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Original Article

Shared Inflammatory Pathways in Periodontitis and Orthodontic Tooth Movement: Implications for Bone Remodeling

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ABSTRACT

Periodontitis and orthodontic tooth movement (OTM) represent two distinct yet interconnected processes in oral health, both characterized by inflammatory responses that drive bone remodeling. Periodontitis, a chronic bacterial-induced inflammatory disease, leads to progressive destruction of periodontal tissues, including alveolar bone loss through dysregulated immune responses and osteoclast activation. In contrast, OTM is a controlled, aseptic inflammatory process triggered by mechanical forces, facilitating tooth repositioning via coordinated bone resorption and formation within the periodontal ligament (PDL) and alveolar bone. Despite their differences—one pathological and the other therapeutic—these conditions share common inflammatory pathways, including cytokine signaling (e.g., IL-1, IL-6, TNF-α), RANKL/OPG axis, and immune-stromal cell interactions, which modulate osteoclastogenesis and osteoblast activity. This narrative review synthesizes recent evidence from peer-reviewed studies (2020–2025) to elucidate these shared mechanisms and their implications for bone remodeling. In periodontitis, bacterial dysbiosis activates innate and adaptive immunity, promoting pro-inflammatory mediators that uncouple bone resorption from formation, resulting in net bone loss. Similarly, in OTM, mechanical stress induces a sterile inflammation, with compression-side resorption and tension-side apposition, but excessive or dysregulated inflammation can lead to complications like root resorption. Overlapping pathways, such as NF-κB, MAPK, and Wnt signaling, highlight how systemic factors (e.g., obesity, diabetes) exacerbate both conditions. Advanced glycation end products (AGEs), glycolysis reprogramming, and mechanosensitive channels like Piezo1/2 further link metabolic and mechanical cues to inflammation. Understanding these convergences offers therapeutic insights, including immunomodulation (e.g., targeting CCR2+ macrophages or sclerostin) to enhance OTM efficiency while mitigating periodontitis progression. Adjunctive therapies like low-intensity pulsed ultrasound (LIPUS) or photobiomodulation (PBM) may optimize bone remodeling by dampening inflammation. This review underscores the osteoimmunological framework uniting periodontitis and OTM, paving the way for integrated clinical strategies to preserve alveolar bone integrity.

Keywords: Periodontitis, Orthodontic tooth movement, Inflammatory pathways, Bone remodeling, Osteoimmunology, Cytokines

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Introduction

Periodontitis is a highly prevalent, chronic inflammatory disease that targets the supporting structures of the teeth, including the gingiva, periodontal ligament (PDL), cementum, and alveolar bone [1,2]. It arises from a dysbiotic microbial biofilm that disrupts the delicate balance between the host immune system and the oral microbiome. Pathogenic

bacteria, such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, secrete virulence factors that activate epithelial and immune cells through pattern recognition receptors, notably Toll-like receptors (TLRs). This activation triggers a robust inflammatory cascade characterized by the release of pro-inflammatory cytokines—including interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and receptor activator of nuclear factor kappa-B ligand (RANKL)—which promote osteoclast differentiation and activity while simultaneously inhibiting osteoblast function [3, 4]. The resulting imbalance leads to uncoupled bone remodeling, marked by excessive resorption and insufficient formation, ultimately compromising alveolar bone integrity and tooth stability [5]. Epidemiologically, severe periodontitis affects approximately 19% of adults worldwide, representing a major public health concern due to its association with tooth loss and systemic conditions such as cardiovascular disease, diabetes, and chronic kidney disease [6].

In contrast, orthodontic tooth movement (OTM) represents a deliberate, controlled clinical intervention designed to correct malocclusions and optimize occlusal function. OTM relies on the application of calibrated mechanical forces to teeth via fixed appliances (braces) or removable aligners, which generate localized stress within the PDL and adjacent alveolar bone [7]. This mechanical loading induces a sterile, aseptic inflammatory response that is essential for adaptive bone remodeling: osteoclast-mediated resorption occurs on the compression side, while osteoblast-driven bone formation occurs on the tension side, enabling teeth to move predictably within the alveolar socket [8,9]. Tens of millions of patients worldwide undergo orthodontic therapy annually, and the rate of tooth movement is influenced by force magnitude, duration, and individual biological variability, including age, hormonal status, and genetic factors [10]. Importantly, OTM shares mechanistic features with periodontitis, including the involvement of inflammatory mediators, chemokines, and immune cells that coordinate osteoclast–osteoblast crosstalk [11]. However, while periodontitis is a pathological process characterized by irreversible tissue destruction, OTM represents a physiological adaptation aimed at achieving spatial equilibrium; yet, complications such as orthodontically induced inflammatory root resorption (OIIRR) may arise if the inflammatory response becomes dysregulated or excessive [12].

