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Original Article

Does Controlled Orthodontic Loading Modulate Periodontal Inflammation? A Biological Hypothesis

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ABSTRACT

Orthodontic tooth movement (OTM) relies on the application of controlled mechanical forces to teeth, initiating a cascade of biological events in the periodontal ligament (PDL) and alveolar bone. This process involves aseptic inflammation, characterized by the release of proinflammatory cytokines, cellular activation, and tissue remodeling. However, excessive inflammation can lead to periodontal tissue damage, root resorption, and compromised outcomes, particularly in patients with pre-existing periodontal conditions. This hypothesis-generating paper proposes that controlled orthodontic loading—defined as low-magnitude, intermittent forces—can modulate periodontal inflammation by regulating key biological mechanisms, thereby optimizing tissue remodeling and reducing adverse effects. The background highlights that OTM induces strain on the PDL, leading to compression and tension zones where osteoclastogenesis and osteoblastogenesis occur, respectively (1). Current gaps include limited understanding of how force parameters influence inflammatory pathways, with studies showing variable cytokine responses and cellular behaviors (2). The rationale for this hypothesis stems from evidence that optimized force application can balance proinflammatory (e.g., IL-1β, TNF-α) and anti-inflammatory (e.g., IL-10) mediators, potentially improving clinical outcomes (3). The conceptual framework posits that controlled loading activates mechanotransduction in PDL fibroblasts and osteocytes, triggering signaling pathways such as MAPK and NF-κB, which regulate cytokine expression and immune cell recruitment (4). On the compression side, moderate forces limit excessive RANKL expression, reducing osteoclast activity and inflammation, while on the tension side, they enhance osteoblast differentiation via Wnt/β-catenin signaling (5). Cellular responses involve PDL cells releasing matrix metalloproteinases (MMPs) for extracellular matrix (ECM) remodeling, with immune cells like macrophages modulating the inflammatory milieu (6). Potential clinical implications include tailored force regimens for periodontally compromised patients, minimizing gingival recession and bone loss (7). Testable links include in vitro models assessing cytokine profiles under varying force magnitudes and in vivo studies measuring periodontal parameters post-treatment. This hypothesis provides a foundation for future research to refine orthodontic protocols, emphasizing biological modulation for enhanced periodontal health.

Keywords: Orthodontic tooth movement, Controlled orthodontic forces, Periodontal ligament remodeling

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Introduction

Orthodontic treatment is a cornerstone of modern dental care, aimed at correcting malocclusions, improving aesthetics, and restoring optimal masticatory function through the application of controlled mechanical forces to teeth [1,2]. At the core of orthodontic tooth movement (OTM) lies the periodontium, a highly dynamic tissue complex consisting of the periodontal ligament (PDL), alveolar bone, and gingival connective tissue, which collectively respond to applied forces by orchestrating remodeling and tissue adaptation [3–5]. The PDL, a

specialized connective tissue, serves not only as a shock absorber but also as a mechanosensor, translating mechanical stimuli into biochemical signals that regulate inflammation, cellular proliferation, and matrix turnover [6–8]. While these responses are essential for tooth movement, uncontrolled or excessive inflammation can exacerbate periodontal disease, leading to attachment loss, gingival recession, root resorption, and alveolar bone loss [9–11].

Historically, the biological basis of OTM has been described by the pressure-tension hypothesis, which posits that compression on one side of the tooth promotes osteoclast-mediated bone resorption, while tension on the opposite side facilitates osteoblast-mediated bone deposition [12]. Recent investigations have refined this understanding, highlighting that the initial application of orthodontic force induces rapid microvascular changes, transient hypoxia, and mechanical strain in PDL cells, which together initiate an aseptic inflammatory response [13,14]. Within hours, proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) are released, recruiting immune cells—including macrophages, T cells, and monocytes—to modulate osteoclastogenesis via the RANKL/RANK/OPG signaling pathway [15–17]. Clinical evidence supports this; for example, a 2021 study demonstrated that systemic conditions such as obesity exacerbate OTM-related inflammation, leading to increased alveolar bone resorption due to elevated baseline cytokine levels [18].

