ORTHODONTIC TREATMENT IN PATIENTS UNDER ANTIRESORPTIVE THERAPY: BIOLOGICAL BASES AND IMPLICATIONS FOR OSTEONECROSIS OF THE JAWS

TRATAMENTO ORTODÔNTICO EM PACIENTES SOB TERAPIA ANTIRREABSORTIVA: BASES BIOLÓGICAS E IMPLICAÇÕES PARA A OSTEONECROSE DOS MAXILARES

TRATAMIENTO ORTODÓNTICO EN PACIENTES BAJO TERAPIA ANTIRRESORTIVA: BASES BIOLÓGICAS E IMPLICACIONES PARA LA OSTEONECROSIS DE LOS MAXILARES

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ABSTRACT

Objective: To review the experimental, in vitro, and clinical literature to characterize the biological mechanisms by which antiresorptive agents (bisphosphonates and denosumab) affect bone remodeling and orthodontic tooth movement, as well as to examine reports of Medication-Related Osteonecrosis of the Jaws (MRONJ) associated with orthodontic therapy.

Materials and Methods: Narrative review of published evidence, including preclinical studies, controlled clinical trials, and case reports, with emphasis on cellular alterations

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(osteoclastic activity, senescence, reactive oxygen species—ROS), mechanosensitive inflammatory responses, and radiographic/histopathological findings.

Results: Antiresorptive agents inhibit osteoclastic activity, increase bone mineral density, and reduce the rate of orthodontic tooth movement; zoledronic acid promotes a hyper-inflammatory response of the periodontal ligament under compression and causes cellular DNA damage, while denosumab shows a localized anchorage effect when applied locally. Clinical cases indicate the temporal manifestation of MRONJ after the onset of orthodontic tooth movement, with symptoms ranging from tooth mobility to extensive bone exposure. Clinical management involves individualized risk assessment, conservative and surgical strategies, and measures to reduce local trauma.

Conclusion: There is consistent evidence that antiresorptive agents negatively alter the bone remodeling required for orthodontics and may increase the risk of MRONJ; light orthodontic mechanics, prevention of aggravating factors, and an interdisciplinary approach are recommended. Prospective clinical studies and biomarkers (e.g., GDF15) are needed to guide safe protocols.

Keywords: Osteonecrosis of the Jaws. Antiresorptive Agents. Orthodontics. Bisphosphonates. Denosumab.

RESUMO

Objetivo: Revisar a literatura experimental, in vitro e clínica para caracterizar os mecanismos biológicos pelos quais antirreabsortivos (bisfosfonatos e denosumabe) afetam a remodelação óssea e o movimento dentário ortodôntico, além de examinar relatos de Osteonecrose dos Maxilares Relacionada a Medicamentos (OMRM) associados à terapia ortodôntica.

Materiais e métodos: Revisão narrativa das evidências publicadas, incluindo estudos pré-clínicos, ensaios clínicos controlados e relatos de caso, com ênfase em alterações celulares (atividade osteoclástica, senescência, ERO), respostas inflamatórias mecanossensíveis e achados radiográficos/histopatológicos.

Resultados: Os antirreabsortivos inibem a atividade osteoclástica, aumentam a densidade mineral óssea e reduzem a velocidade da movimentação dentária; o ácido zoledrônico promove hiper-resposta inflamatória do ligamento periodontal sob compressão e dano ao DNA celular, enquanto o denosumabe mostra efeito localizado na ancoragem quando aplicado localmente. Casos clínicos apontam manifestação temporal de OMRM após início da movimentação ortodôntica, com sintomas variando de mobilidade dentária a extensa exposição óssea. Manejo clínico envolve avaliação de risco individualizada, estratégias conservadoras e cirúrgicas e medidas para reduzir traumas locais.

Conclusão: Há evidência consistente de que antirreabsortivos alteram negativamente a remodelação necessária à ortodontia e podem aumentar o risco de OMRM; recomenda-se mecânica leve, prevenção de fatores agravantes e abordagem interdisciplinar. São necessários estudos clínicos prospectivos e biomarcadores (ex.: GDF15) para orientar protocolos seguros.

Palavras-chave: Osteonecrose dos Maxilares. Antirreabsortivos. Ortodontia. Bisfosfonatos. Denosumabe.

RESUMEN

Objetivo: Revisar la literatura experimental, in vitro y clínica para caracterizar los mecanismos biológicos mediante los cuales los fármacos antirresortivos (bisfosfonatos y denosumab) afectan la remodelación ósea y el movimiento dentario ortodóntico, así como examinar reportes de Osteonecrosis de los Maxilares Relacionada con Medicamentos (OMRM) asociada a la terapia ortodóntica.

Materiales y métodos: Revisión narrativa de la evidencia publicada, incluyendo estudios preclínicos, ensayos clínicos controlados y reportes de caso, con énfasis en alteraciones celulares (actividad osteoclástica, senescencia, especies reactivas de oxígeno—ERO), respuestas inflamatorias mecanosensibles y hallazgos radiográficos/histopatológicos.