Despite their distinct etiologies—microbial in periodontitis versus mechanical in OTM—these conditions converge at the level of shared inflammatory and osteoimmunological pathways that govern bone remodeling. Osteoimmunology, the field that studies the interface between immune and skeletal systems, provides a framework for understanding how leukocytes, stromal cells, and osteocytes interact to modulate key pathways such as RANKL/osteoprotegerin (OPG) ratios, NF-κB activation, mitogen-activated protein kinase (MAPK) signaling, and cellular metabolic reprogramming [1,13]. For example, bacterial lipopolysaccharides (LPS) in periodontitis can activate transcription factors and cytokine cascades similar to those induced by mechanical stress in OTM, resulting in overlapping inflammatory profiles and molecular signatures [2,14]. Furthermore, systemic comorbidities—including obesity, hyperglycemia, and metabolic syndrome—can amplify these shared pathways, as adipose tissue-derived cytokines and advanced glycation end products (AGEs) exacerbate local inflammation, promote osteoclastogenesis, and potentially impair the efficiency of OTM [15].

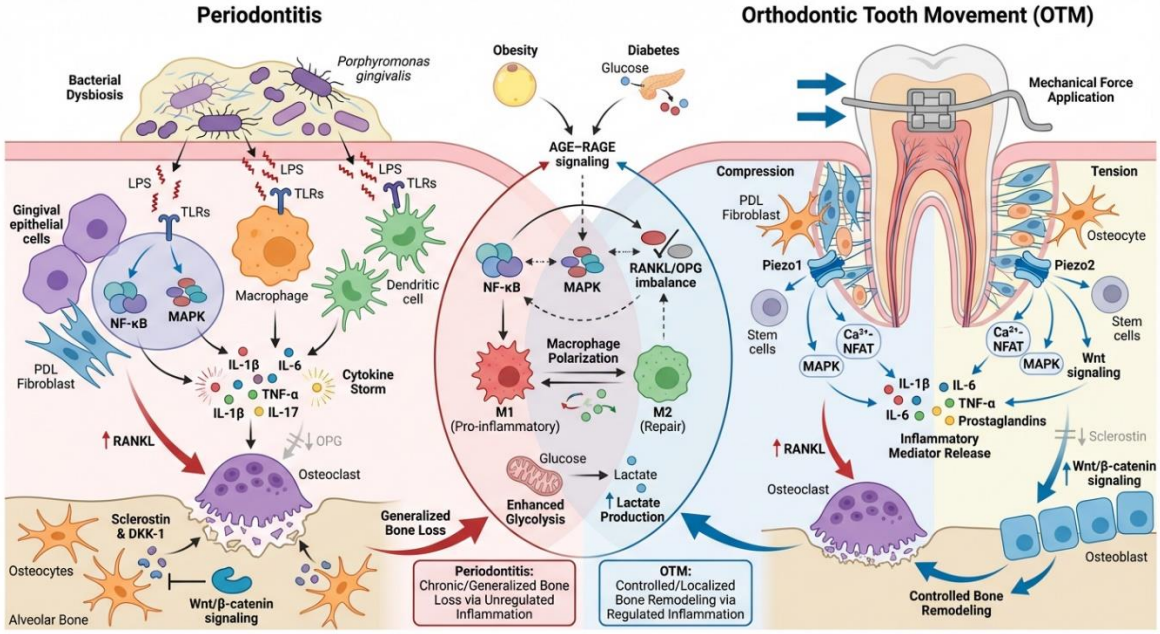

Figure 1. Shared inflammatory and osteoimmunological pathways in periodontitis and orthodontic tooth movement

Emerging evidence also highlights additional shared molecular players that bridge inflammation and bone remodeling. Mechanosensitive ion channels such as Piezo1 and Piezo2 transduce mechanical signals into intracellular responses, linking physical stress with cytokine production and osteoclast–osteoblast coordination [16]. Similarly, metabolic intermediates from glycolysis and oxidative phosphorylation modulate immune cell function and local tissue adaptation, suggesting a critical role for cellular metabolism in both pathological and physiological bone remodeling [17]. PANoptosis-associated genes and signaling pathways further indicate that programmed cell death mechanisms contribute to the intersection of inflammation and remodeling in both conditions, with implications for comorbidity and tissue resilience.