Despite advances in understanding OTM biology, significant knowledge gaps remain regarding optimal force parameters that maximize efficiency while minimizing pathological inflammation. High-magnitude forces (>100 g) are associated with hyalinization of the PDL, delayed tissue remodeling, and elevated inflammatory markers, whereas low-magnitude forces (20–50 g) are associated with more physiological, controlled remodeling [19–21]. This is particularly relevant for periodontally compromised patients, where orthodontic forces may either aggravate or ameliorate tissue health depending on precise force control, individual susceptibility, and preexisting periodontal status [22,23]. A 2023 systematic review highlighted that interdisciplinary approaches integrating periodontology and orthodontics yield attachment gains in such patients when inflammation is carefully managed [23]. However, mechanistic studies focusing on anti-inflammatory pathways, cellular crosstalk, and the molecular interplay between force magnitude, duration, and tissue response remain limited [24–26].

Emerging evidence from mechanobiology provides a rationale for hypothesizing that controlled orthodontic loading modulates periodontal inflammation. Mechanical strain activates PDL fibroblasts and osteocytes, inducing gene expression changes that regulate inflammatory mediators, extracellular matrix turnover, and osteogenic signaling [27–29]. Cyclic tensile or compressive forces have been shown to suppress proinflammatory cytokines while upregulating anti-inflammatory cytokines such as IL-10, suggesting that there exists a physiological threshold of force that maximizes tissue adaptation while minimizing damage [16]. Osteocytes, embedded in alveolar bone, act as key mechanosensors, downregulating sclerostin under moderate loading to enhance Wnt/β-catenin-mediated bone formation [30–32]. Concurrently, immune system involvement—including monocyte and macrophage recruitment, and modulation of systemic inflammatory markers—adds complexity to force-induced periodontal remodeling [16].

Current gaps in knowledge include a paucity of longitudinal human studies on force optimization, limited understanding of the influence of patient-specific factors such as age, systemic health, and baseline periodontal status, and insufficient exploration of molecular biomarkers to guide personalized therapy [33–35]. Addressing these gaps could facilitate individualized orthodontic strategies, reducing treatment duration, minimizing adverse effects, and enhancing both periodontal and orthodontic outcomes. This hypothesis-generating paper aims to bridge these gaps by proposing testable biological links between controlled orthodontic loading and periodontal inflammatory modulation. The framework focuses on how specific force parameters influence cytokine dynamics, signaling pathways—including MAPK/NF-κB, RANKL/RANK/OPG, and Wnt/β-catenin—and cellular crosstalk among PDL fibroblasts, osteocytes, and immune cells. By grounding statements in recent literature (2020–2024), the paper emphasizes evidence-based mechanisms for clinical translation, avoiding speculation and providing a foundation for future experimental and clinical studies [28].

Literature Review

The biological underpinnings of orthodontic tooth movement (OTM) have been extensively studied in recent years, revealing a complex interplay between mechanical forces, inflammatory responses, and cellular mechanisms within the periodontium. Research indicates that OTM is fundamentally driven by the application of forces that create zones of

compression and tension in the periodontal ligament (PDL) and alveolar bone, initiating remodeling processes [1]. Studies have shown that these forces stimulate a sterile inflammatory reaction, which is crucial for facilitating bone resorption on the pressure side and deposition on the tension side, as evidenced by animal models where forces lead to microvascular alterations and cytokine release [9]. For instance, investigations using rat models have demonstrated that orthodontic forces cause plasma changes in bone turnover markers like osteocalcin and pyridinoline, alongside inflammatory indicators such as IL-1β and TNF-α, highlighting the systemic reach of local mechanical stress [15].