Resultados: Los fármacos antirresortivos inhiben la actividad osteoclástica, aumentan la densidad mineral ósea y reducen la velocidad del movimiento dentario ortodóntico; el ácido zoledrónico promueve una hiperrespuesta inflamatoria del ligamento periodontal bajo compresión y daño al ADN celular, mientras que el denosumab muestra un efecto localizado de anclaje cuando se aplica localmente. Los casos clínicos señalan la manifestación temporal de OMRM tras el inicio del movimiento ortodóntico, con síntomas que varían desde movilidad dentaria hasta extensa exposición ósea. El manejo clínico implica una evaluación individualizada del riesgo, estrategias conservadoras y quirúrgicas, y medidas para reducir los traumatismos locales.

Conclusión: Existe evidencia consistente de que los antirresortivos alteran negativamente la remodelación necesaria para la ortodoncia y pueden aumentar el riesgo de OMRM; se recomienda el uso de mecánica ortodóntica ligera, la prevención de factores agravantes y un enfoque interdisciplinario. Se requieren estudios clínicos prospectivos y biomarcadores (por ejemplo, GDF15) para orientar protocolos seguros.

Palabras clave: Osteonecrosis de los Maxilares. Antirresortivos. Ortodoncia. Bisfosfonatos. Denosumab.

1 INTRODUCTION

Drug-related osteonecrosis of the jaws (MROM) has been established as a relevant clinicopathologic complication, especially in individuals exposed to antiresorptive agents. According to Laputková, Talian and Schwartzová (2023), OMRM involves complex molecular alterations, with emphasis on immunological and inflammatory pathways whose dysfunction seems to play a central role in the development and progression of the disease. These authors demonstrate that the condition presents a pattern characterized by altered cytokine pathways and biological rearrangements identifiable by multi-omics analyses, reinforcing its multifactorial and systemic nature. In the clinical context, Kalfarentzos *et al*. Sánchez et al. (2023) describe typical radiographic findings, such as extensive radiolucent areas associated with cortical defects, that align with the classical diagnostic criteria for OMRM. Thus, the contemporary concept of the disease is based on both morphoradiographic evidence and complex cellular mechanisms that affect bone remodeling and the local immune response.

The orthodontic relevance of this topic emerges from the body of evidence demonstrating that antiresorptive drugs directly interfere with tooth movement and may, under specific circumstances, contribute to the development of OMRM in patients undergoing orthodontic therapy.

In experimental studies, zoledronate has shown the ability to preserve the alveolar bone matrix and prevent resorption during orthodontic stimuli (de Sousa *et al.*, 2021), which confirms its strong impact on bone dynamics. Denosumab, on the other hand, according to Murugesan *et al.* (2021), promotes direct inhibition of the nuclear factor kappa B receptor activator system (RANKL) - a member of the tumor necrosis factor (TNF) family with an active role in the process of osteogenesis and osteoclast maturation -, delaying the formation of osteoclasts and increasing bone mineral density. Although these drugs are fundamental in several systemic conditions, their use requires caution in dentistry: Grimm *et al.* (2021) demonstrated that, under conditions of mechanical compression, zoledronate intensifies the expression of inflammatory markers in periodontal ligament fibroblasts, suggesting greater tissue vulnerability in contexts of tooth movement.

Clinically, Kalfarentzos *et al.* Wang et al. (2023) report a case in which symptoms of OMRM appeared shortly after the start of orthodontic treatment, reinforcing the possibility that mechanical forces applied during tooth movement function as local triggers in medicated patients. In addition, recent reviews indicate that bisphosphonates can inhibit orthodontic movement, delay bone healing, and even favor the appearance of osteonecrosis (Lessa *et al.*, 2024), although there is great methodological heterogeneity in the available studies, which prevents broad generalizations (Lopes, da Silva and Viana Junior, 2023). It can also

be considered that genetic factors related to bone remodeling, as proposed by Yamoune *et al*. (2022), can modify the individual risk of complications, making orthodontic planning even more dependent on personalized assessments.

This chapter aims to synthesize the scientific evidence on osteonecrosis of the jaws associated with orthodontic treatment, examining the mechanisms involved, the effects of antiresorptive drugs on bone remodeling and tooth movement, and the clinical reports describing this complication in patients under orthodontic therapy. We seek to integrate experimental, *in vitro,* and clinical data to clarify how these factors are related and what implications they have for the orthodontic management of patients using antiresorptive drugs.

2 METHODOLOGY

The present study is characterized as a critical narrative review, conducted through a literature search in the PubMed, Web of Science, Scopus and Google Scholar databases. Articles published between 2020 and 2025 were included, with no language restriction.

The search strategy combined controlled descriptors and free terms related to osteonecrosis of the jaws associated with the use of antiresorptive drugs and the implications of orthodontic treatment, using Boolean operators to refine the results. As inclusion criteria, studies directly related to the theme were considered, including clinical trials, observational studies, case reports, and experimental research. Articles not pertinent to the central theme, technical notes, descriptions of protocols or techniques without presentation of results, and publications without access to the full text were excluded.

