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Decoding the Biochemical Pathways of Orthodontic Tooth Movement: A Focus on Salivary IL-17A and 1,25-Dihydroxycholecalciferol

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Abstract

Orthodontic treatment leads to significant alterations in the oral environment, including changes in salivary biomarker levels. Among these, interleukin-17A (IL-17A) and 1,25-dihydroxycholecalciferol (1,25(OH)$_2$D$_3$) play crucial roles in immune regulation and bone metabolism, respectively. IL-17A is a proinflammatory cytokine involved in immune responses and bone remodelling, while 1,25(OH)$_2$D$_3$, the active form of vitamin D, influences calcium homeostasis and skeletal health. Understanding the dynamic interplay between these biomarkers during orthodontic treatment may provide valuable insights into the biological mechanisms underlying inflammation and bone remodelling. This review systematically examines existing literature on the correlation between salivary IL-17A and 1,25(OH)$_2$D$_3$ levels in patients undergoing orthodontic interventions. By analyzing studies that investigate these biomarkers, this paper aims to elucidate their role in orthodontic-induced bone remodelling and inflammatory responses. Identifying potential patterns in their expression may help predict treatment outcomes and assess patient-specific variations in response to orthodontic forces. Furthermore, this review highlights the clinical implications of monitoring salivary IL-17A and 1,25(OH)$_2$D$_3$ levels, as fluctuations in these biomarkers could serve as indicators of treatment progress and tissue adaptation. A deeper understanding of these biochemical interactions may contribute to optimizing orthodontic treatment strategies and developing novel therapeutic approaches to enhance patient care. By bridging the gap between orthodontics and molecular biology, this review provides a foundation for future research exploring personalized treatment plans based on biomarker profiling.

Keywords: *Bone Remodeling, Immune Regulation, Inflammatory Response, Orthodontic Treatment, Salivary Biomarkers, Vitamin D Metabolism.*

Introduction

Orthodontics is a specialized field of dentistry focused on diagnosing, preventing, and correcting dental and facial irregularities. It involves a range of interventions, including preventive, interceptive, and corrective measures, to manage tooth alignment and associated structures from early childhood to full dental maturity. The primary objectives of orthodontic treatment are to achieve a well-balanced occlusion, enhance functional efficiency, and improve facial aesthetics [1].

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These goals are effectively summarized by Jackson's triad, which highlights functional efficiency, structural balance, and aesthetic harmony as the fundamental principles of treatment.

Despite significant advancements in treatment planning and biomechanics, prolonged treatment duration remains a major challenge in orthodontics. Extended orthodontic therapy is associated with several complications, such as an increased risk of dental caries, periodontal problems, and root resorption. To address these concerns, various strategies have been explored to accelerate Orthodontic Tooth Movement (OTM), including biological, biomechanical, physical, and surgical techniques. Among these, biological methods involve the use of specific molecules—such as prostaglandins (PGs), interleukins (ILs), receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG), vitamin D, parathyroid hormone (PTH), and relaxin—which play crucial roles in bone remodeling and facilitate a more rapid response to orthodontic forces [2].

Experimental studies on animal models have shown promising outcomes using these biological agents, either individually or in combination. However, their clinical application in human orthodontics remains limited due to factors such as patient compliance, ethical concerns, and potential adverse effects [3]. Among these biomolecules, interleukin-17A (IL-17A), a proinflammatory cytokine, and 1,25-dihydroxycholecalciferol, the active form of vitamin D, have garnered interest for their roles in bone metabolism and immune regulation. Their potential to enhance orthodontic tooth movement makes them particularly relevant for further investigation.

Prolonged orthodontic treatment presents significant challenges, including patient discomfort, increased oral health risks, and reduced compliance. Identifying biological markers that can enhance the efficiency of tooth movement could help mitigate these issues. Several approaches have been investigated, such as mechanical force modulation, corticotomy, piezocision, laser therapy, and pharmacological agents like PGs, ILs, and vitamin D derivatives. Among these, IL-17A and 1,25-dihydroxycholecalciferol stand out due to their dual functions in immune modulation and bone metabolism, offering a potentially safe and effective means to accelerate orthodontic tooth movement [4]. However, despite encouraging results in animal studies, human trials assessing their efficacy and safety remain limited. Challenges such as individual variability in response, ethical considerations, and long-term effects require further investigation.

Existing evidence in the literature suggests that IL-17A and vitamin D significantly influence bone remodelling, underscoring their potential role in optimizing orthodontic treatment outcomes. This review aims to assess the correlation between salivary IL-17A and 1,25-dihydroxycholecalciferol levels during orthodontic treatment and their potential impact on accelerating tooth movement. Additionally, it explores the diagnostic potential of salivary biomarkers as a non-invasive and efficient method for monitoring orthodontic treatment outcomes.

Orthodontic Tooth Movement: Mechanisms, Theories, and Influencing Factors

Orthodontic tooth movement (OTM) is a biologically complex process that occurs in response to mechanical forces applied to teeth through orthodontic appliances. The process is governed by bone remodelling, involving both resorption and formation, mediated by cellular and biochemical responses within the periodontal ligament (PDL) and alveolar bone. These responses are influenced by various mechanical, biological, and systemic factors,

ultimately determining the efficacy and rate of tooth movement [5].

