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Review Article

Role of chemical mediators and biological factors in tooth movement

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ABSTRACT

In recent years, there have been various theories proposed to describe the mechanism causing tooth movement. These theories can be broadly categorized into two perspectives: one focusing on bone as the direct target of mechanical force, and the other highlighting the periodontal ligament (PDL) as the key target. While the direct view suggests that osteoclasts and osteoblasts are directly stimulated by compression and tension stresses, respectively, the indirect view suggests that the PDL responds to orthodontic forces. However, evidence challenges the direct view, as bone does not respond to static forces and implants/ankylosed teeth do not move. The indirect view proposes that orthodontic forces lead to areas of compression and tension within the PDL, causing various cellular responses and inflammatory reactions. Osteoclasts play a crucial role in bone resorption, influencing the rate of tooth movement. Inflammatory mediators, including chemokines, cytokines, prostaglandins, and neuropeptides, are released during orthodontic tooth movement, facilitating osteoclast recruitment and activation. Osteoclast genesis is influenced by factors such as TNF-α, IL-1, IL-6, and prostaglandins. Chemical mediators, including parathyroid hormone, vitamin D3, corticosteroids, and thyroxin, have been explored for their potential to accelerate tooth movement, but their systemic effects and practical application present challenges. Overall, understanding the biology of tooth movement involves considering the interactions among osteocytes, osteoclasts, and osteoblasts, as well as immune cells and inflammatory cytokines. Expediting tooth movement requires further research and the development of effective and safe strategies.

Keywords: PDL, Osteogenesis, Chemical mediators, Osteoblasts, Osteoclast

INTRODUCTION

Orthodontics includes tooth movement in the jaw from one position to another to attain esthetics.[1] Long treatment times are a major problem in the orthodontics. Many patients, especially adults, may refuse therapy completely as a result of its prolonged length, or they may look for alternative remedies that have less desirable results.[2] Consequently, a major challenge in current orthodontic research is identifying a treatment method that reduces the required time while maintaining desired results.[2] To effectively address this challenge, it is essential to comprehend the various factors that contribute to the overall duration of treatment.[3] These contributing factors can generally be classified into three main categories.[2] Firstly, there are practitioner-dependent factors, which include accurate diagnosis and treatment planning, appropriate appliance selection, implementation of mechanotherapy techniques, and timely treatment delivery. Secondly, patient-dependent factors play a role, such as attending regular appointments, maintaining good oral hygiene and appliance integrity, and diligently adhering to the instructions provided by the orthodontic practitioner. Lastly, there are factors beyond the control of both practitioners and patients, primarily dictated by the unique biology of each individual.[2] While each of these

factors has a major impact on the treatment rate, the body's reaction to orthodontic stresses determines how quickly teeth move. Understanding the nature of this biological reaction is essential in order to improve it and hasten tooth movement. Given the complexity of this phenomenon, many ideas have surfaced in recent years to explain the process of tooth movement. The main area of disagreement between these hypotheses is how they see the beginning of the biological reaction. These theories can be broadly split into two categories: According to the first group, orthodontic pressures harm the bone and PDL, which leads to an inflammatory reaction (from a pathologic perspective). The second group (from a physiologic perspective) holds that the PDL and bones immediately respond to physical stimuli. These opposing viewpoints have a big impact on the techniques researchers use to speed up tooth movement. Inflammatory responses in the PDL and bone are thought to be the primary factors influencing tooth movement; hence, proponents of the inflammatory response theory contend that raising inflammatory markers can speed up the process. On the other hand, those who consider orthodontic tooth movement (OTM) as a physiological reaction work to maximise physical stimulation through the use of various tools. Additionally, a certain group of experts has suggested a different strategy to hasten tooth migration. They concentrate on speeding up bone turnover rather than trying to mimic the body's reaction to orthodontic pressure. This is done by locally or systemically introducing different chemical agents, which alter bone remodelling in the target location and eventually speed up tooth movement. It is significant to note that all hypotheses concur that the activation of osteoclasts is the main element regulating the speed of orthodontic tooth movement, despite some disagreements on the early processes that cause bone resorption and tooth movement. Hence, one of the most important goals in orthodontics is to solve the issue of lengthy treatment times. It is crucial to comprehend the variables affecting therapy length, including those influenced by practitioners, patients, and biology. Researchers have developed many theories regarding how teeth move, with variations focused on the start of the biological response. These opposing viewpoints have an effect on the methods employed to speed tooth movement, whether those methods entail inducing an inflammatory response, increasing physical stimulation, or increasing bone turnover. All theories, notwithstanding their variances, concur that the primary factor affecting how rapidly orthodontic teeth move is osteoclast activation. The objective of this paper is to review role of chemical mediators and biological factors in tooth movement.