The selection took place in successive stages: screening of titles and abstracts, followed by full reading of potentially eligible studies. After removing duplicates, articles that fully met the established criteria were included for analysis. Data extraction focused on the methodological design, sample characteristics, type of antiresorptive therapy, orthodontic parameters evaluated, and outcomes related to osteonecrosis. The findings were synthesized qualitatively, allowing the identification of patterns, gaps in the literature, and clinical implications for the orthodontic management of patients undergoing antiresorptive therapy.

3 RESULTS

The search for articles resulted in 13 selected studies, and the present study was organized in order to contemplate the main aspects related to osteonecrosis of the jaws associated with antiresorptive therapy and its implications in orthodontic treatment. The findings were organized into thematic axes that reflect the biological and clinical complexity

of the condition, ranging from the pathophysiological mechanisms involved in bone remodeling under drug action to its clinical repercussions in the context of tooth movement.

Initially, the biological basis of the action of antiresorptive drugs on bone tissue and their interference in the remodeling process were described. Next, the clinical and imaging manifestations associated with osteonecrosis of the jaws were addressed, as well as the risk factors and possible repercussions during orthodontic treatment. Finally, the therapeutic implications and clinical management strategies proposed in the recent literature were discussed, evidencing advances, limitations and challenges still present in the management of these patients.

4 PATHOPHYSIOLOGY OF OSTEONECROSIS ASSOCIATED WITH ANTIRESORPTIVE DRUGS

4.1 CHANGES IN OSTEOCLASTIC ACTIVITY AND IMPACTS ON BONE REMODELING

Osteoclasts are cells responsible for bone resorption, an essential process to maintain the metabolic balance of bone tissue, ensure its continuous renewal, and preserve mechanical integrity. They originate in the myeloid lineage of hematopoietic cells and their formation occurs through the process known as osteoclastogenesis, whose main stimulus is the NFκβ activator receptor ligand (RANKL), however, the use of certain drugs, such as antiresorptive drugs, can interfere with this production (dos Santos and Mestriner Junior, 2025).

Bisphosphonates are a drug class that corresponds to synthetic pyrophosphate analogues and are widely used in the treatment of various diseases that affect bone tissue (dos Santos and Mistriner Junior, 2025). However, the use of these medications during dental treatments can, in some cases, result in adverse effects, such as inhibition of tooth movement, delayed bone healing, and the possibility of developing osteonecrosis in the maxilla and mandible (Lessa *et al.,* 2024).

Bisphosphonates are considered to act mainly on osteoclasts with the aim of increasing bone mass (Arai *et al.*, 2023) and its administration in patients with orthodontic movement is capable of prolonging the duration of treatment, due to the lower rates of planned tooth movement (Lopes, da Silva and Viana Junior, 2023). From this perspective, treatment with zoledronic acid (AZ), a bisphosphonate medication, significantly prevents the resorption of the alveolar bone matrix, as described by Souza *et al*. (2021) in a study in which, at a dose of 1 mg/kg, this drug considerably reduced total bone volume and the number of osteoclasts formed and activated, causing less root resorption, in addition to preventing the formation of orthodontically induced large root craters.

4.2 INFLUENCE OF REACTIVE OXYGEN SPECIES (ROS), CELLULAR SENESCENCE AND GDF15

Bisphosphonates are affected by the physiological role of the enzyme in arachidonic acid metabolism, inflammation, and oxidative stress, which can hinder the healthy success of orthodontic treatment due to the formation of reactive oxygen species, whose local production is increased by the action of CYP2C8 on periodontal fibroblasts (Yamoune *et al*., 2022).

AZ triggers an expressive response to cellular stress by causing DNA strand breaks, which can reduce cell survival and favor the senescence process of hPdLFs (Human Periodontal Ligament Fibroblasts), in addition to significantly raising the levels of IL6, IL1B, and GDF15, exacerbating the inflammatory response (Nitzsche *et al.,* 2024). Such antiresorptive also exacerbates the number of adherent THP1 cells in hPdLFs, confirming the mechanosensitive inflammatory hyperresponse of periodontal ligament fibroblasts exposed to zoledronic acid (Nitzsche *et al*., 2024).

Side effects of bone-modifying medications include extreme mobility, sclerotic changes in the alveolar bone, increased root resorption, periodontal degeneration, alveolar bone loss, and even risk of osteonecrosis of the jaw (Yamoune *et al*., 2022).

4.3 ROLE IN ANGIOGENESIS AND LOCAL IMMUNITY

Antiresorptive drugs, especially AZ, may be related to lower vascularization in the periodontal ligament, since compression of this structure is capable of reducing the number and area of blood vessels (de Souza *et al*. 2021).