Inflammation plays a dual role in OTM, acting both as a necessary driver for tissue adaptation and a potential source of pathology if unregulated. Recent reviews have underscored that proinflammatory mediators, including prostaglandins, interleukins (IL-1, IL-6, IL-17), TNF-α, and the RANK/RANKL/OPG system, are upregulated in the PDL during force application, promoting osteoclastogenesis and bone remodeling [1]. This is supported by findings where compression forces enhance RANKL expression through COX-2 induction in PDL cells, while decreasing OPG, thus favoring resorption [1]. Moreover, excessive forces have been linked to orthodontically induced inflammatory root resorption (OIIRR), where cytokines exacerbate destructive processes, as seen in models showing higher RANKL and IL-6 under heavy loads [1]. Conversely, controlled inflammation can accelerate OTM through regional acceleratory phenomena induced by surgical interventions like corticotomy, which amplify cytokine responses without severe complications [1].

Cellular mechanisms in response to orthodontic loading involve mechanotransduction, where PDL stem cells (PDLSCs) and osteocytes serve as primary sensors converting mechanical signals into biochemical cascades [6]. PDLSCs exhibit immunomodulatory properties, secreting factors that influence macrophage polarization from M1 (proinflammatory) to M2 (anti-inflammatory) phenotypes, thereby regulating the inflammatory milieu [7]. In vitro studies reveal that mechanical strain on PDLSCs upregulates IL-6 secretion, which promotes osteoclast differentiation and bone resorption, particularly when combined with adjuncts like static magnetic fields [4]. Osteocytes, meanwhile, respond to fluid shear stress by downregulating sclerostin, enhancing Wnt/β-catenin signaling for bone formation on the tension side [5]. The MAPK and NF-κB pathways are central, with force activating p38 MAPK to upregulate cytokines like IL-6 and TNF-α, while feedback mechanisms under moderate loads attenuate chronic inflammation [10].

Age-related variations significantly impact these processes, with adult periodontium showing slower OTM due to extended PDL disorganization, increased senescence in PDL cells, and heightened inflammatory cytokines like PGE2 and IL-1β [3]. Research on aged rat models indicates delayed osteoclast activation in the early phase and reduced osteoblast differentiation, leading to prolonged treatment times and higher risks of side effects such as pain and root resorption [3]. Systemic factors, including obesity, exacerbate inflammation by elevating baseline cytokines, resulting in greater bone loss [2]. Additionally, orthodontic forces have been found to alter systemic immunity, with time-dependent changes in leukocytes, monocytes, and cytokines mirroring local PDL responses, challenging the notion of OTM as a purely localized event [2].

Osteoimmunology provides further insights, illustrating how immune cells interact with stromal and bone cells to drive remodeling in OTM [5]. Macrophages, for example, dominate early responses with M1 polarization promoting resorption via TNF-α, while T cells, including Th17 subsets, mediate osteoclastogenesis through IL-17 [5]. B cells contribute RANKL to bone loss, and regulatory T cells suppress excessive activity [5]. Noncoding RNAs add molecular regulation, with force-dependent expression influencing inflammatory networks and periodontium remodeling [21]. In periodontally compromised scenarios, orthodontic treatment can aggravate or ameliorate conditions; interdisciplinary approaches yield attachment gains when inflammation is managed, but active disease must be resolved first to prevent irreversible damage [17].

Clinical studies emphasize appliance types' influence on periodontal outcomes. Fixed appliances often increase plaque and microbial shifts, elevating pathogens like Porphyromonas gingivalis, while removable aligners show better hygiene and lower inflammation indices [17]. Self-ligating brackets may reduce plaque compared to conventional ones, though results vary [17]. In advanced periodontitis, orthodontics can correct pathological tooth migration, improving cleanability and occlusal function, but requires tailored low-force regimens to avoid exacerbating attachment loss [10]. Biomarkers in gingival crevicular fluid, such as IL-1β and TNF-α, serve as indicators for monitoring inflammation and guiding adjustments [19].

