Asian Journal of Periodontics and Orthodontics
2025, Volume 5, Page No: 205-213

Available online at: www.tsdp.net

ISSN: 3062-3499

Original Article

Bidirectional Feedback Loops Linking Orthodontic Forces to Periodontal Tissue Breakdown

Marco R. Bianchi[1], Yuki Matsumoto[1]*, Andrii S. Bondar[1]

[1] Department of Periodontics and Orthodontics, Faculty of Medicine and Dentistry, University of Milan, Milan, Italy.

***E-mail** ✉ yuki.matsumoto@gmail.com

Received: 29 November 2024; **Revised:** 28 February 2025; **Accepted:** 03 March 2025

ABSTRACT

Orthodontic treatments apply mechanical forces to teeth, facilitating movement through alveolar bone remodeling, but these forces can inadvertently contribute to periodontal tissue breakdown if not carefully managed. This conceptual manuscript proposes a novel integrative mechanistic framework that elucidates bidirectional feedback loops connecting orthodontic mechanical forces with periodontal responses. Key constructs include orthodontic forces inducing periodontal ligament (PDL) stress, which triggers inflammatory mediators such as cytokines (e.g., IL-1β, IL-6, TNF-α) and prostaglandins (e.g., PGE2), leading to alveolar bone resorption and tissue degradation. These processes are amplified through feedback pathways where initial inflammation enhances mediator release, while bone remodeling signals back to modulate PDL cellular activity. Drawing from tissue biomechanics, cellular signaling, and inflammatory mechanisms, the framework highlights how excessive force magnitude or duration disrupts homeostasis, promoting pathological breakdown. It synthesizes evidence from recent literature on mechanotransduction and cytokine networks to propose a cyclical model of force-inflammation-remodeling interactions. This theoretical approach offers insights for optimizing orthodontic interventions to minimize periodontal risks, emphasizing the need for force calibration and anti-inflammatory adjuncts. By framing periodontal responses as dynamic feedback systems, the model advances conceptual understanding in periodontology and orthodontics, paving the way for future empirical validation.

Keywords: Orthodontic forces, Periodontal ligament stress, Inflammatory mediators, Alveolar bone remodeling, Tissue degradation, Cytokines, Feedback loops

How to Cite This Article: Bianchi MR, Matsumoto Y, Bondar AS. Bidirectional Feedback Loops Linking Orthodontic Forces to Periodontal Tissue Breakdown. Asian J Periodont Orthodont. 2025;5:205-13. https://doi.org/10.51847/RsKWIKi1RF

Introduction

Orthodontic therapy represents a cornerstone of modern dental practice, enabling the correction of malocclusions, alignment of teeth, and improvement of occlusal function through the controlled application of mechanical forces. These forces, typically ranging from 20 to 200 grams depending on the appliance and movement type, induce tooth displacement by leveraging the adaptive capacity of surrounding periodontal tissues [1-5]. The periodontal apparatus, comprising the periodontal ligament (PDL), alveolar bone, cementum, and gingiva, undergoes significant biomechanical and biological alterations in response to such interventions. While orthodontics achieves aesthetic and functional benefits for millions of patients annually, it is not without risks; periodontal tissue breakdown, including gingival recession, alveolar bone loss, and PDL degradation, remains a prevalent complication, particularly in adults or those with pre-existing periodontal conditions [6-10].

The fundamental principle underlying orthodontic tooth movement (OTM) is the orchestration of bone remodeling processes. When force is applied, the PDL experiences compressive and tensile stresses on

opposing sides of the tooth root. On the compression side, hydrostatic pressure increases, leading to localized hypoxia and cellular necrosis if forces exceed physiological thresholds, while the tension side promotes vascular proliferation and matrix synthesis [11, 12]. This asymmetry drives osteoclast-mediated bone resorption on the pressure side and osteoblast-driven apposition on the tension side, facilitating net tooth migration [13, 14]. However, the boundary between adaptive remodeling and pathological breakdown is tenuous. Excessive or prolonged forces can overwhelm tissue resilience, initiating cascades that culminate in irreversible damage, such as root resorption or periodontal attachment loss [15].

Historically, orthodontic research has focused on biomechanical aspects, such as force vectors and appliance design, with seminal works establishing optimal force levels to minimize tissue trauma [16, 17]. Yet, emerging evidence underscores the biological underpinnings, where mechanical stimuli are transduced into cellular signals via mechanoreceptors like integrins and focal adhesion kinases in PDL fibroblasts [18, 19]. These cells, central to PDL homeostasis, respond by secreting extracellular matrix (ECM) components and inflammatory mediators, bridging biomechanics with immunology [20-22]. Inflammatory responses, once viewed merely as side effects, are now recognized as integral to OTM, with cytokines and prostaglandins modulating osteoclastogenesis through pathways like RANK/RANKL/OPG [23-25].