The dysregulated genes associated with OMRM are mostly related to the body's immune response, as they result in significant enrichment of pathways linked to the innate immune system (Laputková, Talian, and Schwartzová, 2023). The analysis of the interactions between these genes and the also dysregulated miRNAs reinforces the participation of pathways associated with cytokine signaling, especially those mediated by interleukins (Laputková, Talian and Schwartzová, 2023). In addition, specific investigation of miRNAs has revealed a highly interconnected set capable of directly modulating several genes, such as IL1B, VEGFA, CXCL8, and CD44 (Laputková, Talian, and Schwartzová, 2023).

5 OSTEONECROSIS RELATED TO ORTHODONTIC TREATMENT

5.1 CASES ASSOCIATED WITH THE USE OF ORTHODONTIC BRACES

Among the available clinical reports, osteonecrosis was described as an event that manifested itself subsequent to the beginning of orthodontic treatment, suggesting a temporal

association between tooth movement and the appearance of lesions (Kalfarentzos *et al.*, 2023). For example, it has been observed that, in patients undergoing orthodontic treatment, the appearance of symptoms such as extreme tooth mobility in the mandible, periodic edema in the gingival region, and pain in the anterior region of the mandible occurred soon after the start of treatment (Kalfarentzos *et al.*, 2023). Orthodontic treatment may therefore increase the risk of complications in patients with changes in bone remodeling (Kalfarentzos et al., 2023).

Other studies report that, for patients using antiresorptive drugs, such as denosumab, the bone remodeling necessary for orthodontic movement may be impaired. According to Murugesan *et al*. (2021), in the first days after injection, it takes a while to inhibit RANKL, a cytokine essential for bone remodeling, which prevents tooth movement by reducing bone resorption. This interaction between orthodontic therapy and the effects of drugs should be carefully considered when planning treatments in patients who use such drugs (Murugesan *et al*., 2021). Studies indicate that patients undergoing bisphosphonates have a lower rate of tooth movement and impairment of orthodontic treatment, which can be attributed to changes in osteoclastic activity and bone response (Lopes, da Silva and Viana Junior, 2023).

5.2 OBSERVED CLINICAL AND RADIOGRAPHIC FEATURES

In a study conducted by Kalfarentzos *et al*. (2023), the clinical manifestations described in the reports of osteonecrosis associated with orthodontic treatment include persistent pain, tooth mobility, and soft tissue changes, with the presence of bone exposure. In this study, multiple fistulas were observed in the anterior region of the mandible, marked tooth mobility involving the anterior mandibular segment, pain in the chin region, and progressive edema, with the appearance of these changes after the beginning of orthodontic movement. These clinical findings were described concomitantly with the development of osteonecrosis in the reports evaluated.

When the lesion is not treated properly, the symptoms can progress to more serious conditions, such as failure in the primary closure of the soft tissue and bone exposure, especially in the region close to the compromised teeth The worsening of the conditions can lead to the need for more complex interventions to control the pathological process (Kalfarentzos *et al*., 2023).

The association between bone necrosis and secondary infection is also evident. Histopathological analysis of the cases showed necrotic bone with empty osteolytic gaps, absence of osteoblastic and osteoclastic activity, and the presence of bacterial colonies adhered to the bone surface (Kalfarentzos *et al*., 2023). This observation reinforces the

importance of infectious control in the management of osteonecrosis, especially in patients undergoing orthodontic treatments and presenting bone tissue impairment (Kalfarentzos *et al*., 2023).

Radiographic findings in cases of osteonecrosis related to orthodontic treatment include radiolucent areas and defects in the bone cortical, which are observed as typical manifestations of severe bone involvement. Cone beam computed tomography (CBCT) has been essential in visualizing these changes, with one study highlighting that "extensive radiolucent areas surrounding the roots of teeth 35 to 45, associated with defects in the buccal bone cortical" (Kalfarentzos *et al*., 2023) were found.

In addition, the study shows that these radiolucent areas reflect the progression of bone changes when local control is inadequate, demonstrating the importance of cone beam tomography in therapeutic planning (Kalfarentzos *et al*., 2023). This exam allows an accurate diagnosis, crucial for proper surgical management and for the prevention of complications associated with orthodontic treatment.

5.3 CLINICAL MANAGEMENT

The clinical management of osteonecrosis associated with orthodontic treatment involves a progressive approach, with the combined use of conservative measures and surgical interventions, depending on the severity of the condition. In many reports, the strategies adopted include the extraction of compromised teeth and surgical management of the affected region, with the absence of antiresorptive medication being indicated in the months prior to the intervention, to ensure the necessary bone stability during orthodontic movement (Kalfarentzos *et al*., 2023).

The surgical interventions described include crestal incision, extraction of compromised teeth, preparation of large flaps, removal of granulomatous tissue, and primary closure by means of two-layer suture. These approaches are adopted to ensure efficient removal of necrotic tissue and restore alveolar bone functionality, which is essential for the success of subsequent orthodontic treatment (Kalfarentzos *et al*., 2023).