The objectives of this narrative review are threefold: (1) to delineate the inflammatory mechanisms underlying periodontitis and OTM individually; (2) to identify and analyze shared pathways, including key mediators, cellular interactions, and systemic modulators; and (3) to explore implications for bone remodeling in clinical scenarios where these conditions coexist, particularly during orthodontic treatment in periodontally compromised patients [18-25]. By integrating findings from recent literature (2020–2025), this review aims to provide a comprehensive and mechanistic framework for understanding the convergence of microbial, mechanical, and systemic factors in bone remodeling, ultimately informing therapeutic strategies to optimize outcomes in both periodontal and orthodontic care.

Pathophysiology of Periodontitis: Inflammatory Mechanisms and Bone Loss

Periodontitis initiates with the accumulation of dental plaque [26-28], a polymicrobial biofilm that disrupts the host-microbe equilibrium, leading to dysbiosis [1]. Key pathogens, such as *Porphyromonas gingivalis*, trigger an innate immune response through toll-like receptors (TLRs) on gingival epithelial cells and fibroblasts, activating downstream pathways like NF-κB and mitogen-activated protein kinases (MAPKs) [3]. This results in the release of chemokines (e.g., CXCL8) and cytokines (e.g., IL-1β, IL-6, TNF-α), recruiting neutrophils, monocytes, and lymphocytes to the site [5,6]. The adaptive immune response further amplifies inflammation, with T-helper 17 (Th17) cells producing IL-17, which synergizes with RANKL to enhance osteoclastogenesis [4].

Bone loss in periodontitis is a hallmark of disease progression, driven by uncoupled remodeling where osteoclast activity predominates [2]. Osteocytes, embedded within the bone matrix, play a pivotal role by upregulating RANKL and sclerostin expression in response to inflammatory signals, promoting osteoclast differentiation from monocyte precursors while inhibiting osteoblast maturation [29]. Apoptosis, ferroptosis, and senescence of osteocytes exacerbate this process, releasing damage-associated molecular patterns (DAMPs) that sustain cytokine cascades [29].

Additionally, metabolic alterations, such as enhanced glycolysis in immune and stromal cells, fuel pro-inflammatory states by generating lactate, which further activates NF-κB and hinders resolution [30].

Systemic factors compound local inflammation. In obesity, adipose tissue acts as an inflammatory organ, secreting adipokines like leptin and resistin that impair periodontal barrier function and promote extracellular matrix (ECM) degradation [15]. Advanced glycation end products (AGEs), prevalent in diabetes, bind to RAGE receptors, inducing oxidative stress, MMP activation, and neuro-immune crosstalk, creating a vicious cycle of tissue destruction [17]. Cross-talk with other conditions, such as atherosclerosis, involves shared PANoptosis-related genes (e.g., MLKL, ZBP1, CD14, IL6), linking periodontal inflammation to systemic vascular pathology via immune infiltration [31].

Therapeutic implications arise from these mechanisms [32-36]. For instance, targeting glycolysis or AGE-RAGE signaling could mitigate inflammation, while interventions like anti-RANKL antibodies (e.g., denosumab) show promise in reducing bone loss [17, 29]. Low-intensity pulsed ultrasound (LIPUS) emerges as a non-invasive strategy, inhibiting inflammatory factors and promoting PDLC regeneration in inflammatory environments [37]. Similarly, Dickkopf-1 (DKK-1), a Wnt inhibitor elevated in periodontitis, serves as a biomarker for bone destruction, with potential for targeted inhibition to restore osteoblast activity [38].

Mechanisms of Orthodontic Tooth Movement: Force-Induced Inflammation and Bone Remodeling

Orthodontic tooth movement (OTM) relies on the biological response to mechanical forces, typically 50–100 g, applied to teeth [7]. This induces compression and tension within the PDL, triggering a biphasic remodeling process: resorption on the pressure side and formation on the tension side [8]. Unlike periodontitis, OTM inflammation is aseptic, initiated by mechanotransduction rather than bacteria [1]. Mechanosensitive channels like Piezo1 and Piezo2 in PDL fibroblasts, osteocytes, and dental stem cells convert force into biochemical signals, activating pathways such as Ca2+-NFAT, MAPK, and Wnt/β-catenin [16, 39].