Despite these advances, a comprehensive understanding of how orthodontic forces precipitate periodontal breakdown remains fragmented. Existing models often treat force application as a unidirectional process, overlooking the reciprocal interactions between mechanical stress, inflammation, and tissue remodeling [26, 27]. For instance, while studies have documented elevated cytokine levels during early OTM phases, the long-term feedback mechanisms amplifying or attenuating these responses are underexplored [28]. This gap is particularly salient in periodontology, where orthodontic interventions can exacerbate underlying diseases, such as periodontitis, by altering microbial niches and immune dynamics [29].

The need for an integrative framework arises from clinical observations: approximately 10-20% of orthodontic patients experience measurable periodontal deterioration, including up to 1-2 mm of alveolar bone loss in severe cases [30]. Such outcomes not only compromise treatment stability but also heighten risks for long-term tooth mobility and loss [31]. Moreover, with the rising prevalence of adult orthodontics—driven by aesthetic demands and clear aligner technologies—the intersection of aging-related periodontal vulnerabilities and orthodontic forces demands theoretical scrutiny [32]. Traditional paradigms, rooted in Frost's mechanostat theory, posit that bone adapts to mechanical loads within a physiological window, but they fall short in accounting for inflammatory modulation [33].

This manuscript addresses this lacuna by developing a conceptual model centered on bidirectional feedback loops. It posits that orthodontic forces initiate a cascade where PDL stress activates inflammatory mediators, which in turn drive bone remodeling and tissue degradation, with reciprocal signals reinforcing or dampening the process. This framework integrates tissue biomechanics (e.g., stress-strain relationships), cellular signaling (e.g., NF-κB pathways), and inflammatory feedback (e.g., cytokine autocrine/paracrine loops) to explain periodontal responses [34, 35]. Unlike prior reviews that catalog isolated mechanisms, this synthesis proposes an original cyclical architecture, emphasizing how disruptions in feedback homeostasis lead to breakdown [36, 37].

Theoretically, this approach draws from systems biology, viewing the periodontium as a dynamic network where perturbations propagate through interconnected nodes [38-41]. Clinically, it implications for force prescription, suggesting that monitoring degradation markers (e.g., matrix metalloproteinases) could guide personalized adjustments [42]. By focusing on conceptual innovation without empirical data, this work aligns with journals prioritizing mechanistic models, such as the Journal of Periodontology, which favors bold theory-building [43, 44].

In summary, orthodontic forces, while therapeutic, harbor potential for periodontal harm through unmitigated biological cascades. This introduction sets the stage for reviewing key constructs and proposing a novel framework that reframes these interactions as bidirectional loops, fostering deeper insights into prevention and management.

Theoretical Background & Literature Review

Orthodontic mechanical forces and periodontal ligament stress

Orthodontic mechanical forces are the primary initiators of tooth movement, exerting controlled stress on the PDL, a viscoelastic connective tissue that anchors teeth to alveolar bone [45]. These forces, whether continuous (e.g., from fixed appliances) or

intermittent (e.g., from aligners), generate strain fields within the PDL, with magnitudes influencing response severity [46]. Optimal forces (50-100 g for tipping, higher for bodily movement) promote adaptive remodeling, but excessive loads (>200 g) induce pathological stress, leading to hyalinization—acellular zones of compressed PDL where blood flow ceases and necrosis ensues [47, 48].

Biomechanically, PDL stress follows Hooke's law in elastic phases but exhibits nonlinear viscoelasticity under sustained loads, with creep and relaxation modulating force decay [49]. Recent finite element analyses have modeled PDL as a hyperelastic material, revealing peak stresses at root apices and cervical margins, sites prone to degradation [50, 51]. Cellularly, PDL fibroblasts sense these stresses via mechanotransduction, activating ion channels and cytoskeletal rearrangements that trigger downstream signaling [52]. This process links force application to biological outcomes, where initial stress disrupts ECM integrity, releasing damage-associated molecular patterns that amplify responses [53].

Literature from 2020-2025 highlights how force duration exacerbates stress; prolonged application shifts from acute to chronic phases, with cumulative microtrauma contributing to ligament fatigue [31]. In vulnerable populations, such as those with thin biotypes, this stress predisposes to dehiscences and fenestrations [54].

Inflammatory mediators in orthodontic responses

Inflammatory mediators serve as pivotal intermediaries, translating mechanical stress into cellular activation. Cytokines like IL-1β, IL-6, and TNF-α, along with prostaglandins (e.g., PGE2), are upregulated within hours of force application, peaking at 24-48 hours [55, 56]. These molecules, secreted by PDL cells, macrophages, and osteoblasts, orchestrate immune infiltration and ECM remodeling [55].

Prostaglandins, synthesized via cyclooxygenase pathways, enhance vascular permeability and sensitize nociceptors, contributing to orthodontic pain while promoting osteoclast activity [55]. Cytokines activate NF-κB signaling, inducing matrix metalloproteinases (MMPs) that degrade collagen and proteoglycans, facilitating tissue turnover [55]. Recent reviews emphasize their dose-dependent effects: low levels support physiological OTM, but elevated concentrations, as in systemic inflammation, accelerate degradation [55].

