Asian Journal of Periodontics and Orthodontics
2024, Volume 4, Page No: 285-295

Available online at: www.tsdp.net

ISSN: 3062-3499

Review Article

Cytokine and Chemokine Profiles in Orthodontic Treatment with Reduced Periodontal Support

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Received: 16 August 2024; **Revised:** 01 December 2024; **Accepted:** 02 December 2024

ABSTRACT

Orthodontic treatment in patients with reduced periodontal support, often resulting from a history of periodontitis, presents significant clinical challenges due to the heightened risk of alveolar bone loss and periodontal tissue destruction. This narrative review synthesizes recent evidence from peer-reviewed studies on the cytokine and chemokine profiles during orthodontic tooth movement (OTM) in the context of compromised periodontal health. Cytokines such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and chemokines including C-X-C motif ligand 1 (CXCL1), CXCL2, CXCL5, CXCL8, and CXCL10 play pivotal roles in mediating inflammation, immune cell recruitment, and bone remodeling. In animal models and in vitro studies, bacterial stimuli from periodontopathogens like *Fusobacterium nucleatum* and *Porphyromonas gingivalis* upregulate these mediators, exacerbating inflammatory responses. Mechanical forces associated with OTM can further modulate these profiles, sometimes amplifying bacteria-induced expression, as seen in elevated RANKL/OPG ratios leading to enhanced osteoclastogenesis. However, certain studies indicate that biomechanical strain may counteract proinflammatory effects under specific conditions. Key findings highlight protective interventions, such as recombinant irisin or semaphorin 3A, which mitigate bone loss by altering cytokine levels. This review underscores the interplay between microbial and mechanical signals in altering cytokine and chemokine dynamics, offering insights into molecular mechanisms that could inform safer orthodontic strategies for periodontally compromised patients. Understanding these profiles may facilitate targeted therapies to minimize adverse outcomes during treatment.

Keywords: Orthodontic tooth movement, Periodontitis, Cytokines, Chemokines, Inflammation, Alveolar bone remodeling

How to Cite This Article: Miller DR, Grant SL, Patel MJ, Brooks HK. Cytokine and Chemokine Profiles in Orthodontic Treatment with Reduced Periodontal Support. Asian J Periodont Orthodont. 2024;4:285-95. https://doi.org/10.51847/GekcnQJIK7

Introduction

Orthodontic treatment aims to correct malocclusions and improve dental aesthetics and function through controlled application of mechanical forces, which induce tooth movement via alveolar bone remodeling [1]. This process, known as orthodontic tooth movement (OTM), relies on a delicate balance of osteoclastic bone resorption on the compression side and osteoblastic bone formation on the tension side of the periodontal ligament (PDL) [1–3]. However, in patients with reduced periodontal support—typically defined as diminished alveolar bone height and attachment loss due to prior or ongoing periodontal disease—the application of orthodontic forces can exacerbate tissue destruction, leading to increased mobility, root resorption, and potential tooth loss [4–7].

Periodontitis, a chronic inflammatory condition driven by dysbiotic microbial biofilms, is a primary cause of reduced periodontal support [8]. It affects

approximately 40-50% of adults globally and is characterized by progressive loss of periodontal attachment and alveolar bone, mediated by an aberrant host immune response [8–10]. In such patients, orthodontic intervention must be approached cautiously, as the compromised periodontium may respond unpredictably to mechanical stress, potentially accelerating inflammatory processes [2, 11, 12]. Recent advancements in osteoimmunology have highlighted the critical role of cytokines and chemokines in bridging immune responses with bone metabolism in both periodontitis and OTM [1, 13].

Cytokines are small signaling proteins that orchestrate inflammation and tissue remodeling, while chemokines are a subset specialized in directing leukocyte migration [14]. In healthy OTM, cytokines like IL-1β, IL-6, and TNF-α facilitate osteoclast activation through the RANKL/OPG pathway, ensuring controlled bone turnover [1, 15]. In periodontitis, these same mediators, elicited by periodontopathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, drive excessive inflammation and bone resorption [16–19]. The convergence of these conditions—orthodontic forces superimposed on a periodontally inflamed environment—creates a complex interplay where microbial and mechanical stimuli may synergistically or antagonistically influence mediator profiles, ultimately affecting treatment outcomes [11, 20–22].

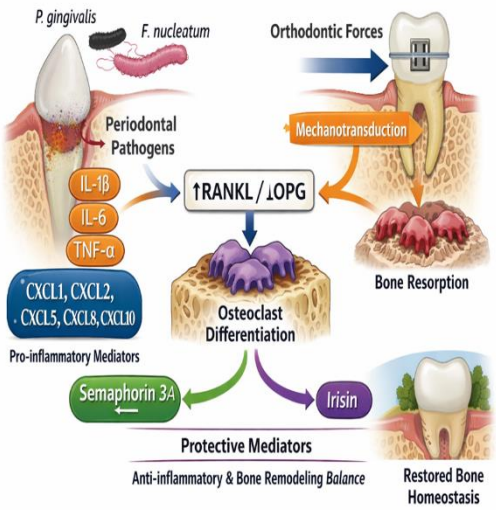

Figure 1. Integrated Pathophysiology of Orthodontic Tooth Movement in Reduced Periodontal Support

Despite growing interest, the specific cytokine and chemokine profiles in orthodontic treatment with reduced periodontal support remain underexplored, with most evidence derived from animal models and in vitro studies. This gap is significant, as understanding these profiles could guide risk assessment, treatment planning, and adjunctive therapies to mitigate adverse effects. The objectives of this narrative review are to: (1) provide an overview of the biological mechanisms underlying OTM and periodontitis; (2) examine recent evidence on cytokine and chemokine expressions in combined periodontal-orthodontic scenarios; (3) discuss the modulatory effects of mechanical forces on inflammatory responses; and (4) highlight clinical implications for managing patients with reduced periodontal support.

Biological mechanisms of orthodontic tooth movement

Orthodontic tooth movement is a sterile inflammatory process initiated by mechanical force application, leading to localized alveolar bone remodeling [1, 23, 24]. When force is applied, the PDL experiences compression and tension, triggering cellular responses in periodontal fibroblasts, osteoblasts, and osteoclasts [1, 25–27]. On the compression side, pressure induces hypoxia and cellular apoptosis, promoting osteoclastogenesis via upregulation of receptor activator of nuclear factor-κB ligand (RANKL) and downregulation of osteoprotegerin (OPG), its decoy receptor [1, 28–32]. Conversely, tension stimulates osteogenesis through increased expression of runt-related transcription factor 2 (RUNX2) and alkaline phosphatase (ALP) [25, 33, 34].

