in the extracellular membrane. The target TGF-β is platelet and bone cells and involves monocytes and fibroblasts for angiogenesis. In orthodontic tooth movements, TGF-β involves several biological processes such as growth, differentiation, apoptosis, and alveolar bone remodeling.[19] Although some studies describe the role of different TGF-β in the movement of the tooth in an orthodontic manner, most of them show that this cytokine can inhibit the recruitment of osteoclast precursors and osteoclasts activity mediators in the pressure side.[18]

The application of orthodontic force also activates several growth factors, including colony stimulating growth factor (CSF), bone morphogenetic proteins (BMPS), insulin growth factor (IGF), RUNX2, and Osterix (OSX).[21,19] CSF, which includes granulocyte colony stimulating growth factor (G-CSF) and macrophage colony stimulating growth factor (M-CSF), plays a role in the osteoclasticogenesis process. IGF has a function that is almost the same as TGF-β. During tooth movement, IGF increases cell proliferation and differentiation as well as metabolic effects such as insulin. IGF is regulated by various local or systemic factors, which include growth hormone (GH), parathyroid hormone (PTH), vitamin D3, IL-1, and PDGF.[19] RUNX2 is a multifunctional transcription factor expressed during the osteoblast differentiation process and is involved in the initial response of alveolar bone cells to the presence of orthodontic forces. Like RUNX2, OSX is also a transcription factor in the development and differentiation of osteoblasts and bone tissue and is involved in the initial response of the orthodontic force.[21]

Hypoxia in orthodontic tooth movements affects the increase of nitric oxide (NO) synthesis. The production of NO is catalyzed by several enzymes, including neuronal nitric oxide synthase (nNOS), inducible nos (iNOS), and endothelial nos (eNOS). NO has an essential role in cellular oxygen regulations, one of which is through hypoxia-inducible factor (HIF), which will activate the transcription program to increase the survival of cells in inadequate oxygen supply conditions. NO production is closely related to oxygen homeostasis. Oxygen is the primary substrate to produce NO and impacts enzymatic activity and the expression of enzymes that catalyze the production of NO, namely NOS.[22] Hypoxia can cause increased release of iNOS and eNOS in endothelial cells in periodontal disease models. This process shows that the condition of hypoxia can affect angiogenesis, which is a vascular response to periodontal tissue inflammation.[23]

In general, hypoxic conditions through HIF can cause an increase in the expression of several genes involved in cell proliferation, apoptosis, glucose metabolism and

energy, immune responses, vascular remodeling, and angiogenesis. Endothelial cells play a role in maintaining vascular homeostasis through their influence on vascular tone, recruitment of inflammatory cells, proinflammatory cytokine production, and maintaining barrier and antithrombotic function. Hypoxia affects the dysfunction of endothelial cells, one of which is caused by excessive production of ROS from mitochondria.[24]

In orthodontic tooth movements, NO is a vital regulator of the bone response to mechanical force. NO produced from eNOS or iNOS plays a role in mediating the formation of adaptive bone, osteoclast activity, and preventing osteocyte apoptosis. In addition, inhibition of NO production can increase osteoclastogenesis. The application of orthodontic forces produces tension in the bone, causing fluid flow that leads to the production of NO by osteocytes.[25] eNOS is proven to mediate bone formation on the tension side so that eNOS can be used as a marker of osteoblast activity.[10]

Metabolic changes also occur in periodontal ligament cells due to hypoxia and decreased nutritional levels. In hypoxia conditions, cells will depend on anaerobic glycolysis. Furthermore, cells in the periodontal ligament experience apoptosis and necrosis, an acute aseptic inflammatory process occurs, and the release of chemokines from local cells. Necrosis occurs because the orthodontic force causes hyalinization in the periodontal ligament.[10] Chemokine is a small protein released by local cells that can attract other cells to certain areas. The release of chemokines in response to the orthodontic force facilitates the expression of adhesion molecules in blood vessels and stimulates the inflammatory and osteoclastogenesis processes. Chemokine released included monocyte chemoattractant protein-1 (MCP-1 or CCL2), which played a role in the differentiation of monocytes into macrophages and osteoclasts, and CCL3 and CCL5 (RANTES), which played a role in differentiation and activation of osteoclasts.[3]

