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Original Article

Alveolar Bone Biology Under Orthodontic Loading: Mechanotransduction and Cellular Responses

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ABSTRACT

Orthodontic treatment involves the application of mechanical forces to teeth, inducing directed tooth movement through adaptive remodeling of the alveolar bone. This process is governed by mechanotransduction, where mechanical stimuli are converted into biochemical signals that orchestrate cellular responses. This narrative review synthesizes recent findings from peer-reviewed literature published between 2020 and 2025 on the biology of alveolar bone under orthodontic loading. Key topics include the anatomy and physiology of alveolar bone, principles of orthodontic force application, mechanisms of mechanotransduction, and the roles of key cells such as osteocytes, osteoblasts, and osteoclasts in bone remodeling. Signaling pathways like RANKL/OPG, Wnt/β-catenin, and cytokine networks are examined, highlighting their contributions to tension- and compression-side responses. Factors influencing these processes, including age-related changes, inflammation, and neural regulation, are also discussed. The review underscores the importance of understanding these mechanisms to optimize orthodontic outcomes, minimize adverse effects like root resorption, and explore novel therapeutic interventions such as photobiomodulation or targeted molecular modulation. By integrating cellular, molecular, and biomechanical perspectives, this article provides a comprehensive framework for advancing orthodontic research and clinical practice.

Keywords: Alveolar bone, Orthodontic loading, Mechanotransduction, Cellular responses, Bone remodeling, Osteocytes

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Introduction

The alveolar bone is a dynamic tissue that supports the dentition and responds to mechanical stimuli throughout life [1-4]. Orthodontic therapy leverages this adaptability by applying controlled forces to teeth, resulting in tooth movement via coordinated bone resorption and formation [5,6]. This process, known as orthodontic tooth movement (OTM), is fundamentally a biological response to mechanical loading, involving complex interactions between cells, extracellular matrix, and signaling molecules [7].

Historically, OTM has been described by the "pressure-tension" hypothesis, where compression leads to bone resorption and tension to bone apposition [8-10]. Recent advances, however, have shifted focus to the molecular and cellular levels, revealing mechanotransduction as the key bridge between mechanical force and biological adaptation [11-13]. Mechanotransduction enables cells to sense and respond to forces, triggering cascades that regulate gene expression, cytokine release, and cellular differentiation [14, 15].

Despite progress, challenges remain, such as variable treatment responses in adults versus adolescents, increased risk of alveolar bone loss, and complications

like external root resorption [16-18]. Understanding these mechanisms is essential for developing personalized orthodontic strategies and adjunctive therapies [19-22].

The objectives of this review are to: (1) outline the anatomy and physiology of alveolar bone; (2) describe the principles of orthodontic loading; (3) elucidate mechanotransduction pathways; (4) detail cellular responses in bone remodeling; and (5) discuss influencing factors like age and inflammation. By synthesizing evidence from 2020-2025 studies, this review aims to provide a thematic overview to guide future research and clinical applications.

Anatomy and Physiology of Alveolar Bone

The alveolar bone constitutes the specialized bony structure that supports and anchors teeth within the maxilla and mandible, forming a dynamic interface between the oral cavity and the skeletal system [23,24]. Anatomically, it is composed of several distinct components: the cortical plates (buccal and lingual), which provide structural rigidity; the trabecular or cancellous bone, which serves as a vascularized scaffold facilitating metabolic exchange; and the lamina dura, a thin layer of compact bone lining the alveolar socket, which provides direct attachment for periodontal ligament (PDL) fibers [23, 25, 26]. This architecture allows the alveolar bone to withstand and adapt to continuous functional and orthodontic forces while maintaining the integrity of the dentoalveolar complex.

The alveolar bone is highly vascularized and richly innervated, receiving nutrient supply through both the periosteal and endosteal vessels, as well as neural inputs that regulate remodeling and pain perception [27, 28]. The PDL serves as a critical intermediary between the tooth root and alveolar bone, consisting of a dense network of collagen fibers, fibroblasts, progenitor cells, and extracellular matrix components, including proteoglycans and glycosaminoglycans [29-31]. These structures function biomechanically to absorb and distribute occlusal and orthodontic forces, preventing direct bone-to-tooth contact, minimizing trauma, and facilitating physiologic adaptation. In addition, the PDL contributes to signaling pathways that coordinate osteoclast and osteoblast activity, acting as a mechanosensitive regulator of bone homeostasis.