LITERATURE SEARCH

This study is based on a comprehensive literature search conducted on 2 June 2023, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed role of chemical mediators and biological factors in tooth movement. There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

The biology of tooth movement is a subject of research that has been studied for a long time. What is interesting is our present emphasis on creating innovative devices and therapies that maximize the reactions of certain cells in the skeletal and dental systems, leading to safe and regulated rapid tooth movement. Understanding and utilizing these target cells' responses allows us to pursue two distinct strategies to quicken tooth movement: either directly stimulating the target cells to increase their quantity and activity using artificial, physical, or chemical means, or indirectly stimulating the body to attract and activate more target cells. Identification of the target cells and knowledge of how they are stimulated are crucial in both situations.[1]

Bone cells and their role in the biology of tooth movement

In reaction to mechanical pressures, bone undergoes remodelling making it a dynamic tissue. Specialized cells inside the bone are in charge of sensing these stresses, reacting to them by encouraging bone resorption at certain areas and depositing new bone matrix to withstand the forces. Osteocytes, which are common in the body but have received less research because of their embedding in the bone matrix, are the main mechanosensory cells. Bone resorption is caused by osteoclasts, huge multinucleated cells that are present on the surface of the bone. Osteoblasts, which are mesenchymal stem cells located in the bone marrow, produce the organic bone matrix. Inflammatory cells, such as T lymphocytes and macrophages, regulate osteoclasts and osteoblasts. Because they form a complex network and are implanted into bone matrix lacunae, osteocytes are crucial mechanosensors. By reacting to stress and deformation in the bone through fluid shear stress or electrical potentials, they serve as essential mechanosensors. They create chemicals that induce osteoblasts and osteoclasts to coordinate the remodelling process. While osteoclasts, the primary bone-resorbing cells, regulate how rapidly teeth move, osteocytes play a critical role in stress detection and bone cell coupling. Hematopoietic stem cells undergo differentiation into osteoclasts, which are multinucleated cells that resorb bone through an acidification process. Osteocytes are bent during the physiological process of bone remodelling; osteoclasts remove microfractures, and osteoblasts then build new bone. The development of wholesome, mechanically robust bones is the outcome of this coordinated cellular activity. Integrating immune cells, inflammatory cytokines, and the interactions

between osteocytes, osteoclasts, and osteoblasts is necessary to comprehend the biology of tooth movement. These elements are crucial for creating strategies to quicken tooth mobility.[1]

