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Original Article

Mechanistic Model of Periodontal Inflammation and Orthodontic Force Interactions

Olivia S. Brown[1]*, Ahmad F. Rahman[1], Ahmed K. El Sherif[1]

[1] Department of Periodontics and Orthodontics, Faculty of Dental Sciences, King's College London, London, United Kingdom.

***E-mail** ✉ olivia.brown@outlook.com

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ABSTRACT

Orthodontic treatment relies on the application of mechanical forces to achieve tooth movement, but these forces interact with periodontal tissues in complex ways, often exacerbating or being influenced by inflammatory processes. This conceptual paper proposes an integrative mechanistic framework that synthesizes inflammatory signaling, mechanotransduction pathways, and alveolar bone remodeling into a unified causal pathway. Key constructs include orthodontic mechanical forces that initiate mechanotransduction via cellular sensors, leading to the release of inflammatory mediators such as cytokines (e.g., interleukin-1, tumor necrosis factor-α) and prostaglandins (e.g., prostaglandin E2). These mediators, in turn, modulate bone remodeling through osteoclastogenesis and osteoblast activity, while bidirectional feedback loops amplify tissue responses, potentially resulting in periodontal degradation if dysregulated. The framework highlights how inflammation serves as both a response to and a modulator of mechanical stress, explaining variable clinical outcomes in orthodontic interventions. By integrating cellular and molecular biology with tissue biomechanics, this model addresses gaps in understanding the bidirectional causal pathways between force application and inflammatory feedback. It offers theoretical implications for optimizing orthodontic strategies to minimize tissue damage and enhance remodeling efficiency, without relying on empirical data. This synthesis provides a bold, mechanistic foundation for future research in periodontology and orthodontics.

Keywords: Orthodontic forces, Periodontal inflammation, Mechanotransduction, Bone remodeling, Cytokines, Prostaglandins, Feedback loops

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Introduction

Periodontal health is fundamental to successful orthodontic treatment, as the application of mechanical forces to teeth inevitably engages the surrounding periodontal tissues, including the periodontal ligament (PDL), gingival tissues, and alveolar bone. Orthodontic tooth movement (OTM) is a controlled biological process wherein sustained mechanical loading induces adaptive remodeling of these structures, allowing teeth to reposition within the alveolar arch [1, 2]. However, this process is not isolated from inflammatory dynamics; rather, orthodontic forces trigger aseptic inflammation in the periodontium, which plays a pivotal role in facilitating or hindering tissue adaptation [3, 4]. The interplay between mechanical stress and inflammation can lead to beneficial outcomes, such as efficient bone resorption and apposition, or adverse effects, including accelerated periodontal tissue degradation, root resorption, or gingival recession [5, 6]. Understanding these interactionsat a mechanistic level is crucial for clinicians and researchers, as it informs strategies to mitigate risks and enhance therapeutic efficacy in orthodontic practice [7-12].

Historically, orthodontic research has emphasized the biomechanical aspects of tooth movement, viewing the

periodontium primarily as a viscoelastic medium responsive to force magnitude, direction, and duration [13]. Classic theories, such as the pressure-tension hypothesis, posit that compressive forces lead to bone resorption on the pressure side, while tensile forces promote bone formation on the tension side [14]. Yet, this model overlooks the molecular and cellular mediators that bridge mechanical input to biological output. Advances in cellular biology have revealed that mechanotransduction—the process by which cells convert mechanical signals into biochemical responses—is central to OTM [15, 16]. Cells within the PDL, including fibroblasts, osteoblasts, and osteoclasts, sense force through integrins, cadherins, and ion channels, initiating signaling cascades that regulate gene expression and protein synthesis [17, 18]. Concurrently, inflammation emerges as a key modulator in this context. Orthodontic forces cause microvascular compression and ischemia in the PDL, leading to the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and prostaglandins like prostaglandin E2 (PGE2) [19, 20]. These molecules not only amplify the inflammatory response but also influence bone remodeling by stimulating receptor activator of nuclear factor kappa-B ligand (RANKL) expression, which promotes osteoclast differentiation and activity [21]. In healthy periodontal tissues, this inflammation is transient and resolves to support adaptive remodeling. However, in the presence of pre-existing periodontal disease or excessive force, it can become chronic, resulting in extracellular matrix degradation, loss of attachment, and alveolar bone loss [22, 23].