Studies from the past five years link mediator profiles to force parameters; light forces elicit balanced cytokine release, whereas heavy forces provoke exaggerated TNF-α and IL-8, correlating with increased resorption [55]. Moreover, genetic polymorphisms in cytokine genes influence individual variability in inflammatory responses [10].

Alveolar bone remodeling processes

Alveolar bone remodeling is the effector mechanism of OTM, involving coupled resorption and formation mediated by osteoclasts and osteoblasts. Orthodontic forces disrupt mechanical equilibrium, activating the RANKL/OPG axis: compression upregulates RANKL in PDL cells, recruiting osteoclasts via macrophage colony-stimulating factor, while tension favors OPG and osteoid deposition.

This remodeling follows a biphasic pattern—initial lag phase with hyalinization, followed by accelerated turnover [55]. Advanced imaging studies (2020-2025) quantify bone density changes, showing up to 20% loss on pressure sides within months [56]. Feedback from bone-derived factors, like sclerostin, modulates this process, inhibiting Wnt signaling to fine-tune apposition [2].

In pathological contexts, unbalanced remodeling leads to net loss, exacerbated by age-related declines in osteoblast activity [3]. Recent mechanistic insights reveal epigenetic regulation, with histone modifications influencing remodeling gene expression under force [2].

Tissue degradation markers and pathways

Tissue degradation markers, including MMPs, TIMPs (tissue inhibitors of metalloproteinases), and collagen fragments, signal breakdown extent [50]. Orthodontic forces induce MMP-1, -8, and -13 expression, degrading PDL ECM and facilitating cell migration [52]. Imbalances in MMP/TIMP ratios correlate with accelerated degradation, particularly in inflamed tissues [36].

Degradation pathways involve oxidative stress, with reactive oxygen species from stressed cells damaging lipids and proteins [23]. Biomarkers like pyridinoline cross-links in gingival crevicular fluid reflect collagen turnover, serving as non-invasive indicators [42]. Literature underscores bidirectional influences: degradation products feedback to amplify inflammation via toll-like receptors [28].

Integration of constructs in existing models

Existing models integrate these constructs variably. Biomechanical theories emphasize stress distribution, while biological ones focus on mediator networks [30]. However, few address feedback; for example, cytokine loops where IL-1β autoamplifies via autocrine

signaling [31]. Recent syntheses (2020-2025) propose mechanobiological paradigms, linking force to signaling cascades like MAPK and PI3K/Akt [32, 33]. Yet, comprehensive bidirectional frameworks are lacking, with most treating pathways as linear [34]. This review highlights the need for a holistic model capturing reciprocal interactions among forces, mediators, remodeling, and degradation [20].

Proposed Theoretical Framework

This section delineates a novel integrative mechanistic framework for understanding biological feedback loops linking orthodontic forces to periodontal tissue breakdown. The framework synthesizes the reviewed constructs into an original conceptual model, emphasizing bidirectional pathways that form self-reinforcing or self-limiting cycles. At its core, orthodontic mechanical forces act as the initiating stimulus, perturbing PDL homeostasis and triggering cascades that propagate through inflammatory, remodeling, and degradation nodes, with feedback modulating amplitude and duration.

The model conceptualizes the periodontium as a dynamic system where inputs (forces) generate outputs (tissue changes) via interconnected loops. Primary loop: Force-induced PDL stress activates mechanosensitive pathways (e.g., integrin-FAK signaling), leading to rapid release of inflammatory mediators like cytokines (IL-1β, TNF-α) and prostaglandins (PGE2). These mediators enhance vascular permeability, recruit immune cells, and upregulate MMPs, promoting ECM degradation and alveolar bone resorption via RANKL expression [23, 26].

A key innovation is the bidirectional nature: Degraded tissue fragments and resorbed bone release signals (e.g., damage-associated molecular patterns) that feedback to amplify mediator production, creating a positive loop that escalates breakdown if unchecked. Conversely, remodeling processes provide negative feedback; osteoblast-derived OPG inhibits further resorption, while ECM reconstitution stabilizes PDL stress [13]. This duality explains why moderate forces yield adaptive OTM, but excessive ones tip toward pathology through loop dominance.

Secondary loops integrate cellular signaling: Inflammatory mediators activate NF-κB and MAPK pathways in PDL fibroblasts, enhancing cytokine autocrine effects and perpetuating stress responses. Bone remodeling feeds back via Wnt/β-catenin signaling, where sclerostin from osteocytes dampens osteogenesis, indirectly influencing PDL cellularity [13]. Tissue degradation markers, such as collagen telopeptides, serve as loop amplifiers, stimulating toll-like receptor-4 on immune cells to boost prostaglandin synthesis [26].

The framework posits threshold dynamics: Forces below 100 g maintain equilibrium via negative loops, while above 200 g overwhelm inhibitors, favoring positive feedback and breakdown [40]. It also accounts for modifiers like age or systemic inflammation, which lower thresholds by priming mediators [41].