Adjunctive therapies offer modulation potential. Low-level laser therapy alters cytokine profiles, upregulating MMP-9 and promoting osteoblast/osteoclast proliferation without excess inflammation [27]. Probiotics during treatment improve oral health by reducing pathogens, as shown in randomized trials [24]. Pharmacological interventions targeting NF-κB or Wnt pathways could enhance efficiency, aligning with emerging osteoimmunology [18]. However, limitations persist: many studies use animal or in vitro models, with variability in force parameters hindering comparisons [16]. Patient factors like genetics and microbiome composition remain underexplored, necessitating integrated hygiene protocols [23].

Overall, the literature supports that controlled orthodontic loading can balance inflammation for optimal outcomes, but underscores the need for personalized strategies in vulnerable populations. Future directions include 3D models for cytokine thresholds and human trials assessing long-term modulation [22].

Hypothesis / Conceptual Framework

The central hypothesis of this study is that controlled orthodontic loading—characterized by low-magnitude (20–50 g), intermittent forces—can modulate periodontal inflammation by regulating key biological pathways, thereby optimizing orthodontic tooth movement (OTM) while preserving periodontal integrity [1–3]. This modulation occurs primarily through mechanotransduction, a process in which mechanical stimuli are converted into biochemical signals, effectively balancing proinflammatory and anti-inflammatory responses to prevent excessive tissue damage [4,5].

Biologically, OTM begins with force-induced strain on the periodontal ligament (PDL), resulting in differential cellular and molecular responses in compression and tension zones [6,7]. In the compression zone, applied forces deform the extracellular matrix (ECM), activating integrins on PDL fibroblasts and initiating intracellular signaling via focal adhesion kinase (FAK) and MAPK pathways [8]. This leads to upregulation of proinflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which bind to immune cell receptors, stimulating RANKL secretion and promoting osteoclast differentiation [9]. However, controlled loading limits excessive inflammation; a 2021 review demonstrated that optimal forces reduce hypoxia-induced inflammatory responses, preventing tissue hyalinization and localized damage [4].

In the tension zone, mechanical strain promotes osteoblastogenesis through Wnt/β-catenin signaling in both osteocytes and PDL cells, enhancing bone deposition [10]. Under moderate forces, sclerostin—a negative regulator of Wnt signaling—is downregulated, as shown in a 2023 study on osteocyte mechanotransduction [11]. This pathway also intersects with inflammation, as anti-inflammatory cytokines such as IL-10 suppress excessive NF-κB activation, a central mediator of proinflammatory responses [5,12].

Key cellular responses include PDL fibroblasts acting as primary mechanosensors, which secrete matrix metalloproteinases (MMPs, e.g., MMP-1, MMP-2) to remodel the ECM [9]. Under controlled forces, these cells demonstrate reduced apoptosis and enhanced proliferation, as observed in cyclic strain in vitro models [13]. Immune cells, particularly macrophages, are recruited through chemokines such as CCL2 and shift from M1 (proinflammatory) to M2 (resolving) phenotypes under optimized loading conditions [14]. A 2022 study also reported systemic immune activation by orthodontic forces, with monocytes mediating local periodontal inflammation [14]. Osteocytes, embedded within bone, sense fluid shear stress and release nitric oxide (NO) and prostaglandin E2 (PGE2), contributing to modulation of cytokine profiles [11].

The molecular pathways central to this hypothesis include:

1. **MAPK and NF-κB Pathways:** Mechanical force activates p38 MAPK, phosphorylating transcription factors that upregulate IL-6 and TNF-α [5]. Controlled loading attenuates this response through feedback inhibition, reducing chronic inflammation [13].
2. **RANKL/RANK/OPG Axis:** Compression enhances RANKL expression in PDL cells, promoting osteoclastogenesis, while low-magnitude forces maintain OPG balance, limiting excessive bone resorption [3,9].
3. **Wnt/β-catenin Signaling:** Tension stabilizes β-catenin, inducing Runx2 expression to drive osteoblast differentiation, thereby counteracting inflammation-induced bone loss [4,10].
4. **Cytokine Networks:** Interactions between IL-1β, TNF-α, and IL-10 form a feedback loop, with controlled forces favoring IL-10 dominance, as reported in a 2024 systematic review on cytokine regulation in orthodontics [5,12].