The bidirectional nature of these interactions adds further complexity. Inflammation can sensitize tissues to mechanical forces, lowering the threshold for mechanotransduction activation, while mechanical stress can perpetuate inflammation through sustained cytokine production [24, 25]. For instance, studies have shown that inflamed periodontal tissues exhibit altered biomechanical properties, such as reduced elasticity, which may impede OTM or increase susceptibility to damage [26]. This reciprocity suggests that orthodontic interventions must account for inflammatory status to avoid iatrogenic complications.

Despite these insights, the literature remains fragmented. Reviews on mechanotransduction often focus on isolated cellular pathways without integrating inflammatory feedback [27], while inflammation-centric studies in periodontology seldom address orthodontic-specific mechanics. There is a notable gap in theoretical models that unify these domains into a coherent causal framework. Existing models, such as those emphasizing RANKL/osteoprotegerin (OPG) ratios in bone remodeling, do not fully incorporate the upstream mechanosensory inputs or downstream feedback loops that sustain or resolve inflammation [25, 28].

This paper addresses this gap by developing a new integrative mechanistic framework. Drawing from cellular and molecular biology, tissue biomechanics, and inflammatory mechanisms, the framework posits a unified causal pathway where orthodontic forces initiate mechanotransduction, which triggers inflammatory signaling, subsequently driving bone remodeling. Bidirectional feedbacks are emphasized, illustrating how inflammation modulates force perception and how remodeling outcomes influence inflammatory resolution. This synthesis is purely conceptual, relying on established principles rather than new empirical data, and aims to provide a bold theoretical foundation for understanding periodontal responses to orthodontic interventions.

The framework has implications for clinical practice, such as tailoring force applications based on inflammatory biomarkers or incorporating anti-inflammatory adjuncts to optimize outcomes. It also highlights avenues for future research, including the role of specific signaling molecules in feedback loops. By conceptualizing these interactions as an interconnected system, this model advances periodontology toward more predictive and personalized orthodontic approaches.

In the sections that follow, we review the theoretical background, including key literature on inflammatory signaling, mechanotransduction, and bone remodeling. We then propose the integrative framework, detailing its causal pathways and feedback mechanisms.

Theoretical Background & Literature Review

Inflammatory signaling in periodontal tissues

Inflammatory processes in the periodontium are initiated by various stimuli, including mechanical forces from orthodontic appliances. These forces induce aseptic inflammation, characterized by the release of signaling molecules that orchestrate tissue responses [1, 3]. Key among these are cytokines such as IL-1β and TNF-α, which are upregulated in the PDL shortly after force application [19]. These cytokines promote vascular permeability, leukocyte recruitment, and the production of secondary mediators like PGE2, which further amplifies the response [20, 21].

Prostaglandins, particularly PGE2, play a dual role in inflammation and bone metabolism. Synthesized via cyclooxygenase pathways in response to mechanical stress, PGE2 enhances cytokine effects and directly

stimulates osteoclast activity [2, 4]. In orthodontic contexts, elevated PGE2 levels correlate with increased bone resorption on the compression side of teeth [6, 23]. However, chronic elevation can lead to uncontrolled inflammation, contributing to periodontal breakdown [22, 26].

The resolution of inflammation is equally important, involving anti-inflammatory cytokines like interleukin-10 (IL-10) and lipid mediators such as resolvins [25]. Dysregulation, often seen in periodontal disease, impairs this resolution, perpetuating tissue damage [24, 25].

Mechanotransduction pathways in response to orthodontic forces

Mechanotransduction converts mechanical forces into cellular signals, a process critical for OTM [15, 16]. In the PDL, cells detect force through membrane proteins like integrins and PIEZO1 channels, which activate intracellular pathways including mitogen-activated protein kinases (MAPK) and β-catenin signaling [13, 17, 18, 27].

Integrins link the extracellular matrix to the cytoskeleton, transducing force into focal adhesion kinase activation, which modulates gene expression for matrix remodeling [14,28]. PIEZO1, a mechanosensitive ion channel, responds to force by allowing calcium influx, triggering downstream cascades that influence cell differentiation [19, 29]. In orthodontics, these pathways determine the threshold and directionality of tissue responses [5].