Mechanisms of Orthodontic Tooth Movement

The application of orthodontic forces generates areas of compression and tension within the PDL. This leads to structural and functional changes at both cellular and molecular levels. The key mechanisms involved in OTM include:

Bone Resorption on the Pressure Side: When an orthodontic force is applied, the compressed region of the PDL experiences reduced blood flow, leading to the release of pro-inflammatory mediators and the recruitment of osteoclasts. These osteoclasts facilitate bone resorption, allowing tooth displacement.

Bone Deposition on the Tension Side: On the opposite side of the tooth, the PDL is stretched, leading to an increase in vascularization and recruitment of osteoblasts. Osteoblasts deposit new bone, stabilizing the tooth in its new position.

Cellular and Biochemical Mediators: The remodelling process is regulated by cytokines, growth factors, enzymes, and signalling molecules such as interleukins (IL-1, IL-6), tumour necrosis factor-alpha (TNF-α), receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG), and matrix metalloproteinases (MMPs). These mediators coordinate the balance between bone resorption and formation [6-8].

Phases of Orthodontic Tooth Movement

OTM occurs in distinct phases characterized by variations in cellular activity and tissue response:

Initial Phase: The initial phase begins immediately following the application of orthodontic force. During this stage, the tooth experiences a rapid but limited displacement within the periodontal ligament space. This movement is primarily due to the viscoelastic nature of the PDL, which allows it to deform under pressure. The fluid-filled extracellular matrix of the PDL compresses on the pressure side and stretches on the tension side, allowing for an initial shift in the tooth position.

Despite this early movement, there is no actual bone remodeling yet. However, this phase is biologically active, as the mechanical stress initiates early cellular responses. These include the release of signaling molecules such as prostaglandins, cytokines, and growth factors, which in turn stimulate the recruitment and activation of osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells). These cells begin preparing the tissues for the subsequent remodeling required for sustained tooth movement.

Lag Phase: Following the initial displacement, the tooth enters a lag phase, during which observable movement slows down or even temporarily ceases. This pause is primarily due to a phenomenon known as hyalinization—a sterile, localized necrosis of PDL tissue that occurs in areas subjected to intense and prolonged compressive forces. The hyalinized zones appear histologically as glassy, acellular regions and result from ischemia, or reduced blood flow, in these pressure-loaded areas.

During this phase, active remodeling does not occur until the necrotic tissues are cleared. Macrophages play a vital role in phagocytosing and removing the damaged and necrotic cells. Osteoclasts also contribute by resorbing adjacent alveolar bone, further clearing the path for subsequent tooth movement. This tissue clearance is necessary to restore cellular vitality and re-establish normal PDL architecture before the next phase of movement can proceed.

Post-Lag Phase: Once the necrotic zones have been cleared, the post-lag phase begins. This phase marks the onset of active and continuous tooth movement. It is characterized by coordinated bone remodeling: osteoclastic bone resorption occurs on the pressure side of

the tooth, where the PDL is compressed, while osteoblastic bone deposition occurs on the tension side, where the PDL is stretched. This dual activity ensures that the alveolar bone adapts to the new tooth position, allowing for its gradual and sustained displacement in the direction of the applied force.

The balance between bone resorption and formation during this phase is critical to the success of orthodontic treatment. Any disruption in this balance—such as excessive inflammation, inadequate force application, or nutritional deficiencies—can lead to treatment delays or adverse effects such as root resorption or alveolar bone loss. [9, 10].

Theories of Orthodontic Tooth Movement

Several theories have been proposed to explain the biological mechanisms underlying OTM:

Pressure-Tension Theory: The Pressure-Tension Theory, proposed by Schwarz, is one of the foundational concepts in orthodontics [11]. It suggests that when a tooth is subjected to orthodontic force, the PDL on the pressure side (where the tooth is being pushed) becomes compressed. This compression reduces blood flow, leading to the release of chemical mediators that stimulate osteoclastogenesis and subsequent bone resorption. Conversely, on the tension side, where the PDL is stretched, there is increased blood flow and cellular proliferation, promoting osteoblastic activity and bone formation. This coordinated resorption and deposition allow the tooth to gradually move through the bone.

Bone Bending Theory: The Bone Bending Theory offers another perspective, emphasizing the biomechanical response of alveolar bone to orthodontic forces [12]. When force is applied to a tooth, it creates flexural stress in the surrounding alveolar bone. This bending or deformation of the bone generates strain gradients, which in turn activate mechanosensitive bone cells, such as osteocytes. These cells initiate signaling pathways that lead to strain-induced bone remodeling, contributing to tooth movement. This theory is particularly relevant in younger individuals where bone is more pliable.

Fluid Flow Theory: According to the Fluid Flow Theory, the mechanical forces applied during orthodontic treatment disturb the normal interstitial fluid dynamics within the PDL [13]. These fluid shifts result in the activation of mechanoreceptors and ion channels present in the membranes of PDL fibroblasts and osteocytes. The altered pressure gradients and fluid shear stress are believed to trigger intracellular signaling cascades that regulate the recruitment and activity of bone-resorbing and bone-forming cells. This theory highlights the role of mechanotransduction—the conversion of mechanical stimuli into cellular signals—in orchestrating tissue remodeling during tooth movement.