Cytokines play a central role in orchestrating these events. IL-1β and TNF-α, produced by PDL cells and resident immune cells, enhance RANKL expression, facilitating bone resorption [1, 35]. IL-6 contributes to both pro- and anti-inflammatory effects, modulating osteoclast differentiation and fibroblast activity [14, 36–38]. Chemokines, such as CXCL8 (IL-8), recruit neutrophils and macrophages to the site, amplifying the inflammatory cascade necessary for tissue adaptation [39]. In healthy periodontium, this response is self-limiting, resulting in net tooth displacement without permanent damage [1].

However, the magnitude and duration of force influence mediator profiles. Low-magnitude cyclic tensile strain (CTS), mimicking orthodontic forces, has been shown to alter cytokine responses in human PDL stromal cells (hPDLSCs) [2]. For instance, CTS of 6-12% elongation can inhibit TNF-α-induced IL-6 expression while enhancing IL-8 protein levels in a force-dependent manner [2]. This suggests that mechanical strain fine-tunes inflammatory signaling, potentially shifting from pro-resorptive to adaptive remodeling [2, 28, 40].

In vivo models corroborate these findings. Rat studies demonstrate that OTM induces acute cytokine surges,

with IL-1β and TNF-α peaking within days, correlating with osteoclast activation [25]. Epithelial and stromal cells contribute to this via pattern recognition receptor activation, though in sterile conditions, the response resolves rapidly [1]. Understanding these baseline mechanisms is crucial for contextualizing deviations in periodontally compromised scenarios, where pre-existing inflammation may disrupt this balance [11].

Pathophysiology of periodontitis and reduced periodontal support

Periodontitis arises from a dysbiotic shift in subgingival microbiota, where pathogens like *P. gingivalis* and *F. nucleatum* evade host defenses, eliciting chronic inflammation [8, 16, 41]. This leads to gingival pocket formation, attachment loss, and alveolar bone resorption, defining reduced periodontal support [5, 8]. The host response, rather than bacteria alone, drives tissue destruction through dysregulated cytokine networks [17, 42, 43].

Key cytokines include IL-1β, IL-6, and TNF-α, which promote matrix metalloproteinase activity and osteoclastogenesis via RANKL upregulation [1, 8]. In gingival crevicular fluid (GCF) from periodontitis sites, elevated IL-1β correlates with disease severity [5]. TNF-α exacerbates this by inducing apoptosis in PDL fibroblasts and enhancing proinflammatory loops [2, 35]. IL-6, often amplified by bacterial lipopolysaccharides (LPS), supports Th17 cell differentiation, perpetuating inflammation [36, 44].

Chemokines amplify leukocyte infiltration. CXCL1, CXCL5, CXCL8, and CXCL10 recruit neutrophils and monocytes, facilitating bacterial clearance but also collateral damage [39, 45]. CCL2 and CCL5 target monocytes and T cells, contributing to adaptive immunity [46]. In periodontitis, these chemokines are upregulated in gingival tissues, with *F. nucleatum* stimulating their expression via MAPK pathways [45–47].

Multi-omics analyses reveal integrated networks: transcriptomic data show upregulated immune genes like IL2RG and PDGFD, linked to metabolites such as deoxyinosine in ABC transporter pathways [42]. This metabolic-inflammatory axis underscores periodontitis as a systemic risk modifier [42].

In patients with treated but stabilized periodontitis, residual inflammation persists, increasing susceptibility to external stressors like orthodontic forces [5, 11]. Reduced bone density and altered PDL architecture impair force distribution, potentially accelerating resorption [20, 25]. Thus, periodontitis not only reduces support but primes the tissue for exaggerated responses to mechanical insults [11, 48].

Interplay between periodontitis and orthodontic tooth movement

The combination of periodontitis and OTM creates a synergistic environment where microbial inflammation and mechanical stress intersect, often leading to aggravated alveolar bone loss [11, 20, 25]. In rat models, experimental periodontitis induced by ligature placement increases bone resorption, which is further exacerbated by OTM [25, 49]. This interplay is mediated by heightened osteoclastogenesis, as evidenced by increased tartrate-resistant acid phosphatase (TRAP)-positive cells and elevated RANKL/OPG ratios [25, 29, 50].

Mechanical forces can modulate bacteria-induced responses. In vitro, CTS applied to hPDLSCs pre-stimulated with TNF-α downregulates VCAM-1 and ICAM-1 expression, potentially limiting leukocyte adhesion, but enhances IL-8 secretion in a magnitude-dependent fashion [2]. This suggests force may amplify chemokine-driven recruitment while suppressing adhesion molecules [2].

In vivo, orthodontic forces in periodontally inflamed rats reduce bacteria-upregulated cytokines like IL-6 and CXCL2, yet overall bone loss intensifies [20, 29, 51]. Semaphorin 3A administration in such models protects against loss by suppressing TRAP cells and proinflammatory cytokines (IL-1β, IL-6, TNF-α) [29]. Similarly, recombinant irisin ameliorates bone destruction by elevating OPG/RANKL ratios and reducing cytokine levels [25].

Human studies echo these findings: in stabilized periodontitis patients undergoing orthodontics, poor oral hygiene correlates with higher GCF IL-1β and pain, linking residual inflammation to adverse outcomes [5]. Mechanical force alone induces osteoclastogenesis independently of inflammation, but combined stimuli enhance it via distinct pathways [28]. Growth factors like GDF15 support LPS-induced inflammation in compressed PDL fibroblasts, upregulating IL-6 and IL-8 [35]. This indicates that compressive forces exacerbate pathogen-driven responses, potentially via MAPK signaling [35].

Overall, the interplay heightens resorptive tendencies, emphasizing the need for periodontal stability before OTM [11, 20].