Physiologically, alveolar bone is a highly dynamic tissue, undergoing continuous remodeling to maintain structural and functional homeostasis [32-34]. Bone remodeling is a tightly regulated balance between osteoclastic resorption and osteoblastic formation, influenced by local signaling molecules—including RANKL, OPG, sclerostin, and pro-inflammatory cytokines—as well as systemic regulators such as parathyroid hormone, estrogen, vitamin D, and mechanical loading [35, 36]. In regions of reduced functional load, such as edentulous areas, alveolar bone density diminishes due to osteoclastic predominance, while areas subjected to functional loading maintain or increase bone volume and mineralization [37, 38]. These adaptive responses underscore the importance of mechanical stimulation in preserving alveolar architecture and highlight the consequences of disuse or pathological conditions.

During orthodontic tooth movement (OTM), controlled mechanical forces temporarily disrupt this homeostatic equilibrium, inducing site-specific remodeling that allows teeth to migrate through the alveolar bone [39-41]. On the compression side, mechanical strain reduces perfusion and generates localized hypoxia, leading to hyalinization of PDL fibers and recruitment of osteoclasts to remove damaged bone via indirect resorption. Conversely, on the tension side, stretching of PDL fibers stimulates osteoblast proliferation and osteoid deposition, promoting new bone formation. This spatially coordinated response ensures that tooth movement occurs without compromising overall alveolar stability. Advanced finite element analyses have further elucidated these biomechanical effects, demonstrating stress concentration patterns in both loaded and edentulous regions, and predicting areas susceptible to excessive resorption or compromised bone quality [5, 42].

Beyond mechanical adaptation, alveolar bone physiology is modulated by systemic and local inflammatory signals, neural inputs, and metabolic status. Conditions such as periodontitis, diabetes, and osteoporosis can perturb the normal remodeling cycle, altering osteoclast/osteoblast ratios and compromising bone integrity. Additionally, emerging evidence suggests that mechanosensitive ion channels (e.g., Piezo1) and cellular metabolic pathways modulate osteocyte-mediated sensing of mechanical load, integrating local and systemic cues to fine-tune alveolar bone remodeling. These insights emphasize that alveolar bone is not merely a passive scaffold but an active, responsive tissue that integrates biomechanical, cellular, and molecular signals to maintain oral health and facilitate orthodontic interventions.

Principles of Orthodontic Loading

Orthodontic tooth movement (OTM) relies on the precise application of mechanical forces to teeth, which

are typically light and continuous, ranging from approximately 20 to 150 grams, depending on the tooth type, root morphology, and treatment objectives [43, 44]. These forces are transmitted through appliances such as fixed brackets and archwires, removable aligners, or functional appliances, creating controlled stress within the periodontal ligament (PDL) and alveolar bone. The magnitude, duration, frequency, and direction of these forces collectively determine the biological response: optimal forces promote efficient bone remodeling and predictable tooth movement, whereas excessive or improperly directed forces can cause tissue damage, hyalinization of the PDL, root resorption, and alveolar bone loss [45, 46].

Mechanically, orthodontic loading generates distinct pressure (compression) and tension zones within the PDL and surrounding alveolar bone [46, 47]. On the compression side, PDL fibers are compressed, vascular perfusion is reduced, and localized hypoxia occurs, leading to recruitment of osteoclasts and activation of resorption pathways. On the tension side, fibers are stretched, stimulating osteoblast differentiation, collagen deposition, and osteoid formation, which together facilitate adaptive bone apposition. This spatially coordinated response ensures that teeth migrate through the alveolar socket without compromising structural integrity.

The underlying principle governing these adaptations aligns with Wolff's law, which states that bone remodels in response to mechanical demands: functional loading stimulates osteogenesis, while reduced or absent load promotes resorption [48, 49]. Orthodontic forces, therefore, act as physiologic stimuli that direct bone remodeling in a site-specific manner, with osteocytes serving as the principal mechanosensors that detect strain and orchestrate downstream cellular responses. Recent research has emphasized the importance of force type static versus dynamic in modulating bone and PDL responses. Dynamic or vibrational loading, for example, has been shown to accelerate OTM by enhancing osteoclast recruitment and activity, increasing bone turnover rates, and promoting more rapid tooth movement [50, 51].

At the cellular level, mechanotransduction pathways play a pivotal role. Piezo1 ion channels expressed in PDL fibroblasts and osteocytes sense mechanical strain, translating it into intracellular calcium signaling and activation of downstream pathways such as RANKL/OPG modulation, NF-κB, and MAPK signaling, which collectively regulate osteoclastogenesis and osteoblast activity [52]. Additionally, mechanical forces influence local production of prostaglandins, cytokines, and growth factors, which coordinate remodeling across the bone–PDL–tooth complex. The extracellular matrix itself contributes to mechanosensation, with collagen fiber orientation, cross-linking, and viscoelastic properties modulating strain distribution and force transmission.