The inflammatory cascade begins acutely with resident cell activation, releasing prostaglandins (PGs), IL-1, IL-6, and TNF-α, which recruit innate immune cells (e.g., macrophages, neutrophils) [9,12]. Macrophages, particularly CCR2+ subsets, polarize to M1 pro-inflammatory phenotypes via NF-κB, upregulating RANKL and promoting osteoclastogenesis [40]. On the tension side, M2 macrophages and osteogenic factors (e.g., BMPs, IGF-1) facilitate osteoblast recruitment and bone apposition [11]. Autophagy and apoptosis balance is critical; in healthy periodontia, autophagy supports adaptive remodeling, but disruptions lead to excessive resorption [41].

Complications arise when inflammation persists, as in OIIRR, where heavy forces elevate cytokines, inducing clast-mediated root damage [12]. Nociceptors, expressing TRPV1 and neuropeptides like CGRP, not only signal pain but may modulate bone remodeling, suggesting neuroskeletal interactions [42]. Medications [43-45] influence OTM rates; anti-inflammatories like NSAIDs slow movement by inhibiting PGs, while statins like simvastatin enhance osteogenesis [10, 46].

Adjunctive therapies accelerate OTM by modulating inflammation. Photobiomodulation (PBM) integrates with mechanotransduction, enhancing early osteoclast recruitment and late repair via shared pathways like PI3K-Akt-mTOR and TGF-β/Smad [39]. MicroRNAs in gingival crevicular fluid (GCF) reflect inflammatory and remodeling dynamics, offering biomarkers for monitoring [47]. In varied periodontal conditions, active periodontitis exacerbates OTM imbalances, increasing bone loss and reducing osteogenic activity [41].

Shared Inflammatory Mediators and Pathways

Periodontitis and orthodontic tooth movement (OTM) converge on a network of common inflammatory mediators that orchestrate bone remodeling and tissue adaptation [1,2]. Both conditions involve the upregulation of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and IL-17, which act as central regulators of osteoclastogenesis. These cytokines activate intracellular signaling cascades such as NF-κB and MAPK pathways, leading to increased RANKL expression in stromal cells and osteocytes, ultimately promoting osteoclast differentiation and bone resorption [3,9]. In periodontitis, bacterial lipopolysaccharide (LPS) from pathogenic biofilms engages Toll-like receptors (TLRs), triggering these inflammatory responses. In contrast, OTM induces similar signaling through mechanotransduction via Piezo channels and other mechanosensitive receptors, highlighting a convergence of microbial and mechanical stress stimuli [16]. The RANKL/OPG ratio, which is critical for maintaining osteoclast–osteoblast balance, is shifted toward bone resorption in both conditions, although OTM preserves spatially

controlled remodeling, preventing generalized bone loss [4,8].

Metabolic reprogramming further links these processes. In periodontitis, increased glycolytic activity in immune cells fuels inflammatory responses, sustaining chronic tissue damage. Conversely, in OTM, lactate produced through glycolysis can act as a signaling metabolite that modulates local inflammation and may promote resolution phases [30]. Advanced glycation end products (AGEs), which accumulate during chronic inflammation, perpetuate osteolytic cycles in periodontitis. In diabetic patients, AGEs may also impair OTM through activation of the RAGE–NF-κB axis, potentially compromising orthodontic outcomes [17]. Genes associated with PANoptosis, including IL6 and CD14, indicate overlapping programmed cell death mechanisms, which may underlie increased susceptibility to comorbid tissue destruction [31].

Immune–stromal crosstalk plays a pivotal role in both contexts. Macrophages and T cells interact with periodontal ligament (PDL) fibroblasts, osteoblasts, and osteocytes, modulating extracellular matrix remodeling, autophagy, and apoptosis [11, 40, 41]. Osteocytes in both periodontitis and OTM secrete inhibitory molecules such as sclerostin and DKK-1, which antagonize Wnt-driven osteogenesis, thereby fine-tuning bone formation versus resorption [29, 38]. Additionally, adipose-derived signals in obesity exacerbate these shared inflammatory pathways, increasing cytokine burden and potentially worsening tissue remodeling outcomes [15]. This integrated network of inflammatory, metabolic, and immune–stromal interactions highlights the molecular and cellular overlap between periodontitis and OTM, suggesting that systemic factors and local tissue conditions can modulate both processes in concert.