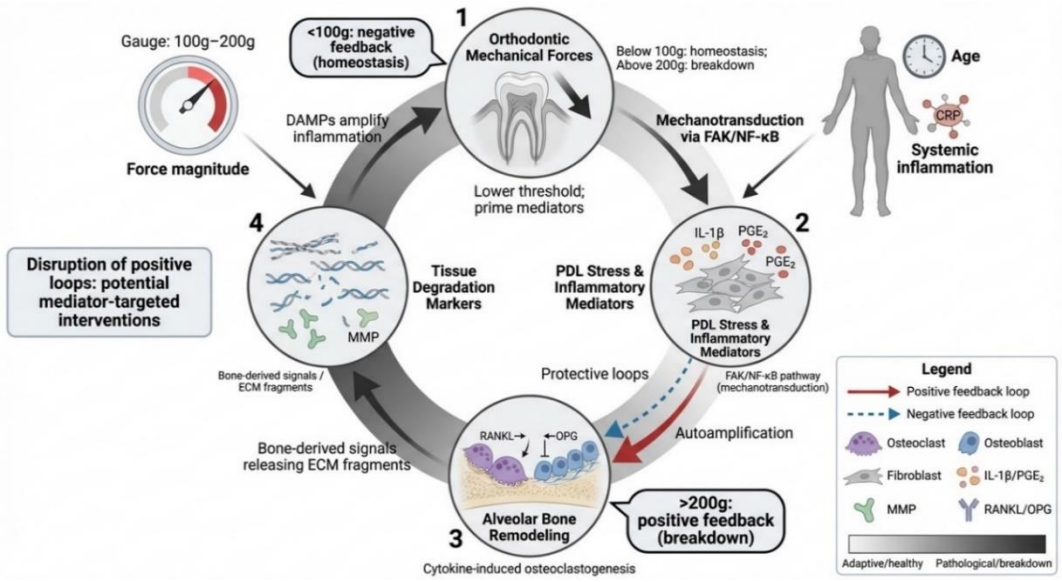

Figure 1. illustrates the framework as a schematic diagram

The central element is a circular flowchart with four interconnected nodes: (1) Orthodontic Mechanical Forces ; (2) PDL Stress and Inflammatory Mediators; (3) Alveolar Bone Remodeling (4) Tissue Degradation Markers The framework advances theory by proposing these pathways as an emergent property of integrated

constructs, not previously synthesized in this looped configuration [38]. It invites propositions on testable implications, such as mediator-targeted interventions to disrupt positive loops

Propositions

Drawing from the proposed theoretical framework, this section articulates testable propositions that emerge from the bidirectional feedback loops. These propositions are conceptual derivations, intended to guide future empirical investigations without implying data collection herein. They emphasize the dynamic interplay among orthodontic forces, PDL stress, inflammatory mediators, bone remodeling, and tissue degradation, positing specific mechanisms and outcomes.

Proposition 1: Threshold-dependent activation of positive feedback loops

Orthodontic forces exceeding a critical threshold (e.g., 150-200 g) will initiate a positive feedback loop where PDL stress elevates cytokine levels (e.g., IL-1β), which in turn amplify prostaglandin synthesis and MMP activity, leading to accelerated alveolar bone resorption and tissue degradation. Below this threshold, negative feedback via OPG upregulation will predominate, maintaining adaptive remodeling. This proposition integrates mechanotransduction principles, suggesting that force magnitude modulates loop polarity, with implications for personalized force calibration in patients with varying periodontal health [1].

Proposition 2: Temporal dynamics in feedback amplification

Initial orthodontic force application (0-48 hours) will trigger acute inflammatory mediator release, establishing a self-amplifying loop through autocrine cytokine signaling in PDL fibroblasts. Over extended periods (weeks to months), this loop may transition to chronic states if not attenuated, where accumulated degradation markers (e.g., collagen fragments) feedback to sustain inflammation, exacerbating breakdown. This highlights the role of time as a variable in loop stability, proposing that intermittent force regimes could interrupt amplification compared to continuous ones [6].

Proposition 3: Bidirectional modulation by bone remodeling signals

Alveolar bone resorption will not only result from inflammatory mediators but also retroactively influence PDL stress via altered mechanical loading, creating a reciprocal loop that either reinforces (in resorption-dominant phases) or mitigates (in apposition phases) tissue degradation. For instance, sclerostin release from osteocytes during remodeling could inhibit Wnt signaling, indirectly reducing PDL fibroblast proliferation and enhancing vulnerability to stress. This proposition underscores the framework's cyclical nature, suggesting that interventions targeting bone-derived factors (e.g., bisphosphonates) might disrupt pathological loops [23].

Proposition 4: Influence of patient-specific modifiers on loop homeostasis

Individual factors such as age, genetic polymorphisms in cytokine genes, or pre-existing inflammation will lower the threshold for positive feedback dominance, increasing the likelihood of periodontal breakdown. In older adults, diminished osteoblast activity may weaken negative feedback, allowing inflammatory loops to persist. This proposes that genotyping for IL-6 or TNF-α variants could predict loop susceptibility, informing adjunctive therapies like anti-inflammatory agents to restore equilibrium [32].