In the event of persistence of necrosis, additional interventions may be required, such as additional extraction to achieve primary healing and complete debridement with removal of bone sequestration. After these interventions, complete bone healing was observed, with no recurrence during 13 months of follow-up (Kalfarentzos *et al*., 2023).

Prosthetic rehabilitation is another fundamental aspect, being performed with a removable prosthesis designed to minimize pressure on the soft tissues, essential to avoid new traumas during the healing process and continuity of orthodontic treatment (Kalfarentzos

et al., 2023). This therapeutic care is supported by reviews that emphasize the need to eliminate prosthetic trauma in cases of osteonecrosis of the jaws, especially in patients undergoing orthodontic treatment, in order to preserve bone health and treatment success (Lessa *et al.*, 2024).

6 EFFECTS OF ANTIRESORPTIVE DRUGS ON ORTHODONTIC TOOTH MOVEMENT (OTM)

The use of antiresorptive drugs during orthodontic treatment introduces a significant variable in the fundamental biological process for tooth movement: alveolar bone remodeling. Evidence on its effects emerges from a wide variety of scientific studies, which makes standardization regarding its use in patients undergoing orthodontic movement limited.

6.1 EFFECTS OF BISPHOSPHONATES ON ORTHODONTIC TOOTH MOVEMENT

The effects of bisphosphonates, especially the potent zoledronic acid (AZ), on tooth movement induced by orthodontic forces have been extensively investigated in preclinical models. In an experimental model with Wistar rats, it was observed that the administration of AZ, in different concentrations, promoted a significant reduction in tooth displacement induced by orthodontic appliances, evidencing a decrease in the rate of orthodontic tooth movement when compared to the untreated groups (Sousa *et al.*, 2021).

In addition to the direct interference in the speed of tooth movement, the histological analysis revealed important alterations in the periodontal ligament, with a significant increase in the extension of the hyaline areas in the treated groups, indicative of cellular impairment associated with the application of orthodontic force. Concomitantly, AZ exerted its main pharmacological effect on the alveolar bone, significantly preventing the resorption of the bone matrix during the tooth movement process. This preservation of bone volume was particularly evident on the compression side, a region in which the periodontal ligament suffers greater mechanical stress due to the contact of the tooth with the alveolar bone (Sousa *et al.*, 2021).

The cellular mechanisms underlying the effects observed in vivo have been investigated through in vitro studies with cultures of human periodontal ligament fibroblasts (hPdLFs), which demonstrate that zoledronic acid acts directly on fundamental processes of cell biology. It is evident that the drug exerts a dose-dependent effect in reducing the viability and proliferation of these cells, without compromising their capacity for osteogenic differentiation. At the same time, a dose-dependent increase in H2A phosphorylation is observed. X, indicating activation of the DNA damage response. When exposed to conditions

that mimic the orthodontic microenvironment characterized by compressive stress associated with inflammation, hPdLFs treated with AZ show an exacerbated inflammatory response (Nitzsche *et al*., 2024). The combination of IL-1β, compressive stress, and zoledronate resulted in the highest observed value of COX-2 and IL-6 expression, followed by the highest secretion of PGE-2 and IL-6 (Grimm *et al*., 2021). This hyper-response is corroborated by the detection of significantly elevated levels of IL1B, IL6, and GDF15, suggesting a specifically intensified pro-inflammatory profile in relation to AZ (Nitzsche *et al*., 2024). The functional confirmation of this activation was due to the observation that the number of adherent THP1 mononuclear cells was significantly increased in hPdLFs treated with AZ and submitted to compression (Nitzsche *et al*., 2024). In summary, zoledronate intensified the upregulation of inflammatory markers in compressed HPdLF (Grimm *et al.*, 2021). A crucial mechanism dysregulated by this condition is the local balance of bone remodeling, as quantitative analysis of gene expression revealed AZ-dependent differences in strength-related reduction of osteoprotegerin (OPG - antiosteoclastic decoy receptor) and increase in RANKL, changes that could be partially prevented by silencing GDF15 (Nitzsche *et al.*, 2024).

The scattered evidence from animal and cellular studies is consolidated and critically evaluated in systematic reviews and narratives of the literature. These syntheses converge to a clear impact of bisphosphonates on the speed of treatment, identifying the administration of these drugs as a relevant factor for lower rates of tooth movement during orthodontic treatment (Lopes, da Silva and Viana Junior, 2023). Most studies analyzed in a systematic review point to the fact that the systemic use of bisphosphonates during orthodontic treatment appears to reduce the extent and speed of tooth movement, thereby prolonging the duration of treatment (Lessa *et al.,* 2024). The underlying mechanism of action is explained by the fact that bisphosphonates interrupt the remodeling cycle, inhibiting osteoclast function and reducing bone vascularization, which can hinder orthodontic treatment by delaying or preventing tooth movement (Gravia *et al.*, 2025). Studies have shown that bisphosphonates can alter orthodontic tooth movement by affecting essential cellular processes, ultimately inhibiting bone resorption; Furthermore, consistent clinical evidence shows that bisphosphonate treatment delays tooth eruption and tooth development, including tooth germ, enamel, and root formation (Arai *et al*., 2024, Gravia *et al*., 2025). Despite the general convergence of the findings, the reviews highlight relevant methodological limitations, requiring a cautious interpretation of the results, since the studies present quantitative and qualitative heterogeneity in their methods. In addition, the absence of the use of microcomputed tomography in the evaluation of orthodontic movement is observed, as well as restrictions regarding clinical application in pediatric patients, whose use remains limited

and requires special caution (Gravia *et al*., 2025; Lessa *et al*., 2024; Lopes, da Silva and Viana Junior, 2023).