Cellular Interactions in Inflammation and Bone Remodeling

Immune cells are central drivers of bone remodeling in both periodontitis and orthodontic tooth movement (OTM). Early responses are orchestrated by neutrophils and monocytes, which rapidly infiltrate affected tissues and release cytokines and chemokines to recruit additional immune effectors. These innate responses transition to adaptive immunity, where B and T lymphocytes sustain the chronic inflammatory phase and fine-tune osteoclast activity [6,13]. In OTM, specialized subsets such as γδ T cells and dendritic cells contribute to inflammation resolution and tissue remodeling, promoting controlled bone adaptation. Conversely, in periodontitis, a Th17-skewed response dominates, driving persistent inflammation and exacerbating tissue destruction [5,9].

Stromal cells, particularly periodontal ligament (PDL) fibroblasts and osteoblast-lineage cells, act as key signal transducers linking immune activity to structural remodeling. In periodontitis, these cells upregulate matrix metalloproteinases (MMPs) and other proteolytic enzymes, leading to extracellular matrix (ECM) degradation and connective tissue breakdown. During OTM, the same cells produce osteogenic factors such as osteopontin and bone morphogenetic proteins (BMPs), facilitating spatially controlled bone formation in response to mechanical stress [3,8]. Osteocytes, the principal mechanosensors within bone, orchestrate local remodeling through secretion of signaling molecules such as sclerostin and DKK-1; dysregulation of these pathways in either condition shifts the balance toward resorption [29].

Macrophage subsets play distinct roles in modulating bone remodeling. CCR2+ macrophages enhance osteoclast recruitment and NF-κB–mediated signaling, supporting OTM by coordinating resorption and formation phases. In periodontitis, M1-polarized macrophages dominate, promoting inflammatory bone loss through sustained cytokine secretion and tissue-degrading activity [40]. Neuro-immune interactions further amplify these processes; nociceptor activation and advanced glycation end-products (AGEs) influence local immune responses, heightening inflammation and altering bone metabolism [17, 42].

Impact of Systemic Factors on Shared Pathways

Systemic conditions such as diabetes and obesity exert profound effects on both periodontitis and OTM by amplifying shared inflammatory pathways [15, 17]. Hyperglycemia increases the formation of AGEs, which activate the RAGE receptor, enhancing NF-κB–driven inflammation in periodontitis and potentially impairing bone remodeling during OTM [17]. Obesity-related adipose inflammation elevates systemic cytokine levels, reducing resolution efficiency and further aggravating tissue destruction in both scenarios [15]. Aging and comorbidities, such as rheumatoid arthritis, increase circulating levels of DKK-1, linking systemic factors to localized bone loss [38].

Pharmacological and non-pharmacological interventions can modulate these shared pathways. For instance, statins have osteoanabolic effects that enhance bone formation during OTM [46]. Adjunct therapies such as low-intensity pulsed ultrasound (LIPUS) and photobiomodulation (PBM) influence cellular signaling, attenuate inflammation, and promote regeneration in both conditions [37, 39].

Nutraceuticals, including polyphenol-rich coffee extracts, provide anti-inflammatory benefits and modulate immune-stromal interactions [48-53], supporting tissue preservation [54].

Discussion

The interplay between periodontitis and orthodontic tooth movement (OTM) highlights a sophisticated osteoimmunological network in which inflammatory pathways orchestrate bone remodeling. As outlined in preceding sections, both conditions share overlapping mediators—including IL-1β, IL-6, TNF-α, and RANKL—that drive osteoclastogenesis through NF-κB and MAPK signaling cascades [1,6]. In periodontitis, these pathways are subverted by bacterial dysbiosis, resulting in persistent inflammation, enhanced osteoclast activity, and net alveolar bone loss [2,31]. In contrast, OTM induces a transient, controlled inflammatory response, finely balancing bone resorption and formation in accordance with mechanical forces [11,42]. The coexistence of periodontitis and OTM, however, can amplify inflammation beyond physiological levels, disrupting remodeling equilibrium, exacerbating alveolar bone destruction, and complicating orthodontic outcomes [10,12].