Piezoelectric Theory: The Piezoelectric Theory is rooted in Wolff's Law, which states that bone adapts to the mechanical loads placed upon it [14]. According to this theory, mechanical deformation of bone due to orthodontic force generates piezoelectric signals—electrical potentials created by the displacement of charged particles in the bone matrix. These electrical signals influence the behavior of osteoblasts and osteoclasts, promoting bone resorption or formation depending on the nature of the stress. The transient and reversible nature of these piezoelectric signals makes them effective in initiating short-term remodeling events that contribute to OTM.Factors Influencing Orthodontic Tooth Movement

Various factors impact the rate and efficiency of OTM [15-17], including:

Mechanical Factors

Magnitude of Force: The magnitude of the applied force is a critical determinant of the rate and quality of tooth movement. Research

suggests that an optimal force range of approximately 50 to 150 grams is sufficient for most types of orthodontic tooth movements. Forces within this physiological range stimulate controlled bone remodeling without causing significant tissue damage. However, the application of excessively high forces can result in detrimental effects, such as the formation of extensive hyalinized zones within the PDL. These areas of sterile necrosis hinder blood flow and delay bone resorption, ultimately leading to slower tooth movement and increasing the risk of adverse outcomes like root resorption.

Duration and Frequency: The duration and frequency of force application significantly affect the biological response during orthodontic treatment. Continuous forces, which maintain a stable level of pressure over time, are generally more effective in sustaining cellular activity and bone remodeling compared to intermittent or cyclical forces, which allow for periods of biological rest. Continuous force application ensures that the recruited osteoclasts and osteoblasts remain active, thereby facilitating uninterrupted tooth movement. However, the force must remain within the optimal range, as prolonged application of excessive force can result in tissue damage and prolonged lag phases.

Type of F**orce**: The nature or type of force—specifically whether it is light and sustained or heavy and intermittent—plays a crucial role in determining tissue response. Light, continuous forces are preferred in clinical orthodontics as they promote favorable remodeling of the PDL and surrounding alveolar bone with minimal tissue trauma. In contrast, heavy forces, particularly when applied abruptly or over a short duration, can induce significant PDL compression, leading to cellular necrosis, hyalinization, and inflammatory responses that counteract efficient tooth movement. Such forces may also compromise the integrity of the supporting structures and increase the likelihood of side effects such as pain, mobility, or root resorption.

Biological Factors

Age: Age is a critical determinant in the biological response to orthodontic treatment. Younger individuals, particularly children and adolescents, tend to exhibit more rapid tooth movement compared to adults. This can be attributed to their higher cellular turnover, increased vascularity, and a more dynamic bone remodeling environment. In growing individuals, the alveolar bone is less mineralized and more responsive to mechanical stimuli, allowing for quicker reorganization in response to orthodontic forces. As age advances, bone metabolism slows down, and the regenerative capacity of periodontal tissues diminishes, leading to a more gradual and prolonged treatment course in adults.

Bone Density: The density of the alveolar bone significantly impacts the rate of tooth movement. Higher bone density, often observed in older individuals or certain skeletal patterns, offers greater resistance to orthodontic forces and tends to slow down the rate of movement. Conversely, lower bone density, which may occur in younger patients or in specific anatomical regions (such as the maxillary bone), facilitates easier remodeling and faster displacement of teeth. Bone density also affects the balance between osteoclastic resorption and osteoblastic deposition, processes fundamental to effective OTM. Orthodontic treatment planning should, therefore, consider the bone quality of individual patients to optimize force magnitude and duration.

Periodontal Health: The condition of the periodontal ligament (PDL) and surrounding tissues is essential for efficient and safe tooth movement. A healthy periodontium, characterized by intact PDL fibers, normal vascular supply, and controlled inflammation,

supports the biological remodeling required for tooth displacement. In contrast, compromised periodontal health—such as that seen in gingivitis or periodontitis—can impair this process. Chronic inflammation can alter the cellular responses within the PDL, delay healing, and potentially lead to attachment loss or bone destruction if orthodontic forces are applied without proper management. Thus, maintaining good oral hygiene and resolving any periodontal issues prior to initiating orthodontic treatment is crucial for ensuring optimal outcomes and minimizing complications.

Systemic Factors

Hormonal Influence: Hormones are critical regulators of skeletal metabolism and directly impact the biological mechanisms underlying OTM. Parathyroid hormone (PTH) enhances bone resorption by stimulating osteoclast activity and increasing RANKL expression, thus facilitating faster tooth movement when present at physiological or intermittent levels. Conversely, estrogen, particularly in post-pubertal females, plays a protective role by inhibiting osteoclast formation and activity, thereby reducing bone turnover and potentially slowing tooth movement. Additionally, thyroid hormones accelerate metabolic processes, including bone remodeling, and elevated levels may enhance the rate of OTM. These hormonal effects are particularly relevant in growing individuals and patients with endocrine disorders, requiring close monitoring during orthodontic treatment.