In patients presenting with compromised periodontal support, cytokine dynamics during orthodontic tooth movement (OTM) demonstrate a pronounced and dysregulated inflammatory response compared with periodontally healthy conditions [1, 2, 5]. The application of orthodontic forces in a pre-inflamed periodontal environment amplifies local immune signaling, thereby accelerating tissue remodeling and, in some cases, exacerbating periodontal breakdown.

Among the investigated mediators, interleukin-1β (IL-1β) consistently emerges as a central regulator of inflammation-induced bone resorption. Experimental rat models combining periodontitis with OTM show a marked increase in gingival IL-1β levels following force application, with expression levels positively correlating with alveolar bone loss and osteoclastic activity [5, 25]. These findings are supported by human studies in which gingival crevicular fluid (GCF) samples from periodontitis patients undergoing orthodontic treatment reveal elevated IL-1β concentrations, particularly during the early phases of tooth movement [5]. Clinically, heightened IL-1β levels have been associated with increased pain perception and suboptimal oral hygiene, underscoring its relevance as both a biological and symptomatic marker during treatment [5].

Interleukin-6 (IL-6) displays a context-dependent and mechanosensitive response in environments with reduced periodontal support. In vitro studies using human periodontal ligament stem cells (hPDLSCs) demonstrate that tumor necrosis factor-α (TNF-α) robustly induces IL-6 expression, whereas cyclic tensile strain (CTS) suppresses this induction at both transcriptional and protein levels, suggesting that controlled mechanical loading may exert anti-inflammatory effects under certain conditions [2]. In contrast, in vivo models combining experimental periodontitis with orthodontic force application consistently report IL-6 upregulation, implicating this cytokine in the promotion of Th17-mediated inflammatory pathways and progressive periodontal destruction [1, 49]. Additional evidence indicates that growth differentiation factor-15 (GDF15) further amplifies IL-6 expression in lipopolysaccharide (LPS)-stimulated and mechanically compressed gingival fibroblasts, highlighting a synergistic interaction between bacterial challenge and orthodontic force [35].

TNF-α represents another pivotal cytokine involved in inflammation-driven tissue remodeling during OTM in periodontally compromised settings. Mechanical compression of periodontal ligament (PDL) cells enhances TNF-α expression, which in turn promotes apoptotic signaling and upregulates receptor activator of nuclear factor-κB ligand (RANKL), thereby accelerating osteoclast differentiation and activity [28, 36]. Animal studies further demonstrate that pharmacological or biological modulation of TNF-α, including the application of protective agents such as semaphorin 3A, effectively attenuates inflammatory bone loss in periodontitis-OTM models [49]. These findings underscore TNF-α as a potential therapeutic target for mitigating adverse periodontal outcomes during orthodontic treatment.

Beyond classical pro-inflammatory mediators, other cytokines such as interleukin-17 (IL-17) and interferon-γ (IFN-γ) are also significantly elevated in inflamed gingival tissues subjected to orthodontic forces [49]. These cytokines contribute to T-cell activation and perpetuation of local immune responses, further intensifying periodontal tissue degradation. Emerging regulatory mechanisms involving non-coding RNAs have also been identified; for instance, circular RNAs such as circ_0062491 have been shown to attenuate LPS-induced IL-6 expression through the miR-498/SOCS6 signaling axis, suggesting an intrinsic modulatory network capable of dampening excessive inflammation [44].

Recent multi-omics approaches provide additional insight into the complex cytokine landscape associated with periodontitis progression, identifying molecules such as IL2RG as influential regulators of immune responses [42]. Although these findings primarily pertain to periodontitis, their mechanistic relevance likely extends to orthodontic contexts involving reduced periodontal support. Collectively, current evidence indicates that cytokine profiles during OTM in periodontally compromised patients are characterized by sustained upregulation of pro-resorptive and pro-inflammatory mediators, with expression patterns influenced by force magnitude, mechanical loading duration, and bacterial burden [2, 28].

Chemokine profiles in orthodontic treatment with reduced periodontal support

Chemokines play a pivotal role in regulating immune cell recruitment and spatial organization of inflammatory responses during orthodontic tooth movement (OTM in the presence of reduced periodontal support, particularly under conditions of combined periodontitis and mechanical loading [39, 45, 46]. These molecules orchestrate leukocyte trafficking to periodontal tissues, thereby influencing both inflammatory intensity and tissue remodeling outcomes.

CXCL2 has been extensively studied in this context and demonstrates a dynamic response to both bacterial challenge and orthodontic force application. In rat models of experimental periodontitis, CXCL2 expression is significantly elevated in gingival tissues, reflecting heightened neutrophil recruitment [20]. The application of orthodontic forces further enhances CXCL2 levels; however, intriguingly, mechanical loading can partially counteract bacteria-induced overexpression, suggesting a modulatory role of force on chemokine signaling [20]. These in vivo observations are corroborated by in vitro findings,

where Fusobacterium nucleatum stimulation robustly induces CXCL2 expression in periodontal ligament (PDL) fibroblasts, while concurrent exposure to cyclic tensile strain (CTS) suppresses this chemokine at both transcriptional and protein levels [20].

Similar regulatory patterns have been observed for other key chemokines, including CXCL1, CCL2, and CCL5. These mediators are strongly upregulated in response to bacterial components and inflammatory stimuli, promoting monocyte and lymphocyte recruitment into periodontal tissues [46]. However, biomechanical forces applied to periodontal cells attenuate this upregulation, indicating that orthodontic loading may dampen chemokine-driven immune cell infiltration under certain conditions [46]. Notably, animal studies demonstrate that despite reduced chemokine expression under combined bacterial and mechanical stimuli, alveolar bone loss continues to progress, suggesting that tissue destruction during OTM with reduced periodontal support may proceed through recruitment-independent or cytokine-dominated mechanisms [46].