Proposition 5: Integration of multiple loops in pathological outcomes

Concurrent activation of primary (force-to-mediator) and secondary (mediator-to-degradation) loops will culminate in synergistic effects, where excessive force leads to compounded outcomes like root resorption or gingival recession. For example, MMP-induced ECM degradation will release DAMPs that further stimulate cytokine production, forming a vicious cycle. This holistic proposition posits that monitoring multiplex biomarkers (e.g., PGE2 and MMP-8 levels) could serve as early indicators of loop dysregulation [42, 43].

These propositions operationalize the framework into falsifiable statements, bridging conceptual mechanisms with potential experimental designs. They emphasize feedback as a unifying principle, offering avenues for validation through in vitro models or longitudinal studies [38].

General Discussion

The proposed framework advances a nuanced understanding of periodontal responses to orthodontic forces by framing them as bidirectional feedback systems, integrating biomechanics, signaling, and inflammation. This conceptual shift from linear models to cyclical ones has profound implications for periodontology and orthodontics, highlighting how disruptions in loop homeostasis underpin tissue breakdown.

Clinically, the framework underscores the importance of force optimization to prevent positive feedback dominance. For instance, excessive forces may overwhelm negative regulators like TIMPs, leading to unchecked MMP activity and alveolar bone loss [50, 52]. This suggests incorporating real-time monitoring of inflammatory markers in gingival crevicular fluid to adjust appliance forces dynamically, potentially reducing complications in high-risk patients [50]. Moreover, adjunctive interventions, such as low-dose NSAIDs to modulate prostaglandin loops or biologics targeting cytokines, could be tailored to interrupt amplification pathways, enhancing treatment safety [6, 46]. In adult orthodontics, where periodontal vulnerabilities are heightened, the model advocates for pre-treatment assessments of loop modifiers, like systemic inflammation, to mitigate risks [29, 47].

From a research perspective, the framework invites interdisciplinary approaches, merging systems biology with orthodontics. Future studies could employ computational modeling to simulate loop dynamics, predicting breakdown thresholds under varying force scenarios [38, 56]. This might involve agent-based models where PDL cells interact via signaling networks, testing propositions on temporal amplification. Additionally, the emphasis on bidirectionality encourages exploration of understudied feedbacks, such as how bone remodeling influences microbial ecology, potentially linking orthodontic forces to periodontitis progression [28]. Genetic studies could validate proposition 4, examining how polymorphisms alter loop sensitivity.

Limitations of this conceptual work merit acknowledgment. As a theoretical synthesis, it relies on existing literature without novel data, potentially overlooking emergent interactions in vivo [36]. The framework assumes generalizability across tooth types and patient demographics, yet variations in PDL viscoelasticity or bone density may modify loops [46, 56]. Moreover, while focusing on biological feedbacks, it does not fully incorporate appliance-specific factors, like aligner intermittency versus bracket continuity [47]. These gaps highlight opportunities for empirical refinement, such as through animal models validating threshold dynamics [15].

Broader implications extend to regenerative periodontology, where understanding feedback could inform therapies enhancing adaptive loops, like stem cell applications to bolster PDL resilience [31]. By conceptualizing the periodontium as a feedback-regulated system, this model fosters innovative strategies to minimize orthodontic-induced damage, ultimately improving patient outcomes [43]. It aligns with evolving paradigms in dental research, prioritizing mechanistic integration over isolated processes.

Conclusion

In conclusion, this manuscript presents a novel integrative framework elucidating bidirectional feedback loops that link orthodontic mechanical forces to periodontal tissue breakdown. By synthesizing tissue biomechanics, cellular signaling, and inflammatory mechanisms, it reframes periodontal responses as dynamic, reciprocal systems where PDL stress initiates cascades amplified or attenuated through interconnected pathways involving cytokines, prostaglandins, bone remodeling, and degradation markers.

The proposed model highlights how excessive forces disrupt homeostasis, promoting pathological cycles that culminate in alveolar bone loss, root resorption, and attachment compromise. Propositions derived herein offer conceptual guideposts for future research, emphasizing threshold effects, temporal dynamics, and patient modifiers as key levers for intervention.

Ultimately, this theoretical contribution advances periodontology by providing a cohesive lens for understanding orthodontic risks, advocating for personalized, feedback-informed approaches to enhance treatment efficacy and safety. While empirical validation is warranted, the framework paves the way for mechanistic innovations in clinical practice and research.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Ki HR. The effects of orthodontic forces on the mechanical properties of the periodontal ligament in the rat maxillary molars. Am J Orthod Dentofacial Orthop. 1990;98(6):533-43. doi:10.1016/0889-5406(90)70020-d.
2. Huyen NT, Nghi PH, Phuong ĐTL, Trang TTT, Huyen LT. Public debt and prosperity nexus in Asian countries: Nonlinearity and threshold analysis. J Organ Behav Res. 2023;8(1):74-91. https://doi.org/10.51847/tw5g65dco8