Recent reviews highlight how mechanotransduction intersects with inflammation, as force-induced calcium signaling can upregulate cytokine production [30,31]. This integration suggests that mechanical sensitivity is tunable by inflammatory states [32].

Alveolar bone remodeling processes

Alveolar bone remodeling during OTM involves coordinated osteoclast and osteoblast activity [21, 33]. Orthodontic forces create pressure gradients, leading to RANKL-mediated osteoclastogenesis on the compression side and OPG-dominated osteoblast activity on the tension side [2, 4, 34].

Sclerostin, produced by osteocytes, inhibits bone formation but is downregulated under tension, facilitating apposition [24, 35]. Hypoxia from vascular compression further modulates remodeling via hypoxia-inducible factors, promoting angiogenesis and resorption [28, 36].

Bidirectional interactions with inflammation are evident, as cytokines enhance RANKL expression, accelerating remodeling but risking over-resorption if unchecked [6, 7, 23].

Interactions between inflammation and mechanical forces

The bidirectional causal pathways between inflammation and orthodontic forces form a feedback system [24,25]. Mechanical stress induces inflammation, which in turn alters tissue biomechanics, affecting force distribution [3, 5]. For example, inflamed tissues exhibit increased compliance, potentially amplifying stress on adjacent structures [22, 26].

Molecularly, inflammatory mediators like TNF-α sensitize mechanoreceptors, lowering activation thresholds [19, 20]. Conversely, sustained force can prolong inflammation through persistent prostaglandin release [4, 21]. This reciprocity explains why pre-existing inflammation exacerbates orthodontic complications [25].

Periodontal tissue degradation mechanisms

Excessive interactions can lead to degradation, involving matrix metalloproteinases (MMPs) that break down collagen and elastin [8, 25, 29]. MMP-9, upregulated by cytokines, is particularly implicated in gingival and PDL degradation during OTM [9].

Inflammatory feedback accelerates this, as PGE2 stimulates MMP expression, creating a vicious cycle [20, 23]. Protective mechanisms, such as tissue inhibitors of metalloproteinases, can mitigate this, but overload from force or inflammation tips the balance toward pathology [10, 25].

This review synthesizes these elements, revealing the need for an integrated model.

Proposed theoretical framework

The proposed framework integrates inflammatory signaling, mechanotransduction, and bone remodeling into a unified causal pathway, emphasizing bidirectional feedbacks to explain periodontal responses to orthodontic forces. At its core, orthodontic mechanical forces act as the initiating stimulus, applied via appliances to teeth and transmitted to the PDL and alveolar bone [37, 38]. These forces are sensed through mechanotransduction pathways, where cellular sensors like integrins and PIEZO1 channels convert mechanical energy into biochemical signals, such as calcium influx and MAPK activation [15, 17, 18, 27].

This initial transduction leads to the release of inflammatory mediators, including cytokines (IL-1β, TNF-α) and prostaglandins (PGE2), which propagate an aseptic inflammatory response [1, 3, 19, 20].

In the pathway, inflammation serves as a central hub, modulating downstream bone remodeling. Cytokines upregulate RANKL in osteoblasts and PDL cells, promoting osteoclast differentiation and alveolar bone resorption on the compression side [2, 4, 21]. Simultaneously, on the tension side, reduced inflammation and mechanotransduced signals enhance OPG expression, favoring osteoblast activity and bone apposition [24, 25, 33, 34]. This differential remodeling enables directional tooth movement.

Bidirectional causal pathways are integral: inflammation feeds back to mechanotransduction by sensitizing cellular sensors, for instance, through cytokine-induced expression of mechanosensitive proteins, thereby amplifying force perception [13, 25, 30, 32]. Conversely, ongoing remodeling influences inflammation; bone resorption releases matrix-bound factors that sustain cytokine production, while successful apposition promotes resolution via anti-inflammatory signals [25, 35, 36].

Periodontal tissue degradation emerges as a potential offshoot when feedbacks become dysregulated, with excessive PGE2 and MMPs leading to collagen breakdown and attachment loss [8, 9, 22, 23, 29]. The framework posits that optimal OTM occurs when feedbacks maintain homeostasis, whereas imbalances—due to high force or baseline inflammation—tip toward pathology.