The following process is the release of inflammatory and cytokine mediators when applying orthodontic forces. Inflammatory mediators released include prostaglandin (PGS) and neuropeptide. PGS originates from arachidonic acid metabolism and mediates each stage of inflammation, which includes vasodilation of blood vessels, increased vascular permeability, and adhesion of inflammatory cells. During the tooth movement, these mediators are released by local cells and inflammatory cells in response to the presence of orthodontic forces or indirectly by cytokines. PGS production is strengthened by several agents, such as platelet-derived growth factor (PDGF), parathyroid hormones (PTH), interleukin, or other cytokines. Together with prostacyclin and thromboxane A2, PGS plays a role in increasing orthodontic tooth movement through osteoclastogenesis stimulation. Neuropeptides are also involved in several stages of inflammation in response to the orthodontic force. Neuropeptides are small proteins that can send pain signals, regulate the tone of blood vessels, and modulate the permeability of blood vessels.[3]

Cytokines released during orthodontic tooth movements are proinflammatory (TNF-α, IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-17 and RANKL) and anti-inflammatory cytokines (IL-4, IL -10, and IL-13).[26,19] Cytokines are extracellular proteins that play an essential role in the regulation of inflammatory responses and activation of the bone resorption process. Cytokines are produced by inflammatory cells (macrophages) and local cells such as osteoblasts, fibroblasts, and endothelial cells.[3] RANKL binding to RANK plays a role in the induction of osteoclastogenesis, where RANKL expression increases during orthodontic tooth movements. In contrast, RANKL activity is inhibited by OPG, which plays a role in decreasing tooth movements.[27]

Necrosis Factor tumor (TNF) is a non-glycosylated protein produced in two isoforms (TNF-α and TNF-β) mainly by monocytes/macrophages. Applying mechanical forces can increase TNF levels in periodontal tissue and act as osteoclastogenesis regulators on the pressure side.[18] In addition, TNF will work synergistically with IL-1β and TGFβ for alveolar bone resorption. IL-1 is a potent cytokine that facilitates the survival, fusion, and activation of osteoclasts for the bone resorption process.[19] The application of orthodontic forces also increases IL-1 levels in the pressure side and directly affects the activity of alveolar bone resorption. In addition, IL-1β is also an induction of IL-6 production.[18]

Interleukin-2 (IL-2) is a proinflammatory cytokine produced by t-helper cells and is involved in osteoclast activity during the alveolar bone remodeling process on orthodontic tooth movements. IL-6 is a pleiotropic cytokine synthesized by monocytes/macrophages and other cells such as lymphocytes, fibroblasts, and endothelial cells in response to IL-1 and TNF-α. This cytokine plays a role in regulating the immune response in the inflammatory tissue and the process of osteoclastogenesis. IL-6 levels also increase when applying orthodontic forces, especially in the early stages of tooth movement. IL-8 is secreted mainly by monocytes and is essential in regulating alveolar bone resorption during teeth movement. This cytokine has an intense proinflammatory action that plays a vital role in the recruitment and activation of neutrophils during the initial phase of an inflammatory response.[19]

Interleukin-17 (IL-17) is also detected in the periodontal ligament with the application of orthodontic force. Together with IL-6, IL-17 also stimulates osteoclastogenesis and induces the alveolar bone resorption process.[26] Interferon-γ (IFN-γ) is secreted by T helper 1 (TH1) cells, cytotoxic T cells, dendritic cells, natural killer cells, and activating macrophages through increased NO production. IFN-γ is detected in the pressure side of orthodontic tooth movement and plays a role in inhibiting osteoclastogenesis and tooth movements.[18]

During the tooth movement process, the periodontal ligament also responds to dynamic changes in collagen connective tissue. The orthodontic force can change the mechanical force distribution in the periodontal ligament and induce collagen remodeling in the extracellular matrix in the periodontal ligament through an increase in type 1 and 3 collagen. Type 1 collagen responds to mechanical strength and maintains the stability of the tooth's position. In contrast, type 3 collagen can reduce mechanical pressure affecting the periodontal ligament during tooth movement.[28] Injuri in the periodontal ligament will be forwarded to the alveolar bone. Furthermore, bone remodeling occurs, which is a balance between bone deposition played by osteoblast, bone resorption by osteoclast, and osteocytes, which are mechanosensory cells.[29] Therefore, periodontal ligament remodeling is essential in inducing osteoclastogenesis and alveolar bone osteogenesis during orthodontic tooth movement.