Biomechanical modeling, including finite element analysis (FEA) and in-silico simulations, has provided valuable insights into stress distribution within the PDL and alveolar bone, predicting how force vectors, magnitude, and point of application influence tissue deformation and remodeling [8]. These models allow clinicians to visualize potential areas of compression, tension, or overload, supporting evidence-based adjustments in appliance design and force calibration. Clinically, understanding these principles is essential for minimizing adverse effects such as root resorption, bone dehiscence, or gingival recession, while optimizing tooth movement efficiency [53].

Overall, the principles of orthodontic loading encompass a delicate balance between mechanical force application and biological response, integrating cellular mechanosensing, biochemical signaling, and tissue adaptation. Mastery of these principles enables clinicians to tailor orthodontic mechanics to individual patients, ensuring safe, predictable, and physiologically harmonious tooth movement.

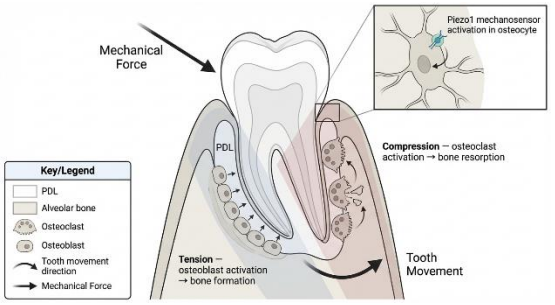

Figure 1. Mechanism of Orthodontic Tooth Movement Under Mechanical Loading

Orthodontic forces create compression and tension zones in the periodontal ligament and alveolar bone. Compression induces osteoclast-mediated resorption, while tension stimulates osteoblast-mediated bone formation, enabling controlled tooth movement.

Mechanotransduction Mechanisms in Bone Cells

Mechanotransduction is the biological process by which mechanical forces are converted into biochemical signals, enabling bone cells to sense and respond to changes in their physical environment [54]. In the alveolar bone, mechanotransduction is central to both physiological remodeling and orthodontic tooth

movement (OTM), ensuring that applied forces result in coordinated osteoclastic and osteoblastic activity while maintaining tissue integrity. Key cellular mechanosensors include integrins, ion channels, primary cilia, and gap junction proteins, each contributing to the detection, amplification, and propagation of mechanical signals [29, 54].

Osteocytes, embedded within the mineralized bone matrix, are considered the principal mechanosensors of the alveolar bone [16, 43]. They detect mechanical stimuli such as fluid shear stress, matrix deformation, and compressive or tensile strain through their dendritic processes and lacuno-canalicular network. Upon mechanical loading, osteocytes initiate a cascade of signaling events, releasing paracrine factors including nitric oxide (NO), prostaglandins (e.g., PGE2), and sclerostin, which regulate the activity of surrounding osteoblasts and osteoclasts [55]. These signals modulate RANKL/OPG ratios, influencing osteoclastogenesis on compression zones, while tension zones are primed for Wnt/β-catenin-mediated osteoblast activation and bone formation [56].

Mechanosensitive ion channels, particularly Piezo1 and Piezo2, are critical mediators in translating mechanical stimuli into intracellular calcium influx, which triggers downstream gene expression programs necessary for bone homeostasis [2]. These channels respond to physiologic strains generated during mastication, functional loading, or orthodontic forces, and their activation coordinates the spatially specific remodeling observed in OTM. For instance, increased Piezo1 activity in osteocytes under compression enhances RANKL expression and osteoclast recruitment, whereas tension-mediated signaling activates anabolic pathways through Wnt ligands, promoting osteoblast differentiation and matrix deposition.

Primary cilia act as antenna-like organelles that sense mechanical deformation and fluid flow, facilitating the orientation of osteocyte responses within the three-dimensional matrix. Connexins, particularly connexin 43 (Cx43), form gap junctions that propagate mechanosensitive signals among osteocytes and between osteocytes and osteoblasts, amplifying local responses to distributed mechanical loads [29]. Recent transcriptomic studies have revealed that osteocytes exposed to orthodontic or functional loads undergo dynamic changes in gene expression, including upregulation of genes associated with cytoskeletal remodeling, extracellular matrix synthesis, and bone homeostasis [57]. These molecular adaptations highlight the complexity of force sensing and the integration of mechanical, chemical, and transcriptional signals in coordinating alveolar bone remodeling.