Medications: Pharmacological agents can significantly alter the tissue response to orthodontic force. Bisphosphonates, commonly used to treat osteoporosis and metastatic bone disease, are potent inhibitors of osteoclast-mediated bone resorption. Their long-term retention in bone tissue can impede normal bone turnover, leading to delayed or diminished orthodontic tooth movement. Similarly, nonsteroidal anti-inflammatory drugs (NSAIDs)—especially when used chronically—can suppress prostaglandin synthesis, a key mediator in the bone remodeling process. This suppression may reduce osteoclastic activity and slow OTM. On the other hand, medications like prostaglandin analogs or vitamin D analogs have been shown in experimental models to accelerate bone turnover and enhance the rate of tooth movement.

Genetic Factors: Individual genetic variability plays a substantial role in modulating the biological response to orthodontic force. Polymorphisms in genes encoding cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and bone-related proteins like RANKL and osteoprotegerin (OPG) can influence the rate of bone resorption and formation. These genetic differences determine how efficiently the periodontal ligament and surrounding bone tissues respond to mechanical stress. Some individuals may exhibit rapid tooth movement, while others may experience delayed or unpredictable responses, despite similar treatment protocols. As genetic screening technologies advance, these insights may pave the way for personalized orthodontic treatments tailored to a patient's genetic makeup.

Patient-Related Factors

Compliance: Adherence to orthodontic treatment protocols, including appliance wear and oral hygiene maintenance, affects treatment efficiency.

Systemic Health Conditions: Conditions like diabetes, osteoporosis, or metabolic disorders can alter bone remodelling and influence tooth movement.

Orthodontic tooth movement is a biologically driven process that relies on bone resorption and formation in response to mechanical forces. The interplay between cellular responses, biochemical mediators, and various influencing factors determines the

efficiency of tooth movement. Understanding these mechanisms and theories is essential for optimizing orthodontic treatment outcomes, ensuring controlled and effective tooth repositioning while minimizing risks such as root resorption or periodontal damage.

Saliva as a Diagnostic Medium in Orthodontic Treatment

Early and accurate disease detection plays a pivotal role in ensuring effective diagnosis and treatment planning in clinical practice. Researchers and clinicians are constantly in search of advanced diagnostic tools that can aid in the early identification of diseases, thereby minimizing patient discomfort while enhancing diagnostic accuracy. Traditional diagnostic methodologies predominantly rely on invasive techniques such as blood sampling or biopsies, which may lead to distress and inconvenience for patients. Consequently, there has been a growing interest in identifying non-invasive, efficient alternatives, which has led to the increased recognition of saliva as a valuable diagnostic fluid in medical and dental fields, including orthodontics.

Saliva, a biofluid secreted primarily by the major salivary glands—the parotid, submandibular, and sublingual glands—has garnered considerable attention due to its ease of collection, non-invasiveness, and potential for disease detection. Minor salivary glands, including the labial, buccal, lingual, and palatal glands, also contribute to saliva production, further expanding its diagnostic potential. The high permeability of the salivary glands facilitates molecular exchange between blood and saliva, allowing the transport of biomarkers that reflect an individual's health status. As a result, saliva is emerging as a viable alternative to serum for diagnostic purposes, providing a pain-free and convenient method for monitoring disease progression and physiological changes, particularly in orthodontic treatment.

Saliva- Composition and Its Diagnostic Potential.

The diagnostic significance of saliva stems from its diverse composition, which includes electrolytes, proteins, immunoglobulins, enzymes, mucins, nitrogenous compounds, and hormones. These constituents interact to maintain oral homeostasis and can serve as biomarkers for detecting various medical conditions, including infections, autoimmune diseases, and metabolic disorders. The buffering action of bicarbonates and phosphates, the microbial clearance properties of mucins and protein macromolecules, the remineralization effects of calcium and phosphate, and the immune defence roles of immunoglobulins and enzymes contribute to saliva’s multifaceted functions in maintaining health. Due to these properties, saliva has been widely utilized in diagnosing oral, systemic, and genetic disorders. It is also useful for monitoring drug and hormone levels, forensic identification, and evaluating bone turnover during orthodontic treatment. Saliva provides a non-invasive means of detecting biomarkers related to inflammatory responses, bone remodelling, and stress responses associated with orthodontic tooth movement (OTM) [18].

Advantages of Salivary Diagnostics Over Conventional Methods

When compared to traditional diagnostic fluids such as blood and gingival crevicular fluid (GCF), saliva offers several distinct advantages. Saliva collection is easier and safer, requiring minimal equipment and posing no risk of bloodborne infections. Additionally, saliva does not clot, simplifying its storage and transport. Its non-invasive nature allows for repeated sample collection over time, making it ideal for longitudinal studies and continuous monitoring of disease progression. However, despite these advantages, challenges remain, such as variations in salivary composition due to physiological and pathological factors, which may hinder standardization.

Additionally, the concentration of certain analytes in saliva is lower than in blood, posing challenges for detection sensitivity [19].

Factors Influencing Salivary Composition

Saliva formation is a dynamic process involving the secretion of fluids from acinar cells within the salivary glands, with minor contributions from the oral mucosa and gingival crevicular fluid. Saliva primarily consists of water, with dissolved ions, proteins, and enzymes playing key roles in maintaining oral and systemic health. The pH of saliva typically ranges between 6 and 7, with secretion rates influenced by circadian rhythms, hydration levels, and external stimuli. In addition to its diagnostic potential, saliva plays a crucial role in digestion, lubrication, antimicrobial defence, and maintaining enamel integrity through remineralization.