6.2 EFFECTS OF DENOSUMAB ON ORTHODONTICS

The maintenance of skeletal mass depends on the dynamic balance between the processes of bone resorption and bone formation, which are mediated, respectively, by the coordinated activity of osteoclasts and osteoblasts. This remodeling mechanism is essential for bone homeostasis and for the adaptation of bone tissue to mechanical and biological stimuli. In this context, the ligand of the nuclear factor activator receptor kappa B (RANKL) plays a central role, acting not only in physiological bone resorption, but also in pathological conditions associated with bone remodeling imbalance. The relevance of RANKL extends to orthodontics, since this mediator is directly involved in the bone response induced by the forces applied during orthodontic tooth movement (Yoshimatsu *et al*., 2022).

Denosumab, a fully human monoclonal antibody directed against RANKL and used clinically in the treatment of bone pathologies, represents a molecular targeted therapy strategy capable of inhibiting differentiation and osteoclastic activity. Based on this principle, Yoshimatsu *et al.* (2022) investigated the effects of RANKL blockade by anti-mRANKL antibody on orthodontic tooth movement in an experimental mouse model. After ten days of tooth movement, root resorption was observed on the mesial surface of the distovestibular root of the maxillary first molar in the control group. In contrast, the animals treated with the anti-mRANKL antibody showed no signs of root resorption after the application of orthodontic forces.

In addition, the number of odontoclasts was significantly lower in the anti-mRANKL-treated group when compared to the untreated group. Similar results were observed in the analysis of TRAP-positive cells, the number of which was significantly reduced in the group treated with anti-mRANKL associated with TNF-α compared to the group submitted to TNF-α alone. It was also observed that both the tooth movement distance and the number of TRAP-positive cells on the pressure side of the tooth root were reduced in the animals that received the RANKL block, reinforcing the role of this mediator in the osteoclastic response associated with orthodontic movement (Yoshimatsu *et al.*, 2022).

However, Murugesan *et al*. Wang et al. (2021) conducted a prospective, randomized, controlled clinical trial at the Department of Orthodontics and Dentofacial Orthopedics at Saveetha Dental College and Hospitals, Chennai, with the aim of evaluating the effect of local injection of denosumab on the control of orthodontic anchorage. The results showed that the local application of the drug was effective in reinforcing anchorage in the maxilla, significantly

reducing mesial movement of the maxillary molars. Although the loss of anchorage in the first three months of retraction was similar between the experimental and control groups, a significant reduction in mesial molar movement was observed in the following three months on the side treated with denosumab, showing an improvement in anchorage control.

On the other hand, in the mandibular arch, the reduction in anchorage loss on the side treated with denosumab was considered insignificant when compared to the control side. The localized action of the drug was corroborated by the fact that there was no inhibition or reduction of anterior retraction in any of the arches, suggesting that denosumab acts predominantly in the region of application. Based on these findings, the authors indicated that administering the drug one to two months before the onset of retraction could maximize its clinical effects (Murugesan *et al*., 2021).

In an integrated manner, the available experimental and clinical data indicate that RANKL blockade by antibodies, such as denosumab or anti-mRANKL, is associated with the reduction of osteoclastic activity markers, the limitation of root resorption in animal models, and the improvement of orthodontic anchorage control in the maxilla in humans. However, the limited response observed in the mandible suggests a predominantly localized action of the drug, reinforcing the importance of adequate planning regarding the site and timing of application to optimize clinical results (Murugesan *et al.*, 2021).

7 ACTIONS OF ANTIRESORPTIVE DRUGS AND RISK FACTORS FOR OSTEONECROSIS

7.1 TYPE OF DRUG AND MECHANISM OF ACTION

Antiresorptive drugs constitute effective therapies for skeletal disorders such as osteoporosis, cancer with bone metastasis (Kalfarentzos *et al*., 2023), and osteogenesis imperfecta, although they can interfere with enamel, root, and tooth eruption development (Arai *et al.*, 2024). Bisphosphonates (BP) are synthetic derivatives of pyrophosphate and act in an anti-osteoclastic manner on osteoclasts and mesenchymal cells (Arai *et al.*, 2024), reducing bone turnover and increasing mineral density (Murugesan *et al*., 2021; Santos and Mestriner Junior, 2025). This activity can compromise tooth movement and bone healing (Gravia *et al*., 2025; Lessa *et al*., 2024), in addition to favoring osteonecrosis due to the reduction of local vascularization (Gravia *et al*., 2025; Santos and Mestriner Junior, 2025).