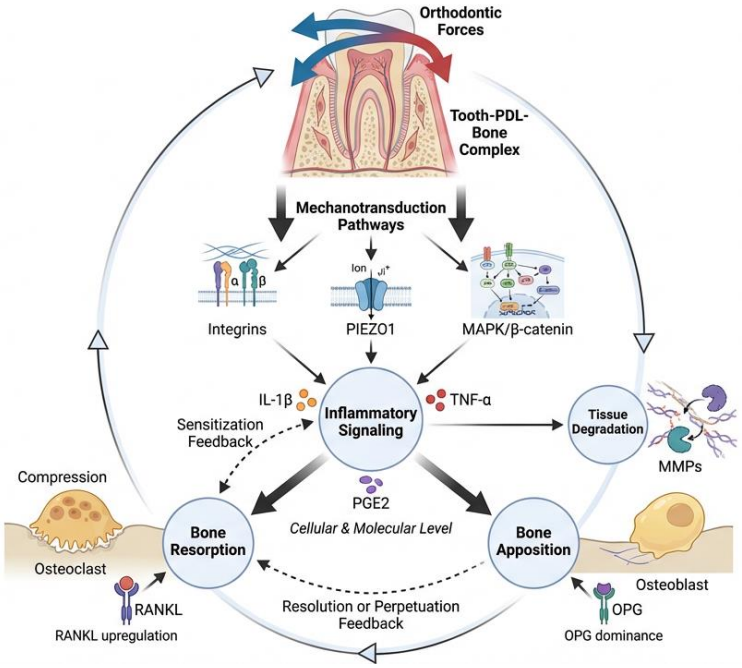

Figure 1. Schematic diagram illustrating orthodontic force applied to the tooth-PDL-bone complex

This model represents an original synthesis, not previously articulated in this form, by framing the processes as a single, feedback-regulated causal chain rather than parallel events.

Propositions

The proposed theoretical framework offers a comprehensive lens to understand the dynamic interplay between orthodontic mechanical forces, inflammatory signaling, and alveolar bone remodeling. Drawing from mechanobiology, immunology, and periodontal research, several testable propositions emerge. These propositions not only provide mechanistic explanations for tissue responses but also illuminate potential pathways for clinical intervention, personalized treatment strategies, and hypothesis-driven research [39-46]. They integrate bidirectional causal relationships and feedback loops, emphasizing the complex, adaptive, and sometimes non-linear nature of periodontal tissue dynamics in response to orthodontic loading.

Proposition 1: Orthodontic mechanical forces trigger inflammatory signaling via mechanotransduction

Sustained orthodontic forces represent a primary stimulus for cellular mechanotransduction within the periodontal ligament (PDL) and alveolar bone. Mechanosensitive elements—including integrins, focal adhesion kinases, PIEZO1 ion channels, stretch-activated channels, and cytoskeletal components—detect applied stress and initiate intracellular signaling cascades that culminate in aseptic inflammation [17, 19-21]. This process involves multiple steps:

1. **Mechanical sensing:** Integrins and stretch-activated channels detect extracellular strain, transmitting mechanical information to intracellular pathways.

2. **Signal amplification:** Downstream mediators such as MAPK, NF-κB, and Wnt/β-catenin are activated, leading to transcriptional upregulation of inflammatory cytokines (IL-1β, TNF-α, IL-6) and prostaglandins (notably PGE2).
3. **Spatial-temporal regulation:** The magnitude, duration, and direction of applied force modulate the intensity and duration of cytokine production. Moderate forces promote a controlled, transient inflammatory response conducive to adaptive remodeling, while excessive forces risk prolonged inflammation, hyalinization of the PDL, ischemia, and tissue necrosis.

This proposition emphasizes that inflammation is not merely a pathological byproduct of orthodontic treatment but a carefully regulated, force-dependent biological process essential for initiating tissue adaptation. It also underscores the mechanistic specificity of force detection, suggesting that targeting mechanosensors pharmacologicallyor mechanically could modulate inflammatory responses for clinical benefit [47-54].