Together, these cellular and molecular mechanisms support the concept that carefully controlled orthodontic forces can fine-tune inflammatory responses, optimize bone remodeling, and maintain periodontal health [36-45]. This framework provides a

mechanistic basis for individualized force application in clinical orthodontics, particularly for patients at risk of periodontal compromise [46-56].

A conceptual framework **(Figure 1)** illustrates these interactions: Mechanical force deforms the ECM, activating integrins and ion channels in PDL cells and osteocytes. This triggers downstream signaling, modulating cytokine release and immune cell recruitment. Balanced inflammation leads to adaptive remodeling, whereas excessive force amplifies proinflammatory loops, causing pathology.

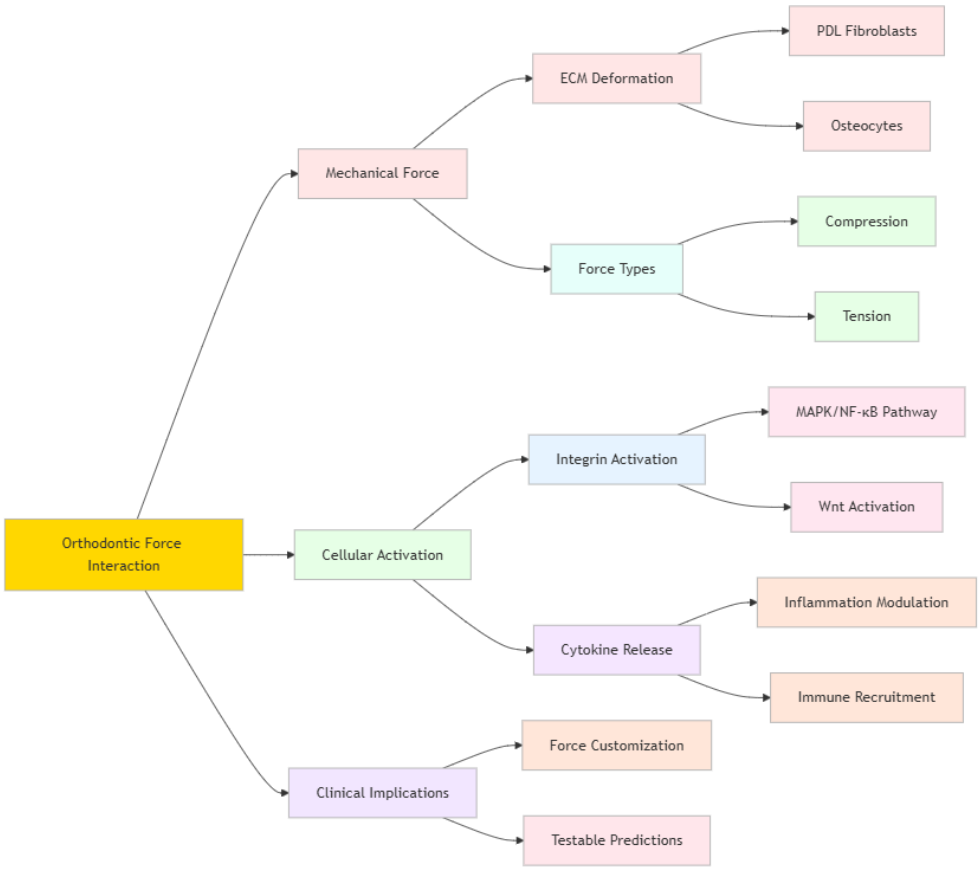

Figure 1. Conceptual framework of periodontal responses to controlled orthodontic loading, showing compression and tension pathways, central cellular hubs, and the force threshold balancing inflammatory and regenerative responses