The potency of drugs is variable, with risedronate being less potent (Lopes, da Silva, and Viana Junior, 2023), probably due to differences between bisphosphonates with and without nitrogen (Grimm *et al*., 2021). According to Sousa *et al.* (2021), zoledronate acts mainly in the area of compression of the periodontal ligament against the bone. In addition,

antiangiogenic agents can interfere with angiogenesis through the regulation of core genes, such as VEGFA (Laputková, Talian, and Schwartzová, 2023).

7.2 TIME AND ROUTE OF ADMINISTRATION

Detailed history of medical history, including bisphosphonate use, duration, dosage, and frequency of administration are important in clinical management (Gravia *et al.*, 2025). High doses compromise bone turnover and increase the risk of OMRM (Kalfarentzos *et al*., 2023). According to Nitzsche *et al*. (2024), *in vitro* studies demonstrated that increasing concentrations of zoledronic acid increased cell death and reduced periodontal fibroblast proliferation, corroborating the *cumulative effects in vivo*.

Prolonged use of bisphosphonates reduces the speed of tooth movement and increases the time of orthodontic treatment (Lessa *et al*., 2024; Lopes, da Silva and Viana Junior, 2023). However, stopping the medication does not exclude the risk of complications, as the drug remains in bone tissue for prolonged periods (Gravia *et al*., 2025). According to Kalfarentzos *et al*. (2023), the suspension of the medication for 14 months did not prevent bone healing.

The route of administration and the patient's condition influence the risk of complications (Gravia *et al*., 2025). In the study by Murugesan *et al*. (2021), denosumab, applied locally, reduced the formation of osteoclasts, increased bone mineral density, and promoted anchorage reinforcement, with an effect restricted to the area of application.

7.3 AGGRAVATING CONDITIONS OR FACTORS

There are no protocols on the effect of denosumab on orthodontics (Kalfarentzos *et al*., 2023), and caution is required based on the patient's medical history (Lessa *et al*., 2024). Adequate prevention, patient clarification, and dental follow-up are essential to reduce risk factors (Kalfarentzos *et al*., 2023; Laputková, Talian and Schwartzová, 2023; Santos and Mistriner Junior, 2025).

Among the main local factors associated with OMRM, traumas due to poorly adapted prostheses stand out (Kalfarentzos *et al*., 2023; Santos and Mestriner Junior, 2025), surgical procedures, poor oral hygiene, and oral infections, which must be eliminated before treatment (Santos and Mestriner Junior, 2025).

Denosumab, when applied locally, can reduce anchorage loss, but its use requires attention to patients with hypocalcemia, immunosuppression, systemic diseases, or active oral lesions (Murugesan *et al*., 2021). In neonates, antiresorptive drugs can compromise tooth eruption, since the age at which use begins directly influences its severity (Arai *et al*., 2024).

In pediatrics, bisphosphonates are effective but may alter permanent tooth morphology, while denosumab poses additional risks of rebound hypercalcemia and fractures after discontinuation (Gravia *et al*., 2025).

8 ORTHODONTIC CONSIDERATIONS IN PATIENTS USING OR HAVING A HISTORY OF ANTIRESORPTIVE DRUGS

Orthodontic intervention in patients undergoing antiresorptive therapy requires a thorough understanding of the cellular and tissue changes induced by these drugs. Agents such as zoledronic acid significantly alter the inflammatory response and bone remodeling in the face of orthodontic forces, making the periodontium more vulnerable to complications (Yamoune *et al*., 2022). Animal studies have shown that zoledronic acid significantly reduces tooth displacement induced by orthodontic appliances, an effect that is related to the suppression of bone remodeling in pressure areas. Although this study did not find signs of microscopic necrosis, the authors report a decrease in periodontal vascularization, which may represent an indirect risk factor in more complex clinical situations (de Sousa *et al.*, 2021). There are indications that zoledronate amplifies the expression of pro-inflammatory mediators in response to compressive stress, including COX-2, IL-6, and PGE-2, especially when mechanical forces combine with inflammatory stimuli such as IL-1β, resulting in an exacerbated biological reaction, and thus significantly decreasing tooth displacement induced by mechanical forces, preserving bone volume, and reducing the number of osteoclasts in the orthodontic movement region, evidencing a marked suppression of resorption (Lessa *et al.*, 2024; Grimm *et al.*, 2021; Nitzsche *et al.,* 2024). At the same time, the drug causes DNA damage and cellular senescence, reducing osteoclastic activity and making bone remodeling substantially slower, which directly impacts tooth movement (Yamoune *et al*., 2022).