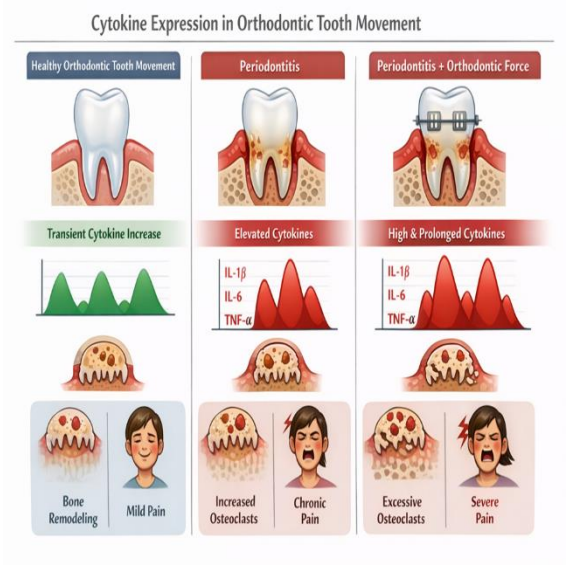

Figure 2. Cytokine Expression Patterns During Orthodontic Tooth Movement With Reduced Periodontal Support

In contrast, other chemokines appear to be enhanced rather than suppressed by the interaction between bacterial signals and mechanical forces. CXCL5, CXCL8, and CXCL10 are regulated primarily through mitogen-activated protein kinase (MAPK) signaling pathways. In gingival keratinocytes, F. nucleatum markedly increases the expression of these chemokines, and the application of orthodontic force further amplifies this response [45]. This force-enhanced chemokine expression may intensify neutrophil and T-cell recruitment, thereby aggravating local inflammation and contributing to periodontal breakdown in patients with reduced periodontal support [45].

Additional chemokine-related pathways have also been implicated in inflammation-associated tissue damage. Activation of the chemerin/ChemR23 axis induces effects analogous to those of CCL2, promoting macrophage recruitment and upregulating TNF-α and IL-6 through the phosphoinositide 3-kinase (PI3K)-Akt signaling pathway [36]. This axis has been linked to increased osteoclastic activity and root resorption during orthodontic treatment, highlighting its pathological relevance in compromised periodontal environments [36]. Furthermore, multi-omics analyses reveal that chemokines are closely integrated with metabolic and immune-regulatory pathways, suggesting that systemic metabolic states may amplify chemokine-mediated inflammatory responses during periodontitis and OTM [42].

Collectively, chemokine profiles in orthodontic treatment with reduced periodontal support indicate a finely balanced but highly context-dependent regulatory network. While chemokines facilitate immune cell recruitment essential for tissue remodeling, mechanical forces can significantly modulate their expression, potentially altering the spatial and temporal patterns of periodontal destruction [20, 45, 46].

Modulatory effects of mechanical forces on inflammatory mediators

Mechanical forces applied during orthodontic treatment exert profound effects on inflammatory mediator expression within the inflamed periodontium, with outcomes varying according to cell type, force magnitude, and inflammatory status [2, 28, 35]. These forces do not act solely as passive drivers of tooth movement but actively interact with immune signaling pathways to either attenuate or exacerbate inflammation.

In vitro studies demonstrate that CTS exerts anti-inflammatory effects in human periodontal ligament stem cells (hPDLSCs) by inhibiting TNF-α-induced expression of interleukin-6 (IL-6) and vascular cell adhesion molecule-1 (VCAM-1) [2]. This suppression is mediated through the MEK1/2 signaling pathway, suggesting that controlled tensile forces may reduce leukocyte adhesion and inflammatory amplification under specific conditions [2]. Such findings support the concept that biomechanical stimuli can actively counterbalance pro-inflammatory cytokine signaling in periodontal tissues.

Conversely, in lipopolysaccharide (LPS)-stimulated gingival fibroblasts, compressive forces have been

shown to enhance inflammatory mediator production. Mechanical compression augments growth differentiation factor-15 (GDF15)-supported IL-6 and IL-8 expression, thereby intensifying inflammatory signaling in an already challenged microenvironment [35]. This divergence highlights the critical influence of force type and direction on cellular responses during orthodontic treatment in periodontitis-affected tissues.

In vivo evidence further underscores the dual nature of mechanical force modulation. Orthodontic loading has been shown to reduce bacteria-induced IL-6 and CXCL2 expression in periodontal tissues, yet simultaneously increase receptor activator of nuclear factor-κB ligand (RANKL) expression independently of inflammatory cytokines [20, 28]. This dissociation suggests that bone resorption during OTM may proceed through mechanotransduction pathways that are not entirely dependent on classical inflammatory mediators.

Emerging therapeutic strategies exploit these modulatory effects of force. Molecules such as irisin and semaphorin 3A leverage mechanical signaling pathways to suppress pro-inflammatory cytokine expression and protect alveolar bone integrity in experimental models [25, 49]. These findings point toward the potential for biologically informed orthodontic force application to minimize adverse periodontal outcomes.

Importantly, force magnitude remains a critical determinant of inflammatory responses. Higher mechanical strains are associated with increased IL-8 production, which may enhance immune cell recruitment and perpetuate inflammation [2]. Taken together, current evidence indicates that mechanical forces can either mitigate or exacerbate inflammatory mediator profiles during orthodontic treatment with reduced periodontal support, depending on the biological context, microbial burden, and mechanical parameters involved [1, 11, 28].

The integration of orthodontic treatment in patients with reduced periodontal support necessitates a comprehensive understanding of the underlying molecular dynamics, particularly the cytokine and chemokine profiles that govern inflammatory and remodeling processes. As delineated in the preceding sections, OTM in a periodontally compromised environment is characterized by an amplified inflammatory response, where microbial stimuli from residual dysbiosis interact with biomechanical forces to modulate mediator expression [1, 11]. This discussion synthesizes the key findings from recent literature, highlighting the synergies and antagonisms in cytokine/chemokine networks, the modulatory influence of mechanical stress, clinical implications, limitations of current evidence, and potential therapeutic avenues.

Central to the pathophysiology is the exacerbation of pro-resorptive cytokines such as IL-1β, IL-6, and TNF-α in the presence of both periodontal inflammation and orthodontic forces [1, 2, 5]. In healthy OTM, these cytokines facilitate controlled osteoclastogenesis via the RANKL/OPG axis, but in reduced periodontal support, their upregulation—often driven by pathogens like *P. gingivalis* and *F. nucleatum*—leads to excessive alveolar bone loss [8, 16]. For instance, in vitro studies demonstrate that TNF-α stimulation of hPDLSCs under CTS results in suppressed IL-6 expression at transcriptional and translational levels, suggesting a protective biomechanical effect against inflammation [2]. However, this is contrasted by in vivo observations where combined periodontitis-OTM models show persistent elevation of IL-6, contributing to Th17-mediated tissue destruction [1, 35]. Such discrepancies underscore the context-dependent nature of cytokine responses: while low-magnitude forces may dampen proinflammatory signals in isolated cells, the multifaceted in vivo milieu—including bacterial LPS and compressive strains—often amplifies them [28, 35].