CONCLUSION

Applying orthodontic force to the teeth causes injury to the periodontal ligament so that the cells and extracellular matrix in the periodontal ligament will experience changes in morphology and function, and periodontal tissue repair will occur. Periodontal ligament remodeling is an active and dynamic process that includes degradation and synthesis of extracellular matrix, which plays a vital role in the induction of osteoclastogenesis in orthodontic tooth movement.

REFERENCES

I. Li Y, Jacox LA, Little SH, and Ko CC. Orthodontic tooth movement: the biology and clinical implications. Kaohsiung Journal of Medical Sciences. 2018; 34: 207-214.

II. Narimiya T, Wada S, Kanzaki H, Ishikawa M, Tsuge A, Yamaguchi Y, and Nakamura Y. Orthodontic tensile strain induces angiogenesis via type IV collagen degradation by matrix metalloproteinase-12. J Periodont Res. 2017; 1–11.

III. Alikhani M, Alansari S, Sangsuwon C, Nervina JM, and Teixeira CC. Biphasic theory of tooth movement: cytokine expression and rate of tooth movement. Dalam: Biology of orthodontic tooth movement current concepts and applications in orthodontic practice. Editor: Bhavna Shroff. Springer International Publishing Switzerland. 2016. p. 45-66.

IV. Niklas A, Proff P, Gosau M, and Römer P. The role of hypoxia in orthodontic tooth movement. International Journal of Dentistry. 2013; 1-8.

V. Li ML, Yia J, Yang Y, Zhang X, Zheng W, Lid Y, and Zhaoe Z. Compression and hypoxia play independent roles while having combinative effects in the osteoclastogenesis induced by periodontal ligament cells. Angle Orthod. 2016; 86: 66–73.

VI. Ullrich N, Schröder A, Jantsch J, Spanier G, Proff P, and Kirschneck C. The role of mechanotransduction versus hypoxia during simulated orthodontic compressive strain-an in vitro study of human periodontal ligament fibroblasts. International Journal of Oral Science. 2019; 11(33): 1-10.

VII. Yu H, Yu W, Liu Y, Yuan X, Yuan R, and Guo Q. Expression of HIF-1α in cycling stretch-induced osteogenic differentiation of bone mesenchymal stem cells. Molecular Medicine Reports. 2019; 20: 4489-4498.

VIII. Zhang X, Chen D, Zheng J, Deng L, Chen Z, Ling J, and Wu L. Effect of microRNA-21 on hypoxia-inducible factor-1α in orthodontic tooth movement and human periodontal ligament cells under hypoxia. Experimental and Therapeutic Medicine. 2019; 17: 2830-2836.

IX. Ferguson DJ and Wilcko MT. Tooth movement mechanobiology: toward a unifying concept. Dalam: Biology of orthodontic tooth movement current concepts and applications in orthodontic practice. Editor: Bhavna Shroff. Springer International Publishing Switzerland. 2016. p. 13-44.

X. Ariffin SHZ, Yamamoto Z, Abidin IZZ, Wahab RMA, and Ariffin ZZ. Cellular and molecular changes in orthodontic tooth movement. The Scientific World Journal. 2011; 11: 1788-1803.

XI. Graves DT, Kayal RA, Oates T, and Garlet GP. Osteoimmunology in the oral cavity (periodontal disease, lesions of endodontic origin and orthodontic tooth movement). Osteoimmunology. Elsevier Inc. 2011. p. 429-432.

XII. Sun X and Feinberg MW. NF-κB and hypoxia: a double-edged sword in atherosclerosis. The American Journal of Pathology. 2012; 181(5); 1513-1517.