Collectively, mechanotransduction mechanisms in alveolar bone cells provide a finely tuned system for interpreting mechanical inputs, ensuring that orthodontic forces elicit controlled resorption and formation. Understanding these pathways has direct clinical implications: targeted modulation of mechanosensors or their downstream effectors may enhance OTM efficiency, minimize adverse outcomes such as root resorption or bone dehiscence, and optimize the preservation of periodontal health in patients with varying alveolar phenotypes.

Cellular Responses in Bone Remodeling

Bone remodeling during orthodontic tooth movement (OTM) is a highly coordinated process involving osteoclasts, osteoblasts, and osteocytes, with contributions from periodontal ligament (PDL) cells, immune cells, and stem cell populations [58]. On the compression side of a tooth subjected to orthodontic forces, osteoclasts are recruited to resorb alveolar bone. This recruitment is primarily driven by RANKL (receptor activator of nuclear factor kappa-B ligand) expressed by osteocytes, PDL fibroblasts, and other stromal cells, which binds to RANK on osteoclast precursors, promoting differentiation, activation, and survival [53]. Conversely, on the tension side, osteoblasts deposit new bone, stimulated by OPG (osteoprotegerin) as a decoy receptor limiting RANKL activity, along with Wnt ligands that enhance osteoblast proliferation and matrix synthesis [48].

Osteocytes serve as central orchestrators of this remodeling process. Mechanosensitive and endocrine functions of osteocytes allow them to integrate mechanical and biochemical signals and coordinate the activity of osteoclasts and osteoblasts. Osteocyte-derived cytokines, such as TNF-α, can amplify RANKL expression and thus promote site-specific osteoclastic resorption [47]. Recent studies have highlighted the paracrine role of immune cells in remodeling, with M2 macrophage-derived exosomes shown to enhance osteogenic differentiation through epigenetic pathways, indicating a complex immune-bone crosstalk that contributes to efficient remodeling [59].

PDL stem cells (PDLSCs) further modulate remodeling, with mechanical forces influencing their differentiation into osteoblast-like cells. Mechanistically, metabolic intermediates such as lactate generated under compressive or tensile stress act as signaling molecules that guide PDLSC fate, linking cellular metabolism to tissue adaptation [39].

Age also significantly affects cellular responses; adult and elderly patients often exhibit delayed or maladaptive remodeling due to reduced osteocyte mechanosensitivity, diminished osteoblast activity, and impaired stem cell proliferation, leading to slower OTM and increased susceptibility to alveolar bone loss [11].

Signaling Pathways Involved

Several key molecular pathways orchestrate cellular responses during bone remodeling in OTM. The RANKL/OPG/RANK axis remains central, regulating osteoclastogenesis in response to mechanical and inflammatory cues [35]. Pro-inflammatory cytokines such as IL-1β and TNF-α further amplify remodeling by upregulating RANKL expression and enhancing osteoclastic activity, linking inflammation to tissue resorption [50]. On the anabolic side, the Wnt/β-catenin pathway promotes osteoblast proliferation, differentiation, and matrix mineralization, with Lrp5 overexpression demonstrated to accelerate OTM in preclinical models [27]. Mechanotransduction pathways, including the YAP/TAZ transcriptional coactivators, transduce mechanical signals from the PDL and bone matrix into gene expression changes that dictate cell fate and tissue adaptation [32].

Neural regulation also influences remodeling, particularly via sympathetic nervous system pathways that modulate osteoblast and osteoclast metabolism. Semaphorins, secreted guidance molecules, provide a link between immune responses and bone remodeling, integrating neural, immune, and skeletal signals to fine-tune cellular activity during OTM [60].

Influencing Factors: Age, Inflammation, and Emerging Therapies

Age is a major determinant of bone remodeling capacity. Senescent osteocytes in older individuals exhibit reduced mechanosensitivity, leading to slower osteoclast recruitment and osteoblast activity, thereby prolonging OTM duration and increasing risk of maladaptive bone changes [11, 56]. Chronic or acute inflammation further exacerbates resorptive responses, as elevated TNF-α and IL-1β levels promote osteoclast differentiation and inhibit osteoblast function, highlighting the importance of periodontal health in orthodontic planning [7].

Emerging therapies target these cellular mechanisms to optimize remodeling and minimize adverse effects. Stem cell-based interventions, potentially mediated through connexin 43 signaling and exosome release, enhance osteogenic potential and tissue regeneration [61]. Micro-osteoperforations, piezosurgical corticotomies, and other minimally invasive mechanical adjuncts have been shown to accelerate OTM while reducing root resorption and enhancing alveolar bone deposition [58]. These strategies, combined with precise force application guided by mechanotransduction principles, offer promising avenues for improving treatment efficiency and periodontal outcomes, particularly in patients with high-risk phenotypes or systemic comorbidities.