Chemokine profiles similarly reflect this complexity, with molecules like CXCL2, CXCL8, and CXCL9 playing pivotal roles in leukocyte recruitment and activation [8, 39]. Bacterial induction of CXCL9-CXCR3 signaling in apical periodontitis models promotes macrophage infiltration and bone resorption, and its inhibition attenuates disease progression [39]. In orthodontic contexts with reduced support, mechanical forces can paradoxically reduce bacteria-induced chemokine expression, as seen with CTS inhibiting *F. nucleatum*-stimulated CXCL2 in PDL fibroblasts [16, 20]. Yet, this does not always translate to reduced tissue damage; persistent RANKL elevation independent of chemokine modulation may sustain osteoclast activity [28]. These findings align with osteoimmunological frameworks, where cytokines and chemokines bridge innate immunity with bone metabolism, often tipping the balance toward catabolism in compromised periodontium [1, 17].

The interplay between microbial and mechanical cues is further illuminated by studies on cellular players such as macrophages and PDL stem cells [20, 28]. Macrophages exhibit phenotypic plasticity, shifting from M1 (proinflammatory) to M2 (reparative) under certain conditions, with PDLSCs promoting M2 polarization via anti-inflammatory cytokines like IL-10 and TGF-β [28]. In periodontitis-OTM, however, hyperglycemia or palmitate exposure can skew toward

M1 dominance, exacerbating COX2/PGE2-mediated hyperinflammation [46, 52].

Epigenetic mechanisms, such as H3K27 trimethylation, repress anti-inflammatory pathways, amplifying IL-6 and other mediators under dual stress [52]. Autophagy in PDL fibroblasts also emerges as a regulator, inducing IL-6 expression under mechanical overload and influencing osteoclastogenesis [35]. These molecular insights suggest that orthodontic forces in reduced support may not only accelerate bone loss but also impair regenerative potential, as evidenced by diminished osteogenic differentiation in PDL cells from stabilized periodontitis patients [53].

Clinical studies corroborate these mechanistic observations, particularly through biomarker analysis in GCF and saliva [5, 44, 54]. Elevated IL-1β in GCF during early OTM phases in periodontitis patients correlates with pain and poor hygiene, serving as a predictor of adverse outcomes [5]. Comparative analyses of fixed appliances versus aligners reveal increased inflammatory markers (e.g., IL-6, MMP-8) with conventional brackets, potentially due to greater plaque accumulation and force distribution [44, 55]. Moreover, matrix metalloproteinases (MMPs) like MMP-8 and MMP-9, often co-regulated with cytokines, exhibit heightened activity in periodontal pathologies, offering diagnostic utility for monitoring OTM progress [56].

Despite these advances, several limitations persist in the evidence base. Predominantly, studies rely on animal models (e.g., ligature-induced periodontitis in rodents) or in vitro systems, which, while informative, may not fully recapitulate human pathophysiology due to species-specific immune responses and force magnitudes [1, 25]. Human investigations are scarce and often limited to biomarker profiling without longitudinal outcomes on bone loss or tooth stability [5, 44]. Furthermore, variability in orthodontic protocols—such as force levels, appliance types, and patient compliance—confounds comparisons [2, 57].

Clinically, these profiles inform risk stratification and management strategies for periodontally compromised patients. Pre-treatment periodontal stabilization is imperative to mitigate exaggerated cytokine surges [11, 25]. Adjunctive therapies targeting mediators, such as semaphorin 3A to suppress IL-1β/TNF-α or photobiomodulation to accelerate OTM while reducing inflammation, show promise [8, 25, 58] Monitoring GCF cytokines could enable personalized force adjustments, minimizing root resorption and attachment loss [14, 28]. Additionally, considering systemic factors like estrogen levels, which modulate resorption via cytokine pathways, is crucial for postmenopausal patients [14].

Table 1. Summary of Experimental and Clinical Evidence

Study (Author, Year)	Model	Orthodontic Force Type	Periodontal Condition	Key Cytokine/Chemokine Findings	Main Outcome
Rat study, 2019	Animal	Continuous force	Experimental periodontitis (ligature-induced)	↑ IL-1β, ↑ TNF-α, ↑ CXCL2	Enhanced osteoclast activity, alveolar bone loss
hPDLSC study, 2020	In vitro	Cyclic tensile strain 6–12%	TNF-α pre-stimulation	↓ IL-6, ↑ IL-8, ↓ VCAM-1/ICAM-1	Anti-inflammatory modulation, selective chemokine enhancement
Rat study, 2021	Animal	Orthodontic force + semaphorin 3A	Periodontitis	↓ IL-1β, ↓ TNF-α, ↓ TRAP-positive cells	Protection against alveolar bone loss
Human study, 2022	Clinical	Fixed orthodontic appliance	Stabilized periodontitis	↑ GCF IL-1β, ↑ pain	Correlation between residual inflammation and adverse outcomes
Gingival fibroblast study, 2022	In vitro	Compressive force	LPS-stimulated fibroblasts	↑ IL-6, ↑ IL-8, ↑ GDF15	Enhanced inflammatory signaling
Human study, 2023	Clinical	Aligners vs. fixed appliance	Periodontitis	↑ IL-6, ↑ MMP-8 (fixed > aligners)	Higher inflammatory marker expression in conventional brackets
Multi-omics study, 2021	Animal/ In vitro	Orthodontic force	Periodontitis	Upregulated IL2RG, CXCL9 pathways	Links immune and metabolic responses to bone resorption

In summary, the cytokine and chemokine landscapes in OTM with reduced periodontal support reveal a precarious balance, where mechanical modulation offers both risks and opportunities for intervention. Addressing evidential gaps through integrated multi-omics and clinical trials will enhance therapeutic precision.