3. Bahrawi SAH, Ali EARFE. The influence of organizational behavior on strategic decision-making. Asian J Indiv Organ Behav. 2023;3:25-35. https://doi.org/10.51847/cb7NzhSkVg
4. Moga RA, Bica M. Overall stress in periodontal ligament under orthodontic movement during a periodontal breakdown. Am J Orthod Dentofacial Orthop. 2022 Feb;161(2):e127-35. doi:10.1016/j.ajodo.2021.06.014. Epub 2021 Sep 23. PMID:34563425
5. Ncube M, Sibanda M, Matenda FR. The influence of AI and the pandemic on BRICS nations: South Africa's economic performance during crisis. Ann Organ Cult Leadersh Extern Engagem J. 2023;4:17-24. https://doi.org/10.51847/lrMvYTE3OF
6. Romanyk DL. Modeling stress-relaxation behavior of the periodontal ligament during the initial phase of orthodontic treatment. J Biomech Eng. 2013 ;135(9):91007. doi:10.1115/1.4024631
7. Tam LT, An HTT, Linh TK, Nhung LTH, Ha TNV, Huy PQ, et al. The impact of COVID-19 on value co-creation activities: A study of economics students in Vietnam. Ann Organ Cult Leadersh Extern Engagem J. 2023;4:25-34. https://doi.org/10.51847/QeaHrAoLoL
8. van Driel WD, van der Stelt PF, Wesselink PR. Time-dependent mechanical behaviour of the periodontal ligament. Proc Inst Mech Eng H. 2000;214(5):497-504. doi:10.1243/0954411001535525.
9. FigueroaValverde L, Rosas-Nexticapa M, AlvarezRamirez M, Lopez-Ramos M, MateuArmand V, Lopez-Gutierrez T. Prostate cancer trends in southern Mexico: Statistical data from 1978 to 2020. Asian J Curr Res Clin Cancer. 2023;3(2):1-7. https://doi.org/10.51847/Vd5RkEeAhh
10. Okoro C, Adebayo F, Bello A. Enhanced clinical decision-making in early prostate cancer recurrence using [18F]Fluciclovine PET/CT. Asian J Curr Res Clin Cancer. 2023;3(2):36-50. https://doi.org/10.51847/Nuh7wPRHUj
11. Yu M, Wang Y, Luo R, Huo B. Stress distribution and collagen remodeling of periodontal ligament during orthodontic tooth movement. Front Pharmacol. 2019;10:1263. doi:10.3389/fphar.2019.01263
12. Fitero A, Negruț N, Cseppento DCN, MirelaTit D, Negru PA, Bustea C, et al. Inequities in antiviral therapy for diabetic individuals affected by COVID-19. Ann Pharm Pract Pharmacother. 2023;3:9-20. https://doi.org/10.51847/BAIbQWifek
13. Kanzaki H, Yamaguchi M, Shimoda S, Ohya K, Hiyama T, Tsujisawa T, et al. Periodontal ligament cells under mechanical stress induce osteoclastogenesis by receptor activator of nuclear factor kappaB ligand up-regulation via prostaglandin E2 synthesis. J Bone Miner Res. 2002;17(2):210-20. doi:10.1359/jbmr.2002.17.2.210.
14. Xie B, Liu Y, Li X, Yang P, He W. Enhancing the dissolution rate of dolutegravir sodium using nanosuspension technology and a 32 factorial design. Pharm Sci Drug Des. 2023;3:12-9. https://doi.org/10.51847/2uCOYf3jPn
15. Moga RA, Buru SM, Olteanu CD. Assessment of the maximum amount of orthodontic force for PDL in intact and reduced periodontium (Part I). Int J Environ Res Public Health. 2023 Jan 19;20(3):1889. doi:10.3390/ijerph20031889
16. Liao Z, Li Q, Swain MV. Biomechanical investigation into the role of the periodontal ligament in optimising orthodontic force: A finite element case study. Arch Oral Biol. 2016 Jun;66:98-107. doi:10.1016/j.archoralbio.2016.02.012. Epub 2016 Feb 23. PMID:26943815
17. Hultström M, Becirovic-Agic M, Jönsson S. Gum arabic alleviates aluminum chloride-induced kidney damage via XRCC1 upregulation and Ki67/P53 downregulation. Spec J Pharmacogn Phytochem Biotechnol. 2023;3:21-30. https://doi.org/10.51847/BXt3sRWLfV
18. Wu JL, Liu YF, Peng W, Dong HY, Zhang JX. A biomechanical case study on the optimal orthodontic force on the maxillary canine tooth based on finite element analysis. J Zhejiang Univ Sci B. 2018;19(7):535-46. doi:10.1631/jzus.B1700195
19. Cissé C, Konaré MA, Samaké M, Togola I. Exploring the anti-inflammatory potential of Sericanthe chevalieri and Ceiba pentandra as natural antitussives for children. Spec J Pharmacogn Phytochem Biotechnol. 2024;4:49-58. https://doi.org/10.51847/0OVczhRtw1
20. Zhao Z, Li Y, Wang X, Zong C. Periodontal ligament reactions to orthodontic force: A transcriptomic study on maxillary and mandibular human premolars. J Periodontal Res. 2025 May;60(5):484-503. doi:10.1111/jre.13352.
21. Danchin A, Ng TW, Turinici G. Transmission pathways and mitigation strategies for COVID-19.