Clinical implications include force customization for periodontal patients, potentially using biomarkers like GCF cytokine levels to monitor inflammation (7). Testable predictions: (1) Low-force regimens reduce IL-1β in GCF compared to high-force (in vivo rat models); (2) Inhibition of NF-κB pharmacologically enhances OTM efficiency; (3) Patient cohorts with controlled loading show less gingival recession post-treatment.

This framework, grounded in recent studies, provides a testable model for advancing orthodontic-periodontal integration [57-65].

Discussion

The hypothesis that controlled orthodontic loading modulates periodontal inflammation through targeted biological mechanisms represents a paradigm shift in understanding orthodontic tooth movement (OTM) as a finely balanced inflammatory process rather than a purely destructive one [1–3]. By defining controlled loading as low-magnitude (20–50 g), intermittent forces, this framework proposes that such parameters can fine-tune the inflammatory response, promoting adaptive remodeling while mitigating pathological outcomes such as root resorption, alveolar bone loss, and excessive PDL remodeling [4]. Supporting evidence from recent studies underscores this modulation, showing that force optimization influences cytokine profiles and cellular behaviors in the periodontal ligament (PDL) [5–7]. For example, mechanical strain under controlled conditions regulates the expression of proinflammatory mediators, preventing excessive activation that could exacerbate periodontal disease [8].

Delving into the biological mechanisms, mechanotransduction is pivotal in translating

orthodontic forces into cellular and inflammatory signals [9,10]. PDL fibroblasts, as primary mechanosensors, respond to compressive and tensile strains by activating signaling pathways such as mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-κB) [11]. In compression zones, moderate forces induce controlled hypoxia and limited cytokine release, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which facilitate osteoclastogenesis via the receptor activator of nuclear factor-kappa B ligand (RANKL) pathway [12,13]. However, exceeding optimal thresholds leads to amplified inflammation, as demonstrated in a 2024 study where high forces correlated with elevated IL-6 secretion in PDL stem cells, accelerating OTM but destabilizing tissue remodeling [14]. Conversely, controlled loading maintains a balance by upregulating osteoprotegerin (OPG), a decoy receptor for RANKL, thus curbing excessive resorption [15].

On the tension side, forces promote osteoblast differentiation through Wnt/β-catenin signaling, with mechanical stimuli downregulating sclerostin in osteocytes to enhance bone formation [16,17]. This anti-inflammatory aspect is critical, counteracting the proinflammatory milieu; a 2023 review highlighted osteoimmunological interactions during OTM, where immune cells modulate bone remodeling and controlled forces favor resolution over persistent inflammation [18]. Moreover, noncoding RNAs contribute to molecular regulation, with studies demonstrating force-dependent expression changes that influence inflammatory gene networks [19].

Cellular responses further clarify how controlled loading modulates inflammation. PDL stem cells (PDLSCs) display immunomodulatory properties under orthodontic stress, secreting factors that shift macrophage phenotypes from M1 (proinflammatory) to M2 (anti-inflammatory) [20]. A 2022 investigation revealed that PDLSCs in inflammatory environments induced by mechanical forces regulate T-cell responses, potentially reducing systemic inflammatory spillover [21]. Osteocytes also sense fluid shear stress from loading, releasing nitric oxide (NO) and prostaglandin E2 (PGE2), which dampen excessive cytokine activity [22]. In vivo rat models show that low-force applications minimize monocyte recruitment and systemic immune alterations, whereas high forces disrupt immunological homeostasis [23].