Proposition 2: Inflammatory mediators modulate alveolar bone remodeling in a site-specific manner

Once initiated, the inflammatory response exerts a spatially and temporally specific effect on alveolar bone remodeling, enabling directional tooth movement. This proposition highlights how compression and tension zones within the PDL create differential microenvironments that selectively recruit and activate bone-resorbing or bone-forming cells:

- **Compression side:** Elevated levels of IL-1β, TNF-α, and prostaglandins induce receptor activator of nuclear factor kappa-B ligand (RANKL) expression, promoting osteoclast differentiation and localized bone resorption. This facilitates the removal of alveolar bone in the direction of tooth movement.
- **Tension side:** Reduced inflammatory signaling allows osteoprotegerin (OPG) to dominate, inhibiting osteoclastogenesis while enhancing osteoblast activity and bone apposition. This promotes bone formation and stabilizes the tooth in its new position [2, 4, 14].

The proposition underscores the necessity of a finely tuned balance between resorption and apposition. Disruption of this balance—caused by excessive forces, systemic inflammatory conditions, or individual variability in cytokine responses—may result in uneven bone remodeling, delayed tooth movement, root resorption, or periodontal damage. Additionally, this site-specificity suggests potential therapeutic opportunities: localized modulation of inflammatory mediators could accelerate movement or protect vulnerable sites from damage.

Proposition 3: Bidirectional feedback loops amplify or attenuate tissue responses

Inflammatory signaling and mechanotransduction do not operate in isolation; they engage in complex, bidirectional feedback loops that can either amplify or attenuate tissue responses [18, 22, 24, 30].

- **Amplification loops:** Pro-inflammatory mediators upregulate mechanosensitive receptors and signaling molecules in PDL cells, effectively lowering the threshold for mechanical force detection and accelerating subsequent remodeling. This creates a feed-forward mechanism where initial force application sensitizes tissues for faster adaptation.
- **Attenuation loops:** Remodeling outcomes, in turn, modulate inflammation. Successful bone apposition triggers anti-inflammatory cytokines such as IL-10 and TGF-β, promoting resolution and restoration of tissue homeostasis. Persistent resorption, however, sustains pro-inflammatory signaling, creating self-reinforcing cycles that may prolong tissue turnover or exacerbate damage [6, 25, 34].

These feedback mechanisms highlight the non-linear nature of orthodontic tissue responses. They also suggest that interventions at specific points in the loop—mechanosensors, cytokines, or osteoclast/osteoblast activity—could modulate the overall trajectory of tissue adaptation, potentially improving clinical predictability.

Proposition 4: Dysregulated interactions lead to periodontal tissue degradation

When the coordination between mechanical forces, inflammatory signaling, and bone remodeling is disrupted, pathological consequences emerge. Excessive inflammatory feedback, driven by prostaglandins, matrix metalloproteinases (MMPs), and other catabolic factors, can degrade the extracellular matrix, resulting in attachment loss, gingival recession, and alveolar bone defects [5, 13, 23, 29, 32].

Several factors can exacerbate this dysregulation:

- **Pre-existing inflammation:** Chronic periodontitis or systemic inflammatory conditions amplify cytokine production, increasing susceptibility to tissue degradation under orthodontic loading.
- **Excessive force application:** High-magnitude or prolonged forces create ischemia and necrosis within the PDL, further stimulating inflammatory cascades.
- **Individual variability:** Genetic and epigenetic differences in inflammatory response,

osteoclast/osteoblast activity, and extracellular matrix composition modulate vulnerability to damage.

This proposition highlights the critical need for force calibration, periodontal health assessment, and inflammatory control prior to and during orthodontic treatment [55-58]. It also provides a mechanistic rationale for adjunctive therapies, such as anti-inflammatory agents or biomodulators, to mitigate tissue degradation risk [59-63].

Proposition 5: The framework explains variable clinical outcomes

Orthodontic treatment outcomes are highly variable, reflecting inter-individual differences in mechanosensitivity, inflammatory responsiveness, systemic health, and genetic background [1, 16, 26, 36]. Some patients exhibit rapid, efficient tooth movement with minimal discomfort, while others experience slow movement, root resorption, or heightened susceptibility to periodontal complications. Key factors influencing this variability include:

- **Age-related changes:** Aging is associated with altered PDL cell mechanosensitivity, reduced osteoblast function, and slower bone remodeling.
- **Systemic conditions:** Diabetes, hormonal imbalances, and osteoporosis influence cytokine profiles, osteoclast/osteoblast activity, and tissue healing.
- **Genetic and epigenetic factors:** Polymorphisms in genes related to inflammatory mediators, mechanosensors, or extracellular matrix proteins modulate individual responses to mechanical forces.