The method of saliva collection significantly impacts its composition and the reliability of biomarker detection. Saliva can be collected using passive drooling, suction, or expectoration, with precautions taken to minimize contamination. Circadian rhythms, dietary habits, and oral hygiene practices also influence salivary biomarker levels, necessitating standardized protocols to enhance diagnostic accuracy. Stimulated saliva, obtained through chewing or gustatory stimulation, provides insights into salivary gland function, whereas unstimulated saliva offers baseline biomarker levels. For optimal collection, patients are often advised to refrain from eating, drinking, or brushing their teeth for at least two hours before sample collection [20, 21].

Recent Advancements in Salivary Diagnostics

Recent developments in molecular diagnostics have broadened the scope of salivary analysis. Proteomic research has identified a diverse range of proteins in saliva, some of which overlap with serum proteins, reinforcing its utility in disease detection. Genomic and transcriptomic analyses of saliva have also provided insights into genetic predispositions and disease mechanisms, making saliva a promising alternative to blood in genetic research.

The salivary transcriptome, which includes messenger RNA molecules, has shown great potential in diagnosing conditions such as cancer and autoimmune diseases. In orthodontics, salivary biomarkers offer valuable insights into bone remodelling and inflammatory processes associated with OTM. The ability to track these changes non-invasively through saliva represents a significant advancement in orthodontic diagnostics [22].

Salivary Biomarkers in Orthodontics

Saliva has emerged as a valuable, non-invasive diagnostic medium for monitoring biological changes during orthodontic treatment. Various salivary biomarkers have been investigated for their potential to reflect the physiological and inflammatory responses associated with orthodontic tooth movement (OTM).

One notable biomarker is myeloperoxidase (MPO), an enzyme predominantly secreted by activated neutrophils. MPO plays a critical role in host defense by producing reactive oxygen species to combat pathogens. In the context of orthodontics, MPO levels in saliva are known to rise following the application of orthodontic forces, particularly after the placement of fixed appliances. This elevation corresponds to the acute inflammatory response initiated within the periodontal ligament (PDL) and surrounding tissues. Thus, salivary MPO can serve as a reliable indicator of inflammation induced by mechanical stress.

Another important salivary biomarker is leptin, a hormone primarily produced by adipose tissue that also influences bone

metabolism and remodeling. During orthodontic treatment, fluctuations in salivary leptin levels have been observed and appear to correlate with the rate of tooth movement. Interestingly, lower levels of leptin are typically noted in overweight or obese individuals, which may partly explain the slower orthodontic tooth movement often observed in these patients. Leptin is thought to modulate bone remodeling through its effects on osteoblast and osteoclast activity, further underscoring its relevance in orthodontic therapy.

Additionally, two osteotropic molecules—soluble receptor activator of nuclear factor kappa-B ligand (sRANKL) and osteoprotegerin (OPG)—have been extensively studied for their involvement in bone metabolism. These molecules function as key regulators of osteoclast differentiation and activity. sRANKL promotes osteoclastogenesis and bone resorption, while OPG acts as a decoy receptor that binds to sRANKL, thereby inhibiting its action. During different stages of OTM, the ratio of sRANKL to OPG shifts, reflecting the changing balance between bone resorption and bone formation. An elevated sRANKL/OPG ratio is typically associated with active bone resorption on the pressure side of the moving tooth, while a lower ratio corresponds to bone formation and stabilization on the tension side.

Collectively, these salivary biomarkers—MPO, leptin, sRANKL, and OPG—offer valuable insights into the biological mechanisms driving orthodontic tooth movement. Their temporal variations mirror the dynamic interplay of inflammation and bone remodeling during treatment. Monitoring these biomarkers could potentially enhance the personalization of orthodontic care by providing clinicians with real-time feedback on treatment progress and tissue response, thereby improving outcomes and reducing complications. [23, 24].

Challenges in Salivary Diagnostics

Despite its potential, salivary diagnostics in orthodontics face several challenges. The transient nature of biomarker secretion, potential contamination from oral microbes, and variability in protein concentrations can impact diagnostic reliability. However, advancements in molecular techniques such as multiplex enzyme-linked immunosorbent assay (ELISA) and biosensors have improved the sensitivity and specificity of salivary biomarker detection. Comparative studies have shown that saliva often exhibits higher sensitivity in detecting biochemical changes associated with orthodontic treatment compared to blood.

Saliva-based research continues to expand, with emerging biomarkers being explored for various applications. The use of saliva in forensic science has been particularly noteworthy, aiding in the identification of individuals through DNA analysis and detecting illicit substances.