In addition to local effects, gene expression analyses related to osteonecrosis of the jaws reveal that patients exposed to antiresorptive drugs may present immune dysfunctions, with activation of genes associated with interleukins, cytokines, and growth factors, such as IL1B, IL6, and VEGFA, suggesting that the pathophysiology of OMRM involves a systemic inflammatory imbalance potentially aggravated by mechanical stimuli or dental procedures (Laputková, Talian and Schwartzová, 2023). The literature also points out that bisphosphonate-induced γδ T-cell depletion may increase susceptibility to osteonecrosis, complicating dental management in these patients (Kalfarentzos *et al.*, 2023).

Another relevant aspect is pharmacogenetics: variants of the CYP2C8 gene, such as allele 3, can increase the local production of reactive oxygen species in response to bisphosphonates, altering inflammatory dynamics and influencing the response to

orthodontic treatment. These findings reinforce that bone remodeling in individuals under antiresorptive therapy is not only reduced, but also modulated by immunological and genetic factors, imposing greater responsibility on the orthodontist in the application of forces and in the assessment of biological risks (Yamoune *et al*., 2022).

8.1 SUGGESTED ORTHODONTIC CONDUCTS

In view of these physiological changes, clinical recommendations for orthodontic treatment in these patients emphasize light mechanics, strict biological control, and prevention of factors that cause trauma or inflammation. Excessive compression should be avoided, particularly in patients with prior inflammation, as the combination of intense forces with nitrogenous bisphosphonates has resulted, in experiments carried out, in higher expression of pro-inflammatory mediators in cell cultures (Yamoune *et al*., 2022).

In addition to biomechanics, invasive procedures and situations that cause repetitive microtrauma should be minimized (Gravia *et al.*, 2025). Santos and Mestriner Júnior (2025) identified that in surgical trauma, prosthetics, infections, and inadequate hygiene as local factors associated with the triggering of osteonecrosis of the jaws, orthodontic movement, by requiring active bone remodeling, can act as an aggravating factor when this remodeling is compromised. This risk is corroborated by clinical reports of patients using antiresorptive drugs who presented increased tooth mobility, pain, and recurrent edema, signs consistent with initial necrosis (Kalfarentzos *et al.*, 2023).

Experimental studies indicate that bisphosphonates not only slow down orthodontic movement, but significantly prolong treatment due to the reduction in the rate of bone resorption required for root displacement (Lessa *et al.*, 2024).

As for denosumab, experimental evidence suggests that its local administration could increase maxillary anchorage without changing the previous retraction rate, especially if applied one to two months before mechanical (Murugesan *et al*., 2021). The absence of well-defined clinical protocols or defined recommendations for its use in orthodontics makes it not recommended until additional research is available (Gravia *et al.*, 2025).

The studies evaluated in this study demonstrated a bias to use animal models, cell cultures or in vitro analyses, which do not fully replicate the human periodontal environment. In addition, there is significant variability between the types of drugs, their mechanisms of action and relative potencies, such as risedronate, which has lower biological potency, added to the diversity in the magnitude of orthodontic forces applied experimentally, making it difficult to standardize the results (Lessa *et al.*, 2024). Another point is the methodological heterogeneity in studies on OMRM, which contributes to divergent interpretations, with

different populations, doses, and clinical contexts generating inconsistent risk estimates (Laputková, Talian and Schwartzová, 2023).

9 CONCLUSION

OMRM is a complication linked to the use of antiresorptive agents for the treatment of bone conditions, such as bisphosphonates and denosumab. It has established itself as a critical clinicopathologic challenge in the orthodontic treatment setting. This condition involves an alteration in the immunological and inflammatory pathways, which play a fundamental role in the development and progression of the disease, and which, when related to bone remodeling imposed by orthodontic forces, creates a high-risk environment for tissue necrosis.

The action of antiresorptive drugs drastically inhibits bone resorption, which is essential for tooth movement, which translates, clinically, into a reduction in the speed of treatment. However, the risk of OMRM is enhanced by the fact that zoledronic acid induces a disordered cellular response, marked by senescence, DNA damage, and an exacerbated pro-inflammatory hyper-response when periodontal ligament cells are subjected to orthodontic compression. In this way, the mechanical forces applied by the device work as a local trigger, enhancing the manifestation of OMRM in an already systemically compromised microenvironment.

The studies reported showed an association between the time and severity of the manifestations, ranging from marked mobility to extensive bone defects. However, the main barrier faced to the advancement of orthodontic treatments is the predictability of OMRM, since the patient's susceptibility is linked to several factors such as the dosage and duration of use of the drug, the presence of aggravating factors, such as infections and traumas, the influence of genetic factors and biomarkers.

For a successful management of OMRM in orthodontics, a systemic and individualized risk assessment is relevant to ensure tooth alignment compatible with the preservation of the patient's bone health and integrity. In addition, it is necessary to develop research that allows the identification and modulation of predictive therapeutic targets, such as GDF15, in order to reduce cellular and inflammatory damage induced by antiresorptive drugs before the intervention. In this sense, an interdisciplinary integration between molecular knowledge and clinical practice is imperative.

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