Discussion

The synthesis of recent literature from 2020 to 2025 reveals a multifaceted understanding of alveolar bone biology during orthodontic loading, emphasizing the pivotal role of mechanotransduction in orchestrating cellular responses. Mechanotransduction, as elucidated in various studies, serves as the foundational mechanism by which mechanical forces are translated into biochemical signals, influencing bone remodeling [1,54]. This process is particularly evident in the differential responses on the compression and tension sides of the periodontal ligament and alveolar bone, where compression induces osteoclast-mediated resorption via upregulated RANKL expression, while tension promotes osteoblast activity through Wnt/β-catenin signaling [8,27,56]. However, the integration of these pathways is not isolated; cross-talk with inflammatory cytokines, such as IL-1β and TNF-α, amplifies the remodeling process, potentially leading to complications like root resorption if forces are excessive [7,50].

One critical insight from the reviewed studies is the age-dependent variability in these responses. In adolescents, robust cellular activity facilitates efficient OTM, whereas in adults, senescent changes in osteocytes and reduced stem cell potency contribute to slower movement and increased risk of alveolar bone loss [2,5,11]. This aligns with findings on mitophagy and autophagy, where age-related declines impair mitochondrial function and RANKL/OPG balance, underscoring the need for tailored force regimens in older patients [2,32]. Furthermore, emerging evidence highlights the modulatory effects of neural and immune factors. For instance, semaphorin signaling and NLRP3 inflammasome activation link mechanical stress to inflammatory cascades, suggesting that neuro-immune interactions could be targeted to enhance treatment efficacy [16,60].

Therapeutic interventions represent a promising avenue for optimizing OTM. Photobiomodulation and low-intensity pulsed ultrasound have been shown to influence autophagy and Piezo1-mediated signaling,

accelerating bone remodeling while mitigating resorption [5,35,39]. Similarly, micro-osteoperforations and anabolic agents like abaloparatide promote osteogenesis through localized trauma or hormonal mimicry, offering minimally invasive adjuncts to traditional orthodontics [45,47,58]. However, challenges persist, including the biomechanical implications of edentulous areas or periodontal conditions, where finite element analyses demonstrate uneven stress distribution that may exacerbate dehiscence [14,53]. These models advocate for personalized appliance designs, such as clear aligners, which distribute forces more uniformly under bone loss scenarios [11,43].

Limitations in the current body of evidence include a predominance of animal models and in vitro studies, which may not fully recapitulate human physiology [8,37]. Human trials, though increasing, often lack long-term follow-up, particularly regarding root resorption and relapse [47,52]. Additionally, the integration of multi-omics approaches, while insightful for identifying novel genes like ADAMTS2 or SNHG5, requires validation in clinical settings [7,32]. The heterogeneity in force application protocols across studies also complicates direct comparisons, highlighting the need for standardized methodologies.

Overall, this review integrates biomechanical, cellular, and molecular perspectives to illustrate how orthodontic loading disrupts alveolar bone homeostasis, with mechanotransduction as the central mediator. By addressing influencing factors like age and inflammation, clinicians can refine strategies to minimize adverse effects and improve outcomes. The convergence of traditional orthodontics with regenerative therapies holds potential for revolutionizing treatment, but further interdisciplinary research is essential to bridge translational gaps.

Conclusions and Future Directions

In conclusion, orthodontic loading induces adaptive remodeling of alveolar bone through mechanotransduction, involving key cells like osteocytes, osteoblasts, and osteoclasts, and signaling pathways such as RANKL/OPG, Wnt/β-catenin, and YAP/TAZ. Recent studies underscore the differential cellular responses to compression and tension, modulated by factors including age, inflammation, and neural inputs. Therapeutic modalities like photobiomodulation, ultrasound, and micro-interventions offer avenues to enhance OTM efficiency and safety.

Future directions should prioritize longitudinal human studies to assess long-term effects on bone health and root integrity. Integrating advanced imaging, such as CBCT with AI-driven analysis, could refine force predictions and personalize treatments [37,43]. Exploring molecular targets, including miRNAs (e.g., miR-138, miR-195-5p) and lncRNAs (e.g., H19, LncTUG1), may yield novel pharmaceuticals to accelerate remodeling without inflammation [2,58]. Additionally, investigating the role of exosomes and stem cell therapies in modulating mechanosensitive pathways could advance regenerative orthodontics [19,54]. Collaborative efforts between biologists, engineers, and clinicians will be crucial to translate these insights into evidence-based practices, ultimately optimizing orthodontic care for diverse patient populations.

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