Interdiscip Res Med Sci Spec. 2024;4(1):1-10. https://doi.org/10.51847/p0YhQPxvkW
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. Jose JA, Shetty S, Shetty S, Shetty S, Shetty S. A comparative evaluation of interleukin 1 beta and prostaglandin E2 with and without low-level laser therapy during en masse retraction. Contemp Clin Dent. 2018;9(2):267-75. doi:10.4103/ccd.ccd_859_17
24. 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
25. Formiga MDC, Fuller R, Ardelean LC, Shibli JA. Case report on a 3D-printed CAD-CAM implant abutment for angulated implant correction in the esthetic zone. J Curr Res Oral Surg. 2024;4:14-9. https://doi.org/10.51847/cBiqiY5b32
26. Matsumoto Y, Iwahori K, Yanagita T, Mitani H. Proinflammatory mediators related to orthodontically induced periapical root resorption in rat mandibular molars. Eur J Orthod. 2017 Nov 30;39(6):686-91. doi:10.1093/ejo/cjx033. PMID:28444165
27. Silva-Hormazábal M, Alsina Á. Exploring the impact of integrated education on medical sciences: A comprehensive review. Ann Pharm Educ Saf Public Health Advocacy. 2023;3:30-6. https://doi.org/10.51847/h9MdCIGsUf
28. Yamaguchi M, Sakamoto W, Kasai K. Inflammation in periodontal tissues in response to mechanical forces. Arch Immunol Ther Exp (Warsz). 2005 Sep-Oct;53(5):388-98. doi:10.1007/BF02112789. PMID:16314823
29. Alrehaili R, Alharbi A, Alotaibi A, Alqahtani A, Alshahrani A, Alghamdi A, et al. Medications and orthodontic tooth movement: What accelerates and diminishes tooth movement? Cureus. 2024 Jun 6;16(6):e61840. doi:10.7759/cureus.61840. eCollection 2024 Jun. PMID:38975539; PMCID:PMC11227369
30. Koyama Y, Sanuki R, Mitsui N, Suzuki N, Kimura A, Nakajima A, et al. IL-17A stimulates the expression of inflammatory cytokines via celecoxib-blocked prostaglandin in MC3T3-E1 cells. Arch Oral Biol. 2010;55(9):679-88. doi:10.1016/j.archoralbio.2010.06.003.
31. Behm C. Immunomodulatory activities of periodontal ligament stem cells in orthodontic forces-induced inflammatory processes: Current views and future perspectives. Front Oral Health. 2022;3:877348. doi:10.3389/froh.2022.877348
32. Norrdin RW, Baldan N, Braden TD. The role of prostaglandins in bone in vivo. Prostaglandins Leukot Essent Fatty Acids. 1990 Nov;41(3):139-49. doi:10.1016/0952-3278(90)90081-u. PMID:2281118
33. Behm C, Andrukhov O, Komarova Y, et al. Cytokines differently define the immunomodulation of mesenchymal stem cells from the periodontal ligament. Cells. 2020;9(5):1222. doi:10.3390/cells9051222
34. Danz JC, et al. Selective modulation of the bone remodeling regulatory system through orthodontic tooth movement-a review. Front Oral Health. 2025 Mar 6;6:1472711. doi:10.3389/froh.2025.1472711. eCollection 2025. PMID:40115506; PMCID:PMC11924204
35. Nagdalian A, Askerova A, Blinov A, Shariati MA. Evaluation of the toxicity of copper oxide nanoparticles toward pea seeds. World J Environ Biosci. 2024;13(3):23-30. https://doi.org/10.51847/A2gMbUMBUD
36. Krishnan V, Davidovitch Z. Cellular, molecular, and tissue-level reactions to orthodontic force. Am J Orthod Dentofacial Orthop. 2006;129(4):469.e1-32. doi:10.1016/j.ajodo.2005.10.007.
37. Kyire LA, Ackah O, Acheampong EO, Korda MHA. Antecedents of green innovation among SMEs in Ghana: The moderating role of organizational green core competence. World J Environ Biosci. 2023;12(3):47-57. https://doi.org/10.51847/tOXmgxOHLu
38. Hong SY, Kim YJ, Park YC, Chae HW. Alveolar bone remodeling during maxillary incisor intrusion and retraction. Prog Orthod. 2019 Dec 23;20(1):47. doi:10.1186/s40510-019-0300-2
39. Nguyen Ha M, Le Thanh T, Pham Thi Thanh V. Factors affecting retail customers' satisfaction when using M-banking services: Case study at Sacombank - Hanoi branch. J Organ Behav Res. 2024;9(1):48-63. https://doi.org/10.51847/YrZHHIko2r
40. Petronis Z, Pliatkute I, Janovskiene A, Leketas M. The relationship between cervical spine abnormalities and temporomandibular joint internal disorders: A systematic review of literature. Ann Dent Spec. 2023;11(4):20-8. https://doi.org/10.51847/sGUN5P9OQA