Conclusion

This narrative review elucidates the intricate cytokine and chemokine profiles during orthodontic treatment in patients with reduced periodontal support, emphasizing their roles in inflammation, immune recruitment, and bone remodeling. Key cytokines (IL-1β, IL-6, TNF-α) and chemokines (CXCL2, CXCL8, CXCL9) are upregulated by the synergy of microbial dysbiosis and mechanical forces, predisposing to accelerated alveolar bone loss [1, 8, 39]. However, biomechanical strain can attenuate certain proinflammatory responses, suggesting adaptive potential [2, 20]. Protective agents like semaphorin 3A and irisin analogs mitigate these effects by restoring RANKL/OPG balance [25].

Future research should prioritize longitudinal human studies to validate animal/in vitro findings, incorporating advanced biomarkers and imaging for real-time monitoring [5, 44]. Exploring targeted inhibitors of cytokine pathways, such as anti-CXCL9 therapies, and integrating nanotechnology for localized delivery could revolutionize management [39, 59].

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Alghamdi B, Ni J, Graves DT. Osteoimmunology in Periodontitis and Orthodontic Tooth Movement. Curr Osteoporos Rep. 2023;21(2):128-146. doi: 10.1007/s11914-023-00774-x.
2. Zhao Z, Schröder N, Blawat K, Nokhbehsaim M, Deschner J, Jäger A, et al. Cyclic tensile strain-induced yes-associated protein activity modulates the response of human periodontal ligament mesenchymal stromal cells to tumor necrosis factor-α. Arch Oral Biol. 2022;143:105527. doi: 10.1016/j.archoralbio.2022.105527.
3. Pruthi DS, Nagpal P, Yadav A, Bansal B, Pandey M, Agarwal N. Emerging Trends in Early-Onset Adult Cancers: A Case Series. Arch Int J Cancer Allied Sci. 2022;2(1):42-8. https://doi.org/10.51847/c8BdxewwGL
4. Singh G, Goel N, Singh A, Gera R. Factors Influencing Time to Diagnosis and Treatment in Pediatric Acute Leukemia: Insights from an Indian Cohort. Arch Int J Cancer Allied Sci. 2022;2(2):37-44. https://doi.org/10.51847/FWfHO4xMyB
5. Baeshen HA. Assessment of salivary pro inflammatory cytokines profile level in patients treated with labial and lingual fixed orthodontic appliances. PLoS One. 2021;16(4):e0249999. doi: 10.1371/journal.pone.0249999.
6. Su Z, Qin M, Hu D. Impact of Lecture Versus Group Discussion-Based Ethics Training on Nurses' Moral Reasoning, Distress, and Sensitivity: A Randomized Clinical Trial. Asian J Ethics Health Med. 2024;4:81-96. https://doi.org/10.51847/iBvPMrJSLE
7. Lin C, Frygner-Holm S. Determining Reasonable Practice: Insights into the Ethical Decision-Making of Vascular Surgeons in Routine Care. Asian J Ethics Health Med. 2024;4:125-35. https://doi.org/10.51847/o2YjbB9K3H
8. Ramadan DE, Hariyani B, Yubiliana R, Rosuliana RW, Diyatri I. Cytokines and Chemokines in Periodontitis. Eur J Dent. 2020;14(3):483-495. doi: 10.1055/s-0040-1712718.
9. Iqbal B, Dey I, Mushtaq I. Exploring Erdheim-Chester Disease: A Histopathological Insight into a Rare Disorder. J Med Sci Interdiscip Res. 2022;2(2):26-30. https://doi.org/10.51847/S7n4idY6zO
10. Noor H, Coțe A, Micu A, Pirvut V. Cognitive Disorders and Psychological Problems Linked to Surgery: Anesthesia-Related Cognitive Issues and Prevention Strategies. J Med Sci Interdiscip Res. 2023;3(2):65-74. https://doi.org/10.51847/I4A6kFIiku
11. Chaushu S, Klein Y, Mandelbaum R, Chaushu G, Palti R, Fleissig O. Immune Changes Induced by Orthodontic Forces: A Critical Review. J Dent Res. 2022;101(1):11-20. doi: 10.1177/00220345211016285.
12. Fredriksson U, Kusanagi KN, Gougoulakis P, Matsuda Y, Kitamura Y. Comparative Analysis of Pharmacy Education Programs: Curriculum and Academic Components in EU Countries and Ukraine. Ann Pharm Educ Saf Public Health