By incorporating these factors, the framework provides a mechanistic explanation for patient-specific outcomes and supports the development of personalized treatment strategies. Clinically, this suggests that tailoring force magnitude, timing, and adjunctive therapies to individual profiles could optimize efficacy, minimize adverse effects, and improve predictability.

Proposition 6: Integrative framework as a tool for research and clinical innovation

Beyond clinical implications, this framework provides a roadmap for research:

- **Hypothesis generation:** Each proposition identifies testable mechanisms, such as the effects of force magnitude on cytokine profiles or the role of mechanosensor upregulation in feedback amplification.
- **Predictive modeling:** By quantifying interactions among forces, inflammation, and remodeling, computational models could simulate tissue responses under different scenarios, guiding clinical decision-making.
- **Translational potential:** The framework informs the design of adjunctive therapies—anti-inflammatory agents, biomodulators, or mechanical optimization protocols—to enhance treatment efficiency and safety.

In summary, these propositions collectively provide a mechanistic, integrative perspective on orthodontic tissue dynamics, bridging molecular, cellular, and clinical scales. They emphasize the adaptive, bidirectional, and context-dependent nature of the periodontal response to orthodontic forces and offer a foundation for both empirical research and personalized treatment approaches.

General Discussion

The integrative framework presented herein synthesizes disparate elements of inflammatory signaling, mechanotransduction, and bone remodeling into a cohesive causal pathway, addressing a critical gap in periodontology and orthodontics. By emphasizing bidirectional feedbacks, the model moves beyond linear descriptions, such as the traditional pressure-tension hypothesis, to portray a dynamic system where inflammation acts as both effector and modulator of mechanical forces [2, 13, 18]. This approach aligns with emerging views in cellular biology, where tissues are seen as adaptive networks responsive to biomechanical cues [17, 22, 24].

Clinically, the framework has implications for optimizing orthodontic interventions. For instance, understanding how cytokines like IL-1β amplify mechanotransduction suggests that monitoring gingival crevicular fluid biomarkers could guide force adjustments, potentially reducing risks of root resorption or periodontal breakdown [1, 3, 19]. In patientswith baseline inflammation, such as those with mild periodontitis, the model predicts heightened sensitivity to forces, advocating for adjunctive anti-inflammatory measures (e.g., low-level laser therapy or pharmacological modulators) to dampen feedback loops [4-6, 33, 64-69]. Conversely, in hypo-responsive cases, strategies to enhance signaling—without exceeding degradation thresholds—could accelerate treatment.

Theoretically, this synthesis contributes to broader mechanobiology by illustrating how feedback mechanisms maintain periodontal homeostasis under stress [20, 21, 27, 28]. It integrates molecular details, such as PGE2's role in MMP upregulation, with tissue-level outcomes like alveolar remodeling, providing a scaffold for modeling similar interactions in other load-

bearing tissues [15, 23, 29, 31]. Limitations include the conceptual nature, which relies on established literature rather than novel data; thus, it does not account for all variables, such as microbial influences or genetic polymorphisms that might alter pathway dynamics [25, 35]. Additionally, while the model is original in its unified pathway, it builds on prior work, necessitating validation through simulation or observational studies.

Future directions could explore computational modeling of the feedback loops to predict outcomes under varying force parameters [14,25,30]. Investigating specific inhibitors of inflammatory nodes (e.g., targeting TNF-α) might reveal ways to decouple beneficial remodeling from degradation [7, 26]. Overall, this framework encourages a shift toward integrative, systems-based approaches in periodontal research, enhancing theoretical rigor and clinical predictability.

Conclusion

This conceptual paper advances a mechanistic model that unifies orthodontic force-induced mechanotransduction, inflammatory signaling, and alveolar bone remodeling into a single causal pathway with bidirectional feedbacks. By synthesizing cellular, molecular, and biomechanical elements, the framework elucidates how inflammation mediates periodontal responses, explaining both adaptive tooth movement and potential degradation. The derived propositions provide testable insights for refining orthodontic strategies, emphasizing the balance of inflammatory dynamics to minimize risks. Ultimately, this integrative perspective fosters bolder theory-building in periodontology, paving the way for more effective, patient-centered interventions.

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