Salivary Diagnostics in Orthodontics

The combination of microfluidic devices and biosensors has facilitated point-of-care salivary diagnostics. Allowing rapid and cost-effective disease screening. In orthodontics, saliva could potentially be used to personalize treatment plans by assessing individual responses to biomechanical forces, predicting treatment outcomes, and minimizing adverse effects. Given its numerous advantages, saliva is an emerging diagnostic medium with significant potential in orthodontics. Its non-invasive nature, ease of collection, and ability to reflect systemic and local changes make it a promising alternative to traditional diagnostic methods [25]. Further research is needed to refine salivary biomarker panels, establish standardized collection and analysis protocols, and enhance the clinical applicability of salivary diagnostics in orthodontic treatment. As molecular diagnostic techniques continue

to evolve, saliva is poised to become a cornerstone in personalized orthodontic care, facilitating real-time monitoring of treatment responses and optimizing therapeutic strategies for improved patient outcomes. The future of orthodontic diagnostics lies in integrating salivary analysis with advanced technologies, ultimately transforming patient care through precision medicine.

The Role of Cytokines in Orthodontic Tooth Movement

Cytokines are essential signalling proteins that facilitate cellular communication and regulate immune responses. These bioactive molecules, including peptides and glycoproteins, function primarily through autocrine and paracrine signalling, coordinating various biological processes even at minimal concentrations. Their role in bone remodelling makes them particularly significant in orthodontic tooth movement (OTM) [26, 27].

Cytokine-Mediated Bone Remodelling in Orthodontics

Bone remodelling is a continuous and dynamic process regulated by numerous cytokines, such as interleukins (IL-1, IL-2, IL-3, IL-6, IL-8), tumour necrosis factor-alpha (TNF-α), gamma interferon (IFN-γ), and osteoclast differentiation factor (ODF). Among these, IL-1 plays a central role in activating osteoclasts via IL-1 type 1 receptors. This activation is influenced by neurotransmitters, bacterial byproducts, and mechanical forces. Osteoblasts function as intermediaries, guiding osteoclast activity, while IL-8 expression increases in periodontal ligament tension sites, reinforcing the remodelling process. Additionally, IL-1 enhances NF-kappaB activation in osteoclast-like cells, further driving bone resorption [28].

TNF-α is another key cytokine influencing bone metabolism by promoting osteoclast differentiation alongside macrophage colony-stimulating factor (M-CSF). Experimental histochemical analyses have shown increased levels of IL-1 and TNF-α in the periodontal ligament and alveolar bone during orthodontic treatment, highlighting their direct role in facilitating tooth movement. IFN-γ, a major immune modulator, regulates macrophage activity and influences IL-1 and TNF-α production. Its ability to induce apoptosis in effector T-cells indirectly affects bone resorption and orthodontic adjustments [29].

Pro-Inflammatory Cytokines and Their Role in Bone Remodelling

Cytokines such as IL-1β, IL-6, and TNF-α significantly influence bone remodelling by stimulating both resorption and formation. Their expression typically peaks three days after the application of orthodontic force, indicating their role in the initial stages of bone resorption. The primary regulatory pathway for osteoclast differentiation is the RANK/RANKL/OPG axis. RANKL binds to its receptor RANK, activating osteoclasts, while osteoprotegerin (OPG) serves as a decoy receptor that inhibits osteoclastic activity. Factors such as IL-1β, TNF-α, vitamin D metabolites, and estrogen regulate OPG expression. Osteocytes, major contributors to RANKL production, also play a role in inflammatory bone loss [30].

Cytokine Expression in Periodontal Ligaments During Rapid Maxillary Expansion

Recent studies analyzing cytokine expression during rapid maxillary expansion have provided valuable insights. TNF-α, RANKL, and matrix metalloproteinase-1 (MMP-1) levels are elevated on the compression side, while IL-10, tissue inhibitor of metalloproteinases-1 (TIMP-1), OPG, and osteocalcin (OCN) increase on the tension side. Interestingly, transforming growth factor-beta (TGF-β) remains consistent across both

regions, suggesting its role in maintaining bone remodelling equilibrium [31].

IL-17A and Its Impact on Bone Metabolism

Interleukin-17A (IL-17A), first identified in 1993, has emerged as a critical cytokine in immune regulation and bone biology. Initially, IL-17A was thought to be produced exclusively by activated T lymphocytes. However, subsequent research has revealed that it is secreted by a wider array of immune cells, including macrophages, natural killer (NK) cells, and dendritic cells, reflecting its broad involvement in inflammatory and immunomodulatory responses.

The principal source of IL-17A remains the T helper 17 (Th17) cell subset, a group of CD4+ T cells that plays a central role in autoimmune and inflammatory conditions. The differentiation and activation of Th17 cells are orchestrated by a network of cytokines, primarily interleukin-1 (IL-1), interleukin-6 (IL-6), and transforming growth factor-beta (TGF-β). These cytokines initiate signaling cascades that drive the expression of the transcription factor RORγt, essential for Th17 lineage commitment.

Th17 cells are not limited to producing IL-17A alone. They also secrete IL-17F, tumor necrosis factor-alpha (TNF-α), IL-21, and IL-22, all of which contribute synergistically to inflammatory tissue destruction. In the context of bone metabolism, these cytokines collectively influence bone resorption and collagen matrix degradation, processes that are fundamental to both physiological bone remodeling and pathological bone loss.