Advocacy. 2023;3:1-11. https://doi.org/10.51847/F99XGyrP86
13. Iurii K, Reva T, Stuchynska N, Pavlo M, Inna K, Chkhalo O. Digital Competence and Information Technology in Pharmacy as Foundations of Professional Competence in Distance Learning for Master of Pharmacy. Ann Pharm Educ Saf Public Health Advocacy. 2023;3:50-7. https://doi.org/10.51847/5Q3yJiWkQG
14. Deng L, Guo J. Estrogen effects on orthodontic tooth movement and orthodontically-induced root resorption. Arch Oral Biol. 2020;118:104840. doi: 10.1016/j.archoralbio.2020.104840.
15. Çınaroğlu M, Ahlatcıoğlu EN, Prins J, Nan M. Psychological Challenges in Cancer Patients and the Impact of Cognitive Behavioral Therapy. Int J Soc Psychol Asp Healthc. 2023;3:21-33. https://doi.org/10.51847/ZDLdztUSsw
16. Groeger S, Domann E, Gonzales JR, Chakraborty T, Meyle J. Pathogenic Mechanisms of Fusobacterium nucleatum on Oral Epithelial Cells. Front Oral Health. 2022;3:831607. doi: 10.3389/froh.2022.831607.
17. Wielento A, Lukomska-Szymanska M, Zarow M, Sokolowski J, Lapinska B. The Role of Gingival Fibroblasts in the Pathogenesis of Periodontitis. J Dent Res. 2023;102(5):489-496. doi: 10.1177/00220345231151921.
18. Zhang Y, Pan A, Wang J, Pan X, Chen J, Li H, et al. Assessing the Role of Play Therapy in Easing Anxiety and Despair in Children with Cancer. Int J Soc Psychol Asp Healthc. 2023;3:40-8. https://doi.org/10.51847/S7vZ2lgmuc
19. Yang J, Tang Z, Shan Z, Leung YY. Integrating Rapid Maxillary Expansion and Le Fort Osteotomy for Esthetic Rehabilitation: A Clinical Case Report. J Curr Res Oral Surg. 2023;3:22-6. https://doi.org/10.51847/E0OEwI52jo
20. Yin L, Cheng N, Tong W, Chu X, Li W, Zhang F, et al. Macrophages in periodontitis: A dynamic shift between tissue destruction and repair. Jpn Dent Sci Rev. 2022;58:336-347. doi: 10.1016/j.jdsr.2022.10.002.
21. Müller FK, Romano LF, Bekele TM. Predictors of 5-Year Survival in Oral Cancer Patients in Mongolia: Age, Urban Residence, Stage, and Recurrence as Key Risk Factors. J Curr Res Oral Surg. 2023;3:61-72. https://doi.org/10.51847/JBLxLMIhUy
22. Wal A, Wal P, Pandey A, Vig H, Ved A, Samal HB. Exploring Myasthenia Gravis Subtypes: Impact on Pregnancy and Recent Treatment Advancements. Interdiscip Res Med Sci Spec. 2023;3(1):26-38. https://doi.org/10.51847/LfGflzk9de
23. Nyamagoud SB, Swamy AHV, Chacko A, James J. A Case Report on Actinomycetoma of the Left Foot: Highlighting a Neglected Tropical Disease and the Consequences of Poor Medication Adherence. Interdiscip Res Med Sci Spec. 2024;4(2):41-7. https://doi.org/10.51847/UcEjBW4qBs
24. Boas GRV, Silveira APSD, Farinelli BCF, Cardoso CAL, Arce E, Oesterreich SA. The Antidepressant Effects of Melilotus officinalis Fruit Ethanolic Extract: A Mouse Model Study. Spec J Pharmacogn Phytochem Biotechnol. 2024;4:21-8. https://doi.org/10.51847/veH0VxtfZi
25. Satomi K, Miyahara H, Katsuyama E, Miyazaki M, Kobayashi H, Nishimura Y, et al. Semaphorin 3A protects against alveolar bone loss during orthodontic tooth movement in mice with periodontitis. J Periodontal Res. 2022;57(5):991-1002. doi: 10.1111/jre.13038.
26. Hong L, Xie X, Xie H, Zhao J, Sui L, Li S. Investigation of the Mechanistic Action of Yinaoan Capsules Hospital Formulation in Epilepsy Therapy Through Multi-Pathway Network Pharmacology Approaches. Spec J Pharmacogn Phytochem Biotechnol. 2023;3:39-50. https://doi.org/10.51847/DtzA0Txe1h
27. Vadla S, Putta V, Nadipudi S, Bilakanti S, Kudumula N. UV-Spectrophotometric Method Development and Validation for Quantifying Dapagliflozin in Bulk and Pharmaceutical Formulations. Pharm Sci Drug Des. 2023;3:31-8. https://doi.org/10.51847/r8kjhgT7Qr
28. Liu J, Li Q, Chen S, Gao L, Wu L, Song Y, et al. Periodontal ligament stem cells promote polarization of M2 macrophages. J Leukoc Biol. 2022;111(6):1185-1197. doi: 10.1002/JLB.1MA1220-853RR.
29. Guzek K, Stelmach A, Rożnowska A, Najbar I, Cichocki Ł, Sadakierska-Chudy A. A Preliminary Investigation of Genetic Variants Linked to Aripiprazole-Induced Adverse Effects. Ann Pharm Pract Pharmacother. 2023;3:40-7. https://doi.org/10.51847/ZT28xcs95J
30. Wong TY, Sung JJY, Lau J, Chan PKS. Comparative Diagnostic Performance of ^{68}Ga-PSMA and ^{68}Ga-DOTA-RM2 PET/MRI in the Evaluation of Recurrent Prostate Cancer. Asian J Curr Res Clin Cancer. 2023;3(1):105-19. https://doi.org/10.51847/Ibu5Dgs8Wp