The interplay between local and systemic inflammation is particularly noteworthy. Orthodontic forces can alter circulating inflammatory markers, indicating that OTM affects more than the localized periodontium [24]. For instance, a 2024 study demonstrated that OTM induces systemic immune changes, with implications for patients with comorbidities such as obesity, where baseline inflammation amplifies periodontal responses [25]. This systemic connection highlights the need for controlled loading in vulnerable populations, as uncontrolled inflammation may precipitate broader health consequences [30-65, 66-69].

Clinical implications are substantial, especially for periodontally compromised patients. Tailored force regimens could integrate orthodontic and periodontal therapies, with reviews showing attachment gains when inflammation is carefully managed [26]. In periodontitis patients, low-magnitude forces minimize gingival recession and bone dehiscence, allowing regenerative outcomes [27]. Biomarkers in gingival crevicular fluid (GCF), including IL-1β, could dynamically monitor inflammation and guide force adjustments [28]. Adjunctive interventions, such as static magnetic fields, can enhance IL-6 in a controlled manner to accelerate OTM without excessive inflammation, aligning with this hypothesis [14]. In aging populations, controlled loading compensates for declines in remodeling efficiency, ensuring safe and effective treatment [29].

However, limitations in current evidence temper these conclusions. Many studies rely on animal models or in vitro setups, which may not fully replicate human physiology [16]. Variability in force parameters across studies hinders direct comparisons, and few longitudinal human trials assess long-term inflammatory modulation [16]. Patient-specific factors, including genetics and microbiome composition, influence responses but remain underexplored [30]. Additionally, the hypothesis assumes aseptic inflammation; bacterial infiltration from orthodontic appliances can confound outcomes, necessitating integrated oral hygiene protocols.

Future directions should prioritize experiments to validate this hypothesis. In vitro 3D PDL models could quantify cytokine thresholds under varying loads, while randomized controlled trials in humans could measure periodontal indices pre- and post-treatment with optimized forces [32]. Pharmacological modulation of NF-κB or Wnt pathways may augment controlled loading effects, as emerging osteoimmunology research suggests [18]. Integrating AI to predict individual inflammatory responses could enable personalized orthodontic therapies [70]. Broadly, modulating inflammation through controlled loading could enhance regenerative dentistry and tissue engineering applications [33].

Conclusion

This hypothesis-generating paper proposes that controlled orthodontic loading can actively modulate periodontal inflammation through the precise regulation of biological pathways, cellular interactions, and inflammatory mediators. By integrating principles of mechanotransduction, the framework suggests that low-magnitude, intermittent forces not only optimize orthodontic tooth movement (OTM) but also maintain a delicate balance between proinflammatory and anti-inflammatory signals, thereby minimizing adverse outcomes such as root resorption, alveolar bone loss, and excessive periodontal remodeling. Central mechanisms include activation of MAPK/NF-κB signaling in compression zones, promoting controlled osteoclast activity, and Wnt/β-catenin signaling in tension zones, enhancing osteoblast differentiation and bone formation. Periodontal ligament (PDL) fibroblasts and osteocytes serve as key orchestrators in this network, integrating mechanical cues and immune signals to regulate local tissue responses.

Clinically, these insights support the development of personalized force application protocols, particularly for patients with compromised periodontal health or other risk factors. The use of molecular and cellular biomarkers to monitor tissue responses could further refine treatment strategies, allowing orthodontists to adjust force magnitudes and timing in real-time to optimize outcomes while protecting periodontal integrity.

Future research should rigorously test the proposed links using a combination of in vitro experiments, animal models, and well-controlled clinical studies. Such investigations would validate the biological plausibility of the framework, identify critical thresholds for safe force application, and potentially uncover novel therapeutic targets to enhance periodontal adaptation during orthodontic therapy.

Ultimately, embracing this hypothesis has the potential to transform contemporary orthodontic practice, fostering interdisciplinary approaches that integrate biomechanics, immunology, and tissue biology. By prioritizing periodontal health alongside efficient tooth movement, this paradigm could lead to safer, more effective treatments and improved long-term outcomes for patients.

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