Theories on biology of tooth movement

Many hypotheses have surfaced in recent years to explain the process of tooth movement. These hypotheses may generally be classified into two broad categories: one posits that the PDL is the primary target of mechanical force (indirect view), and the other indicates that bone is the primary target of mechanical force (direct view). According to the direct view model, the mechanical forces produced by tooth movement directly stimulate osteoclasts through compression stress in the direction of movement and osteoblasts through tension stress in the opposite direction. In this circumstance, it is thought that osteocytes are crucial in regulating the activity of osteoclasts and osteoblasts. There is, however, a lot of data that refutes this claim. Firstly, bone doesn't respond to static stresses like those used in braces.[2] Further proof that bone is not the focus of these pressures is provided by the incapacity of implants and ankylosed teeth to move in response to orthodontic forces. Additionally, research using direct loading of bone, without the involvement of the PDL, has demonstrated that compression pressures promote bone production rather than bone resorption. Conversely, proponents of the indirect viewpoint contend that the PDL is the main target of orthodontic pressures. The discovery that ankylosed teeth, which lack PDL, cannot be moved supports this viewpoint. According to this perspective, the use of orthodontic forces results in regions of compression and tension within the PDL, which vary based on the kind of tooth movement, the strength of the force, and the moment used to move the tooth. The incompressible tissue fluid within the PDL prevents quick tooth movement when orthodontic force is applied for a brief period of time. The tooth will shift inside the PDL area, and the PDL will be compressed if the force is maintained; if not, the fluid will be quickly ejected. The blood vessels in the compressed region narrow as a result, decreasing nourishment and oxygen delivery predisposing tissues to hypoxia. Some cells die specifically by apoptosis, while others pass away indifferently, leaving behind patches of necrosis known as the cell-free zone, depending on the intensity of the pressure and the degree of blood flow restriction. It is important to note that these apoptotic or necrotic alterations are not just present in PDL cells; in response to orthodontic stresses, certain osteoblasts and osteocytes in the nearby alveolar bone also undergo cell death. An aseptic, acute inflammatory response is set off by this chain of events, and it is characterised by the early release of chemokines by local cells. Small proteins called chemokines draw other cells to that location. The production of adhesion molecules in blood vessels is made easier by the release of chemokines, which also encourage the migration of inflammatory and progenitor cells from the microvasculature into the extravascular area. One of the chemokines that is released during tooth movement is monocyte chemoattractant protein (MCP-1 or CCL2), [3] which has an effective role in attracting monocytes. These cells leave the bloodstream and get in the surrounding tissue to become tissue macrophages or osteoclasts. Similarly, the release of CCL3 and CCL5 (RANTES) during orthodontic tooth movement leads to osteoclast recruitment and activation.[4,5] A wider range of inflammatory mediators are released during the course of the first several hours of orthodontic therapy. During orthodontic therapy, cytokines are also secreted in addition to chemokines. These extracellular proteins are crucial in controlling the inflammatory response. Numerous cytokines promote inflammation. They intensify or sustain the inflammatory reaction and bone resorption activation. Some cytokines are anti-inflammatory and stop an uncontrolled inflammatory response. IL-1, TNF-α, and IL-6 are the primary pro-inflammatory cytokines that are generated during orthodontic tooth movement. These cytokines are generated by local cells, including osteoblasts, fibroblasts, and endothelial cells, as well as by inflammatory cells like macrophages. Prostaglandins (PGs) and neuropeptides are a second group of inflammatory mediators that are produced during orthodontic tooth movement. Arachidonic acid metabolism produces PGs, which can mediate nearly every stage of inflammation, including vasodilation, increased vascular permeability, and inflammatory cell adhesion. These mediators can be created directly by local cells, by inflammatory cells in response to mechanical stimulation, or indirectly by cytokines during orthodontic tooth movement. For instance, TNF-α is a strong activator of PGE2 synthesis.[6] Prostaglandins act locally at the site of generation and then decay spontaneously or are enzymatically destroyed.[7] Neuropeptides, like PGs, can take part in various stages of the inflammatory reaction to orthodontic pressures. Neuropeptides are tiny proteins that affect vascular permeability, control vessel tone, and convey pain signals. Examples include substance P.[8] The importance of all these inflammatory makers can be appreciated in the role that they play in osteoclastogenesis.

Osteoclastogenesis

Osteoclasts, multinucleated large cells that resorb bone, are produced from hematopoietic stem cells of the monocyte-macrophage lineage, as was previously mentioned. Osteoclast precursors are recruited to the compression sites and start to transform into osteoclasts after that. Cytokines are important mediators of this process. For example, TNF-α and IL-1 bind formation from precursor cells and osteoclast activation. Additionally, IL-1 and IL-6 can to their receptors, TNFRII and IL-1R, respectively and directly stimulate osteoclast indirectly stimulate local cells or inflammatory cells to express macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor κ-B ligand (RANKL).[9-11] These ligands through cell-to-cell

interactions bind to their respective receptors, c-Fms and RANK, which are both expressed on the surface of osteoclast precursors. Other inflammatory mediators that enhance osteoclast formation through enhancing RANKL expression by stromal cells are PGs, especially PGE2.[12] PGs can be produced by local cells directly in response to orthodontic forces or indirectly as downstream of cytokines such as TNF-α. It should be emphasized that local cells normally try to down regulate osteoclastogenesis by producing a RANKL decoy receptor, osteoprotegerin (OPG).[13] Therefore, OPG levels in compression sites should decrease to enable tooth movement.