XIII. Lee JE, Shin SH, Shin HW, Chun YS, and Park JW. Nuclear FGFR2 negatively regulates hypoxia-induced cell invasion in prostate cancer by interacting with HIF-1 and HIF-2. Nature. 2019; 9(3480): 1-12.

XIV. Krock BL, Skuli N, and Simon MC. Hypoxia-induced angiogenesis: good and evil. Genes & Cancer. 2011; 2(12): 1117–1133.

XV. Yanagita M, Kojima Y, Kubota M, Mori K, Yamashita M, Yamada S, Kitamura M, and Murakami S. Cooperative effects of FGF-2 and VEGF-A in periodontal ligament cells. J Dent Res. 2014; 93(1): 89-95.

XVI. Seifi M, Badiee MR, Abdolazimi Z, and Amdjadi P. Effect of basic Fibroblast Growth Factor on orthodontic tooth movement in rats. Cell Journal (Yakhteh). 2013; 15(3): 230-237.

XVII. Salomao MFL, Reis SRD, Vale VLC, Machado CD, Meyer R, and Nascimento ILO. Immunolocalization of FGF-2 and VEGF in rat periodontal ligament during experimental tooth movement. Dental Press J Orthod. 2014; 19(3): 67-74.

XVIII. Jiang C, Li Z, Quan H, Xiao L, Zhao J, Jiang C, Wang Y, Liu J, Gou Y, An S, Huang Y, Yu W, Zhang Y, He W, Yi Y, Chen Y, and Wang J. Osteoimmunology in orthodontic tooth movement. Oral Diseases. 2014; 1-11.

XIX. Isola G, Matarese G, Cordasco G, Perillo L, and Ramaglia L. Mechanobiology of the tooth movement during the orthodontic treatment: a literature review. Minerva Stomatologica. 2016; 65(5): 299-327.

XX. Zimna A and Kurpisz M. Hypoxia-inducible factor-1 in physiological and pathophysiological angiogenesis: applications and therapies. BioMed Research International. 2015; 1-14.

XXI. Han J and He H. Expression and function of osteogenic genes runt-related transcription factor 2 and osterix in orthodontic tooth movement in rats. Int J Clin Exp Pathol. 2015; 8(9):11895-11900.

XXII. Man HSJ, Tsui AKY, and Marsden PA. Nitric oxide and hypoxia signaling. Vitamins and Hormones. 2014; 96: 161-192.

XXIII. Mendes RT, Nguyen D, Stephens D, Pamuk F, Fernandes D, Hasturk H, Van Dyke TE, and Kantarci A. Hypoxia-induced endothelial cell responses - possible roles during periodontal disease. Clin Exp Dent Res. 2018; 4: 241–248.

XXIV. Gao L, Chen Q, Zhou X, and Fan L. The role of hypoxia-inducible factor 1 in atherosclerosis. J Clin Pathol. 2012; 65: 872–876.

XXV. Baloul S. Osteoclastogenesis and osteogenesis during tooth movement S. Front Oral Biol. 2016; 18: 75-79.

XXVI. Hayashi N, Yamaguchi M, Nakajima R. T-helper 17 cells mediate the osteo/odontoclastogenesis induced by excessive orthodontic forces. Oral Dis. 2012; 18: 375–388.

XXVII. Li B, Zhang YH, Wang LX, Li X, and Zhang XD. Expression of OPG, RANKL, and RUNX2 in rabbit periodontium under orthodontic force. Genetics and Molecular Research. 2015; 14(4): 19382-19388.

XXVIII. Li Z, Yu M, Jin S, Wang Y, Luo R, Huo B, Liu D, He D, Zhou Y, and Liu Y. Stress distribution and collagen remodeling of periodontal ligament during orthodontic tooth movement. Frontiers in Pharmacology. 2019; 10: 1-8.

XXIX. Florencio-Silva R, Sasso GRS, Sasso-Cerri E, Simões MJ, and Cerri PS. Biology of bone tissue: structure, function, and factors that influence bone cells. BioMed Research International. 2015; 421746: 1-17.