Clinically, this interplay underscores the importance of strategic management of periodontally compromised patients undergoing orthodontic therapy [55-58]. Evidence indicates that active periodontitis should be stabilized prior to initiating OTM to prevent excessive bone loss, as bacterial-mediated inflammation synergizes with mechanical stress to upregulate RANKL, sclerostin, and other inhibitory factors [7,15]. For example, studies have shown that orthodontic forces applied to inflamed periodontium enhance osteoclast activity through CRP–IL-6 signaling, resulting in imbalanced bone remodeling [17]. This emphasizes the need for integrated treatment protocols that combine periodontal regeneration, microbial control, and carefully timed OTM to minimize root resorption and optimize tooth stability [9, 16].

Systemic conditions further modulate these shared pathways. Obesity and hyperglycemia, through mechanisms such as AGE–RAGE signaling and adipokine-mediated inflammation, intensify local cytokine production, impair resolution, and prolong tissue destruction [39, 40]. Consequently, clinicians should assess metabolic comorbidities, potentially adjusting orthodontic force magnitudes or incorporating adjunctive therapies to mitigate risks [8, 38].

Therapeutic modulation of convergent pathways presents promising strategies for managing both periodontitis and OTM [59-64]. Targeting inflammasome activity or glycolytic reprogramming may attenuate excessive cytokine production and limit tissue damage [41, 65]. Adjunctive interventions—including low-intensity pulsed ultrasound (LIPUS) and photobiomodulation (PBM)—have demonstrated efficacy in regulating inflammation and enhancing bone regeneration via mechanotransduction and Wnt signaling pathways [29, 30]. In experimental contexts, recombinant proteins such as irisin have shown potential to protect against bone destruction during OTM in periodontitis by modulating immune responses and osteoclast activity [3]. Additionally, biomarkers such as DKK-1 or microRNAs in gingival crevicular fluid (GCF) offer tools for monitoring local inflammatory status and guiding personalized treatment approaches [5, 47]. Nonetheless, translation of these findings into clinical practice remains challenging, as most current evidence arises from animal models or in vitro studies, highlighting the need for robust clinical trials [4, 13].

Beyond clinical implications, the convergence of inflammatory and mechanical cues provides insight into broader osteoimmunological principles. Osteocytes, as central orchestrators of bone remodeling, respond to both microbial and mechanical stimuli by modulating RANKL/OPG ratios, linking local periodontal pathology to systemic bone homeostasis [37, 46]. This mechanism also suggests potential cross-talk with systemic conditions such as osteoporosis, wherein shared pathways of bone loss may amplify periodontal–orthodontic interactions [39]. Future research directions should explore epigenetic modifications, mechanotransduction–immune crosstalk, and microbiome modulation to disentangle these complex pathways, ultimately informing preventive and regenerative strategies [54, 66].

Conclusions and Future Directions

In conclusion, periodontitis and orthodontic tooth movement (OTM) share overlapping inflammatory pathways that critically regulate bone remodeling, with key mediators including pro-inflammatory cytokines, RANKL signaling, and immune–stromal interactions forming the central regulatory network. While periodontitis drives pathological tissue destruction and net bone loss, OTM utilizes controlled, transient inflammation to achieve therapeutic tooth repositioning. However, the convergence of these processes in comorbid scenarios increases the risk of exacerbated alveolar bone resorption, root damage, and

impaired orthodontic outcomes. A thorough understanding of these mechanisms is essential for designing safer orthodontic interventions in periodontally compromised patients, highlighting the importance of inflammation control, periodontal stabilization, and adjunctive therapies such as LIPUS, PBM, and pharmacologic modulators.

Looking forward, future research should focus on longitudinal, well-controlled clinical trials evaluating OTM outcomes following periodontal regeneration, ideally incorporating biomarkers such as DKK-1, RANKL/OPG ratios, or miRNAs to enable real-time monitoring of inflammatory and remodeling dynamics. Exploration of novel molecular targets—including mechanosensitive Piezo channels and PANoptosis-associated genes—may provide opportunities for dual-purpose therapeutic agents that modulate inflammation while supporting controlled bone remodeling. Furthermore, integrating AI-driven predictive modeling of force–inflammation interactions could facilitate personalized orthodontic strategies, optimizing force application and timing to preserve alveolar bone integrity. Collectively, these approaches hold promise not only for improving clinical outcomes in patients with concurrent periodontitis and OTM but also for advancing the broader understanding of osteoimmunological regulation in oral health.

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