31. Al-Twaijri SA, AlKharboush GH, Alohali MA, Arab IF, Alqarni RH, Alharbi MS. Application of Lasers for Soft Tissues in Orthodontic Treatment: A Narrative Review. Bull Pioneer Res Med Clin Sci. 2024;4(1):1-6. https://doi.org/10.51847/OfwnmXu8c3
32. Eteng OE, Bassey N, Eteng EI, Okwe EP, Ekpo G, Ekam V, et al. Effect of Vanillic Acid and Morin on Bisphenol S and Diethyl Phthalate Induce-Nephrotoxicity in Male Rats. Bull Pioneer Res Med Clin Sci. 2023;3(1):25-34. https://doi.org/10.51847/JipHmYy6fi
33. Iftode C, Iurciuc S, Marcovici I, Macasoi I, Coricovac D, Dehelean C, et al. Therapeutic Potential of Aspirin Repurposing in Colon Cancer. Pharm Sci Drug Des. 2024;4:43-50. https://doi.org/10.51847/nyDxRaP7Au
34. Qiao J, Luo B, Ming J, Zhou S, Chen Y, Zhang X. Prevalence and Implications of Non-Prescription Antibiotic Dispensing in Baghdad Community Pharmacies. Ann Pharm Pract Pharmacother. 2024;4:34-41. https://doi.org/10.51847/5SuGTfpren
35. Mayr A, Blawat K, Hardt M, Kirschneck C, Nokhbehsaim M, Behl C, et al. Autophagy Induces Expression of IL-6 in Human Periodontal Ligament Fibroblasts Under Mechanical Load and Overload and Effects Osteoclastogenesis in vitro. Front Physiol. 2021;12:716441. doi: 10.3389/fphys.2021.716441.
36. Li Y, Dong G, Wu Y, Zhao Y, Shi Z, Pak HY, et al. Inflammasomes in Alveolar Bone Loss. Front Immunol. 2021;12:691013. doi: 10.3389/fimmu.2021.691013.
37. Petrauskas G, Kazlauskas R, Jonaitis L. Molecular Regulators of Small Extracellular Vesicle Biogenesis in Colorectal Cancer: Associations with Tumor Expression, Plasma Levels, and Patient Survival. Asian J Curr Res Clin Cancer. 2024;4(2):145-57. https://doi.org/10.51847/1ABppHJUxE
38. Graefen B, Alakbarova G, Hasanli S, Khalilova A, Fazal N. From Campus to Cloud: Transforming Office Hours in a Post-COVID World. Bull Pioneer Res Med Clin Sci. 2024;4(2):48-55. https://doi.org/10.51847/Db2AlNiFKM
39. Hasegawa T, Chosa N, Asakawa T, Yoshimura Y, Ishisaki A, Tanaka M. Inhibition of the CXCL9-CXCR3 axis suppresses the progression of experimental apical periodontitis by blocking macrophage migration and activation. Sci Rep. 2021;11(1):2613. doi: 10.1038/s41598-021-82167-7.
40. Cirik VA, Aksoy B, Bulut E. Studying the Relationship between the Attitude towards Gender Roles of Parents and the Quality of Parent-Child Relationship in Nurses. J Integr Nurs Palliat Care. 2023;4:30-7. https://doi.org/10.51847/90pkztCQgl
41. Chang J, Vivekanand W. Studying the Relationship between Moral Sensitivity and Moral Performance of Nursing Students. J Integr Nurs Palliat Care. 2024;5:62-7. https://doi.org/10.51847/IljINMMyUU
42. Yamashiro K, Ideguchi H, Aoyagi H, Yoshihara H, Nishi M, Suzuki T, et al. High Mobility Group Box 1 Expression in Oral Inflammation and Regeneration. Front Immunol. 2020;11:1461. doi: 10.3389/fimmu.2020.01461.
43. Thazha SK, Cruz JP, Alquwez N, Scaria B, Rengan SS, Almazan JU. Studying the Attitude and Knowledge of Nursing Students towards the Physical Restraint Use in Patients. J Integr Nurs Palliat Care. 2023;4:1-5. https://doi.org/10.51847/cFz2ew4AK8
44. Kamran MA, Alnazeh AA, Almagbol M, Almoammar S, Alhaizaey AHA, Alshahrani I. Role of six cytokines and bone metabolism biomarkers in gingival crevicular fluid in patients undergoing fixed orthodontic appliance treatment in comparison with aligners: a clinical study. Angle Orthod. 2023;93(3):335-340. doi: 10.2319/091722-649.1.
45. Groeger S, Meyle J. Oral Mucosal Epithelial Cells. Front Immunol. 2019;10:208. doi: 10.3389/fimmu.2019.00208.
46. Plemmenos G, Piperi C. Central Regulatory Role of Cytokines in Periodontitis and Targeting Options. Curr Med Chem. 2021;28(15):3032-3058. doi: 10.2174/0929867327666200824112732.
47. Guillen J, Pereira R. Institutional Influence on Gender Entrepreneurship in Latin America. Ann Organ Cult Leadersh Extern Engagem J. 2024;5:28-38. https://doi.org/10.51847/RaQltcyzXu
48. Oran IB, Azer OA. The Evolution of Turkey's Role in International Development: A Globalization Perspective. Ann Organ Cult Leadersh Extern Engagem J. 2023;4:1-8. https://doi.org/10.51847/oNOPb4T9g1
49. Nakai Y, Praneet Ngamsom S, Benso R, Ainola M, Al-Samadi A, Salo T, et al. Mechanisms of Osteoclastogenesis in Orthodontic Tooth

Movement and Orthodontically Induced Tooth Root Resorption. J Bone Metab. 2023;30(4):297-310. doi: 10.11005/jbm.2023.30.4.297.

50. Yen VT, Toan DV, Tai TA. Exploring the Influence of Job-Related Factors on Lecturer Performance: A Case Study in Vietnam. Asian J Indiv Organ Behav. 2024;4:58-66. https://doi.org/10.51847/9dchNRwhGY
51. Maralov VG, Sitarov VA, Kariyev AD, Krezhevskikh OV, Kudaka MA, Ageyeva LY, et al. Personal Development Strategies for Students Across Varying Agency Levels. Asian J Indiv Organ Behav. 2023;3:72-8. https://doi.org/10.51847/co5pvEJaGm
52. Schuldt L, von Bohlen Und Halbach V, Sticht C, Gisder T, Madusch J, Memmert S, et al. Palmitate-Triggered COX2/PGE2-Related Hyperinflammation in Dual-Stressed PdL Fibroblasts Is Mediated by Repressive H3K27 Trimethylation. Cells. 2022;11(6):955. doi: 10.3390/cells11060955.
53. Lin Y, Xu J, Lu J, Gu Y, He S, Sun Y. Periodontal ligament cells from patients with treated stable periodontitis: Characterization and osteogenic differentiation potential. J Periodontal Res. 2023;58(2):237-246. doi: 10.1111/jre.13085.
54. Erdur EA, Karakasli K, Oncu E, Ozturk B, Hakki S. Effect of injectable platelet-rich fibrin (i-PRF) on the rate of tooth movement. Angle Orthod. 2021;91(3):285-292. doi: 10.2319/060320-508.1.
55. Alnazeh AA, Alqahtani AS, Alqahtani MS, Alqahtani AM, Alqahtani AA, Alqahtani AA. Levels of inflammatory and bone metabolic markers in the gingival crevicular fluid of individuals undergoing fixed orthodontic treatment in comparison to those utilizing Invisalign. Medicina (Kaunas). 2023;59(12):2107. doi: 10.3390/medicina59122107.
56. Luchian I, Goriuc A, Sandu D, Covasa M. The Role of Matrix Metalloproteinases (MMP-8, MMP-9, MMP-13) in Periodontal and Peri-Implant Pathological Processes. Int J Mol Sci. 2022;23(3):1806. doi: 10.3390/ijms23031806.
57. Strippoli J, Durand SH, Carnes D, Goudot P, Bensaid M, Nham T, et al. Piezocorticision-assisted orthodontics: Efficiency, safety, and long-term evaluation of the inflammatory process. Am J Orthod Dentofacial Orthop. 2019;155(5):662-669. doi: 10.1016/j.ajodo.2018.06.013.
58. Wang X, Liu Y, He Y, Yang X, Luo S, Lu Q, et al. The Effects and Mechanisms of PBM Therapy in Accelerating Orthodontic Tooth Movement. Biomolecules. 2023;13(7):1140. doi: 10.3390/biom13071140.
59. Hu Y, He Z, Li J, He X, Yu S, Chen Z. Biological mechanism of surgery-mediated acceleration of orthodontic tooth movement: A narrative review. J Int Med Res. 2022;50(9):03000605221123904. doi: 10.1177/03000605221123904.