IL-17A exerts a potent effect on skeletal tissues, particularly through its interaction with bone-forming and bone-resorbing cells. One of its key mechanisms is the upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL) expression in osteoblasts and stromal cells. RANKL is an essential mediator of osteoclast differentiation and activation; its increased expression directly promotes the formation and activity of osteoclasts, the cells responsible for bone resorption. Consequently, IL-17A contributes to enhanced bone turnover and can exacerbate bone loss in conditions such as rheumatoid arthritis, periodontitis, and osteoporosis.

Moreover, IL-17A is known to induce the expression of matrix metalloproteinases (MMPs), enzymes that degrade extracellular matrix components such as collagen, further facilitating connective tissue breakdown. This dual action on bone and soft tissue underscores the significance of IL-17A in both bone remodeling and inflammatory bone pathology.[32].

Methods for Cytokine Detection in Orthodontics

Various methods are employed to detect cytokine levels, each with distinct advantages. Bioassays assess cytokine bioactivity but lack specificity and require extended processing times. Immunoassays, particularly enzyme-linked immunosorbent assays (ELISA), are widely preferred for their specificity and reliability. ELISA utilizes primary antibodies for cytokine capture and secondary antibodies conjugated with enzymes or radioisotopes for detection. Multiplex ELISA systems enable simultaneous analysis of multiple cytokines in biological fluids such as saliva, serum, and urine.

Flow cytometry, often combined with high-performance liquid chromatography, provides rapid and detailed intracellular cytokine analysis. However, challenges such as autofluorescence and gating complexities must be addressed to ensure accuracy. As cytokine research advances, improved detection methods will further enhance clinical applications in orthodontics [33].

The Role of 1,25-Dihydroxycholecalciferol in Orthodontic Tooth Movement and Systemic Health

Calcitriol and Calcium Homeostasis

1,25-Dihydroxycholecalciferol (1,25-DHCC), the biologically active form of vitamin D, is primarily synthesized in the kidneys and functions as a hormone by binding to vitamin D receptors (VDRs). This metabolite plays a central role in calcium homeostasis by enhancing intestinal calcium absorption, regulating blood calcium levels, and modulating parathyroid hormone (PTH) secretion. In response to hypocalcemia, PTH stimulates renal calcium reabsorption, increases phosphate excretion, and promotes 1,25-DHCC production, thereby ensuring optimal mineral balance. Additionally, 1,25-DHCC influences both osteoclastic activation and osteoblastic differentiation in a dose-dependent manner, making it essential for bone metabolism and remodelling [34].

Vitamin D and Its Influence on Bone Remodelling

Vitamin D, first identified in phytoplankton, is vital for calcium regulation across various species. Its endogenous synthesis is influenced by environmental factors such as skin pigmentation, seasonal variations, and sunlight exposure. Vitamin D deficiency is associated with a range of systemic conditions, including cardiovascular diseases, immune dysfunctions, metabolic syndromes, and musculoskeletal disorders. In the field of orthodontics, adequate vitamin D levels are critical for facilitating tooth movement and ensuring post-treatment stability. The remodelling of alveolar bone, a prerequisite for orthodontic tooth movement (OTM), is significantly influenced by vitamin D.

Metabolism and Mechanism of Action

Vitamin D is primarily obtained from dietary sources such as fatty fish, egg yolks, and fortified dairy products. Upon ingestion, it binds to vitamin D-binding proteins (DBPs) and is transported to the liver for hydroxylation, forming 25-hydroxyvitamin D (25(OH)D). A second hydroxylation step in the kidneys converts this intermediate into its active form, 1,25-DHCC (calcitriol). Recent findings indicate that calcitriol synthesis also occurs in extra-renal sites such as gingival fibroblasts and periodontal ligament cells, suggesting localized regulatory functions in dental tissues.

Ultraviolet B (UVB) radiation catalyzes vitamin D synthesis in the skin by converting 7-dehydrocholesterol into its active derivatives. These metabolites enhance calcium and phosphate absorption, which are fundamental for bone mineralization, neuromuscular functions, and systemic homeostasis. Approximately 40% of calcium and 80% of phosphorus absorption rely on 1,25-DHCC, underscoring its importance in maintaining skeletal integrity [35, 36].

Influence of Vitamin D on Orthodontic Tooth Movement

The biologically active form of vitamin D, 1,25-dihydroxycholecalciferol (1,25-DHCC or calcitriol), plays a central role in regulating bone metabolism during orthodontic tooth movement (OTM). This hormone-like compound is instrumental in orchestrating a coordinated balance between osteoclastic bone resorption on the pressure side and osteoblastic bone formation on the tension side of the periodontal ligament. By modulating both cellular processes, 1,25-DHCC facilitates a biologically efficient and stable mechanism for tooth displacement.

Evidence from experimental and animal studies suggests that the local administration of calcitriol, either alone or in conjunction with prostaglandin E2 (PGE2), can significantly accelerate the rate of OTM. These interventions enhance

the remodeling dynamics of the alveolar bone, thereby promoting faster tooth movement. Notably, vitamin D injections have been associated with increased rates of canine retraction, indicating their potential utility in optimizing orthodontic treatment timelines and reducing overall treatment duration.

Furthermore, vitamin D deficiency has been correlated with diminished bone turnover and delayed orthodontic responses. Patients with suboptimal vitamin D levels often exhibit slower rates of tooth movement, which can compromise treatment efficiency and prolong therapy. This association underscores the importance of maintaining adequate systemic vitamin D status throughout the course of orthodontic care to ensure optimal biological responses and favorable clinical outcomes [37].