Role of chemical mediators in tooth movement

Application of any agent that accelerates bone turnover should accelerate tooth movement if bone resorption is the primary factor regulating the pace of tooth movement. In light of this, the use of thyroxin, vitamin D3, corticosteroids, osteocalcin, and parathyroid hormone (PTH) has been investigated. PTH is a hormone released by the parathyroid glands that increases blood calcium levels by promoting bone resorption. Exogenous PTH was shown to significantly increase the pace of tooth movement in a dose-dependent way, but only when it was administered more or less constantly, either by systemic infusion or topically or local delivery every other day in a slow-release formulation.[14,15] It should be noticed that although continuous elevation of PTH leads to bone loss, intermittent short elevations of the hormone level can be anabolic for bone, and perhaps cannot increase the rate of tooth movement. Vitamin D3 (dihydroxycholecalciferol) is another factor that can affect the rate of bone remodelling, and therefore its possible effect on the rate of tooth movement has been studied.[16] By encouraging their intestinal absorption and reabsorption in the kidneys, vitamin D3 controls the levels of calcium and phosphate in the blood. Additionally, it suppresses the release of PTH while encouraging bone deposition. On the basis of these principles, one may anticipate that vitamin D3 might slow tooth mobility. Contrarily, it has been demonstrated that local injections of vitamin D3 can speed up tooth movement.[17,18] This effect can be related to the effect of vitamin D3 on increasing the expression of RANKL by local cells, therefore increasing activation of osteoclasts.[19] Similarly, local injection of osteocalcin (a bone matrix component) caused rapid tooth movement due to the attraction of numerous osteoclasts into the area.[20] Another class of pharmacological substances that have been proposed for quickening tooth mobility is corticosteroids. While corticosteroids' anti-inflammatory effects might slow tooth movement, when cytokines like IL-6 are present, they may also contribute to osteoclastgenesis and osteoporosis.[21] Therefore, the effect of corticosteroids on tooth movement can vary based on the dosage, and whether they are administered before the expression of cytokines (induction period) or after their presence. While some studies demonstrate an increase in rate of tooth movement, others did not report any changes.[22-24] The thyroid hormone (thyroxin), another component, may speed up tooth movement. Thyroxin regulates intestinal calcium absorption, which makes it indirectly related to bone resorption and osteoporosis induction. Exogenous thyroxin has been demonstrated to speed up tooth movement, which may be linked to an increase in bone resorption. Rats have recently been given the hormone relaxin to speed up tooth movement. The connective tissues' level of organisation can be decreased by relaxin, allowing adjacent bones to separate quickly. Sadly, no discernible increase in the rate of tooth movement was found.[25] It should be emphasized that other factors, such as calcitonin or estrogens that can prevent bone resorption, can also decrease the rate of tooth movement.[26] There are various issues with using chemicals to quicken tooth movement. First, the systemic effects of every chemical component create concerns regarding their safety when used in therapeutic settings. Second, the bulk of the components have a brief half-life, necessitating several chemical treatments, which is not feasible. Furthermore, it is currently difficult to administer a factor in a way that permits a uniform distribution along the alveolar bone surface in the compression region. The pattern of resorption and, consequently, the biomechanics of tooth movement can both be altered by uneven distribution.

CONCLUSION

Developing successful solutions to address the issue of longer treatment times in orthodontics requires an understanding of the factors affecting therapy duration, including practitioner-dependent, patient-dependent, and biology-dependent aspects. Diverse viewpoints are offered by theories on the biology of tooth movement, with some emphasising the importance of inflammation and others concentrating on physical stimulation or bone turnover. Chemical mediators that have been studied for their ability to quicken tooth movement include parathyroid hormone, vitamin D3, corticosteroids, and osteocalcin. However, their clinical use is constrained by practical issues and systemic side effects. In order to speed up tooth movement while maintaining patient safety and treatment effectiveness, more research is required to optimise and enhance existing methods.

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