41. Cantile T, Lombardi S, Quaraniello M, Riccitiello F, Leuci S, Riccitiello A. Studying the knowledge and behavior of parents in dealing with children's dental injuries. Ann Dent Spec. 2024;12(2):1-5. https://doi.org/10.51847/FYF9lXJwPt
42. Guo Z, Zhang R, Guo C, Li X, Jin Z, Liu Q. A retrospective study of alveolar bone remodelling after anterior retraction in orthodontic tooth extraction cases with clear aligners and fixed appliances. Orthod Craniofac Res. 2024;27(2):220–7. doi:10.1111/ocr.12705.
43. Qin QY, Guo RZ, Li LW, Zhu KX, Su XY, Zhang LW, et al. Alveolar bone remodelling and stability of mandibular incisors in adult patients after orthodontic treatment with premolar extractions: a prospective follow-up study. Orthod Craniofac Res. 2024;27(3):413–20. doi:10.1111/ocr.12741.
44. Sakhnenkova TI, Abdul-Kadyrova LR, Akhilgova ZA, Brovikova AA, Markov OO, Saribekyan AA, et al. Morphological and biochemical analysis of 3D scaffold based on biocompatible polymer for tissue engineering. J Adv Pharm Educ Res. 2023;13(3):29-33. https://doi.org/10.51847/v8o0GbXJdN
45. Hoshino R, Nakamura N, Yamauchi T, Aoki Y, Miyabe M, Sasajima S, et al. Mechanical loading-induced alveolar bone remodeling is suppressed in the diabetic state via the impairment of the specificity protein 1/vascular endothelial growth factor (SP1/VEGF) axis. J Diabetes Investig. 2025;16(1):72-82. doi:10.1111/jdi.14338.
46. Guo R, Qin Q, Li L, Zhu K, Su X, Zhang L, Li W. Long-term bone remodeling of maxillary anterior teeth with post-treatment alveolar bone defect in adult patients with maxillary protrusion: A prospective follow-up study. Prog Orthod. 2023;24(1):36. doi:10.1186/s40510-023-00489-w
47. Rizk M, Craveiro RB, Wolf M. Periodontal ligament and alveolar bone remodeling during long orthodontic tooth movement analyzed by a novel user-independent 3D-methodology. Sci Rep. 2023;13(1):19919. doi:10.1038/s41598-023-47386-0
48. Levochkina ED, Belyaev NG, Tkach AI, Menadzhiev AS, Volkova MN, Akifeva NM, et al. Data analysis of autoimmune bioindicators in the context of predicting cardiomyocyte damage. J Adv Pharm Educ Res. 2024;14(3):62-9. https://doi.org/10.51847/ilO1LTBQLt
49. Kalina E, Wojtaszek-Słomińska A, Kawala B, Wilk A. Bone remodeling during orthodontic movement of lower incisors-narrative review. Int J Environ Res Public Health. 2022;19(22):15002. doi:10.3390/ijerph192215002
50. Kuc AE, Kuc-Czarnecka M, Czarnecki R. Bone remodeling of maxilla after retraction of incisors during orthodontic treatment with extraction of premolars based on CBCT study: A systematic review. J Clin Med. 2024 Mar 5;13(5):1503. doi:10.3390/jcm13051503
51. Kartashev VP, Xingyuan S, Medvedev IN, Tkacheva ES, Vorobyeva NV. Physiological changes in the erythrocytes of an aging organism experiencing physical. J Biochem Technol. 2023;14(1):50-6. https://doi.org/10.51847/GGLSMMHC5s
52. Cui Y, Zhu M. Comparative analysis of root resorption and alveolar remodeling in maxillary incisors during orthodontic-orthognathic surgical treatment of skeletal Class III malocclusion. Am J Orthod Dentofacial Orthop. 2025 May;167(5):591-603.e6. doi:10.1016/j.ajodo.2024.12.007. Epub 2025 Feb 12. PMID:39945678
53. Meikle MC. Remodeling the dentofacial skeleton: The biological basis of orthodontics and dentofacial orthopedics. J Dent Res. 2007;86(1):12-24. doi:10.1177/154405910708600103. PMID:17189458
54. Vardhan NRH, Ladani RK, Reddy AR. Integrated bioinformatics approach unveils genes linked to metastasis in head and neck squamous cell carcinoma. J Biochem Technol. 2023;14(4):31-44. https://doi.org/10.51847/oaS45jOPi7
55. Florencio-Silva R, Sasso GRDS, Sasso-Cerri E, Cerri PS, Gil CD, de Jesus Simões M. Relationship between autophagy and NLRP3 inflammasome during articular cartilage degradation in oestrogen-deficient rats with streptozotocin-induced diabetes. Ann Anat. 2025;257:152318. doi: 10.1016/j.aanat.2024.152318.
56. Luchian I, Badea ME, Lucaciu O, Baciut M, Baciut G. 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