Vitamin D in Systemic Health

Beyond its role in calcium and bone metabolism, vitamin D has profound effects on various physiological systems:

Immune Function: Vitamin D plays a pivotal role in regulating both the innate and adaptive branches of the immune system. In the innate immune response, vitamin D enhances the activity of key immune cells such as macrophages and dendritic cells. It promotes the expression of antimicrobial peptides like cathelicidin and defensins, which are essential for the destruction of invading pathogens, thereby strengthening the body's first line of defense.

In addition to bolstering antimicrobial functions, vitamin D also helps modulate the secretion of cytokines. It tends to suppress the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), while promoting the production of anti-inflammatory cytokines like interleukin-10 (IL-10). This balance is crucial in preventing chronic inflammation and maintaining immune homeostasis.

Within the adaptive immune system, vitamin D influences the activity and differentiation of T and B lymphocytes. It inhibits the proliferation of pro-inflammatory Th1 and Th17 cells and supports the development of regulatory T cells (Tregs), which play a critical role in controlling immune tolerance and preventing autoimmune responses.

These immunomodulatory effects have significant clinical implications in the field of orthodontics. Orthodontic tooth movement relies on controlled inflammatory processes within the periodontal ligament and surrounding alveolar bone. Excessive or uncontrolled inflammation, however, can lead to tissue damage, delayed bone remodeling, and prolonged treatment duration. By reducing excessive inflammatory responses and promoting tissue healing, vitamin D may help improve the efficiency of orthodontic treatment and reduce complications such as root resorption and periodontal breakdown.

Moreover, vitamin D deficiency has been associated with an increased risk of various immune-related conditions. These include heightened susceptibility to infections (especially respiratory tract infections), autoimmune diseases such as multiple sclerosis, type 1 diabetes, and rheumatoid arthritis, as well as chronic inflammatory disorders like inflammatory bowel disease and psoriasis. Therefore, ensuring adequate vitamin D levels may not only support overall immune function but also contribute to better outcomes in dental and orthodontic care [38].

Cardiovascular Health: Vitamin D plays a protective role in cardiovascular function by regulating blood pressure, reducing arterial stiffness, and modulating inflammatory pathways. Low vitamin D levels are associated with hypertension, endothelial dysfunction, and an increased risk of atherosclerosis. These cardiovascular risks have implications for

orthodontic patients, particularly those with underlying systemic conditions requiring prolonged treatments [38].

Musculoskeletal System: Adequate vitamin D levels are essential for maintaining muscle strength, coordination, and overall musculoskeletal health. Deficiency in vitamin D is linked to muscle weakness, increased risk of falls, and reduced physical performance. In orthodontics, patients with musculoskeletal disorders may experience altered bone metabolism, potentially affecting treatment outcomes [38].

Metabolic and Endocrine Functions: Vitamin D influences insulin sensitivity, glucose metabolism, and lipid regulation. Deficiency has been associated with type 2 diabetes, metabolic syndrome, and obesity. Since orthodontic treatment involves prolonged interactions with patients, assessing metabolic health may help predict treatment responses and potential complications [39].

Neurocognitive Function and Mental Health: Emerging evidence suggests that vitamin D plays a role in neurocognitive health, influencing neurotransmitter synthesis and neuroprotection. Low vitamin D levels have been linked to mood disorders, depression, and cognitive decline. These findings highlight the broader implications of vitamin D beyond bone health, underscoring its importance in overall patient well-being [39, 40].

Clinical Implications and Future Directions

In addition to enhancing bone remodeling, vitamin D plays a key role in periodontal health by modulating immune responses. By reducing pro-inflammatory mediators and promoting anti-inflammatory cytokines, vitamin D minimizes inflammation-related delays in orthodontic tooth movement. Furthermore, the administration of 1,25-DHCC facilitates canine distalization and reduces cancellous bone density, improving OTM efficiency. The correlation between serum and salivary vitamin D levels provides a valuable biomarker for orthodontic treatment planning. Given its extensive physiological impact, vitamin D supplementation may serve as an adjunctive strategy to optimize orthodontic outcomes. Future research should focus on standardizing dosage protocols, evaluating long-term effects, and exploring patient-specific responses to vitamin D therapy.

Conclusion

The present review underscores the intricate interplay between salivary IL-17A and 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$) in the context of orthodontic tooth movement, emphasizing their regulatory roles in inflammatory responses and bone remodelling. The dynamic fluctuations of these biomarkers hold potential clinical significance, offering insights into the biological mechanisms that govern orthodontic treatment. However, the variability in existing literature highlights the need for further investigation to establish definitive correlations and clinical implications. Future research should prioritize studies with larger populations to elucidate biomarker trends across different treatment phases. Additionally, exploring the association between salivary biomarker levels and treatment outcomes could contribute to the advancement of biomarker-driven diagnostic and therapeutic strategies. A deeper understanding of these molecular mediators may facilitate the development of precision-based orthodontic interventions, ultimately enhancing treatment predictability and patient outcomes.

Conflict of Interest

There is no conflict of interest.

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Nil.

Ethical Approval

Not applicable.

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