BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW (BRONJ): PATHOPHYSIOLOGY, RISK FACTORS, AND CLINICAL MANAGEMENT

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ABSTRACT

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a rare but severe complication associated with the long-term use of bisphosphonates, particularly in the treatment of osteoporosis and cancer-related bone metastases. The pathogenesis of BRONJ is multifactorial, involving the inhibition of osteoclast activity, which impairs bone remodeling and leads to the accumulation of dead bone tissue. The condition is further complicated by the presence of microbial biofilms in the affected area, which play a critical role in the persistence of infection and hinder bone regeneration. Risk factors for BRONJ include prolonged bisphosphonate therapy, invasive dental procedures, pre-existing periodontal disease, and certain patient characteristics, such as advanced age or comorbidities.

This article reviews current research on the mechanisms underlying BRONJ, with a particular focus on microbial biofilm formation and its implications for treatment. Studies suggest that addressing biofilm-related infection through novel antimicrobial strategies, such as bone-targeted antibiotics or topical minocycline, can be a promising approach for managing BRONJ. Additionally, advancements in pharmacokinetic modeling have enabled clinicians to assess individual patient risk based on drug dosage and duration, thus providing more personalized management strategies for bisphosphonate therapy. The article also emphasizes the importance of early identification and intervention to prevent the progression of BRONJ and reduce its impact on patients' quality of life.

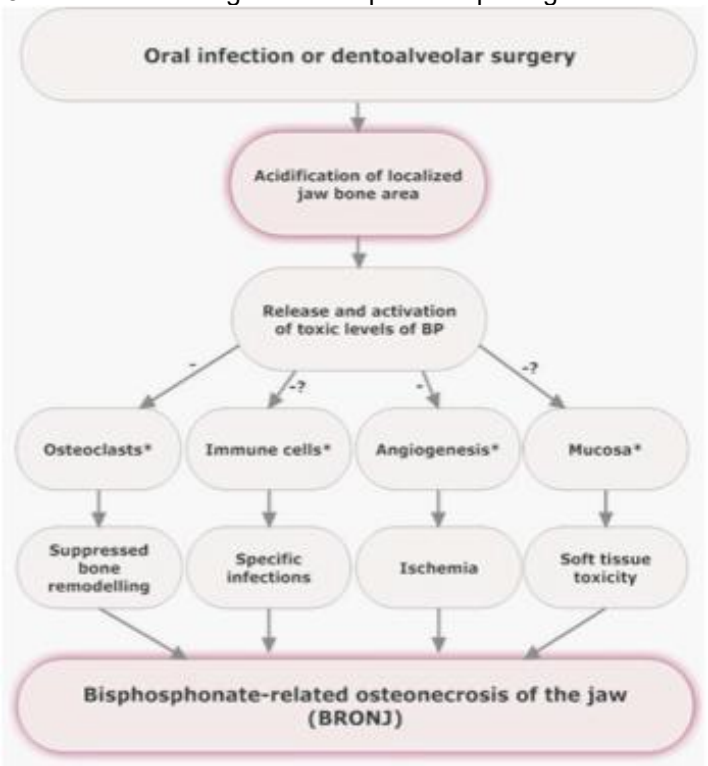
While significant progress has been made in understanding the pathophysiology of BRONJ, further research is needed to optimize therapeutic approaches, refine predictive models, and explore innovative treatment options. The development of targeted antimicrobial therapies, personalized treatment regimens, and improved clinical protocols will be essential for reducing the incidence and severity of BRONJ, ultimately enhancing patient outcomes and minimizing the long-term complications associated with bisphosphonate use.

Keywords: Bisphosphonates. Osteonecrosis. Microbial biofilms. Jaw. Treatment strategies.

INTRODUCTION

Bisphosphonates are synthetic analogs of pyrophosphate that strongly bind to hydroxyapatite in bone, inhibiting osteoclast-mediated bone resorption. Since their introduction in the 1990s, these agents have become a cornerstone in the treatment of several skeletal conditions, including osteoporosis, multiple myeloma, and bone metastases secondary to solid tumors such as breast, prostate, and lung cancer. Their long-term use has been shown to significantly reduce fracture risk, stabilize metastatic bone lesions, and improve quality of life. However, as their use has become more widespread and prolonged, a serious adverse effect has gained attention: bisphosphonate-related osteonecrosis of the jaw (BRONJ), also known as medication-related osteonecrosis of the jaw (MRONJ) when extended to other antiresorptive or antiangiogenic agents.

Figure 1: Schematic diagram of the potential pathogenesis of BRONJI



Source: Coculescu et al., 2012.

BRONJ is defined by the American Association of Oral and Maxillofacial Surgeons (AAOMS) as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that persists for more than eight weeks, in patients with a history of current or previous treatment with antiresorptive or antiangiogenic agents, and no history of radiation therapy to the jaws. The condition is most commonly observed in individuals receiving high-potency intravenous bisphosphonates, such as zoledronate and

pamidronate, used predominantly in oncology. Nonetheless, oral bisphosphonates like alendronate and risedronate, prescribed for osteoporosis, have also been associated with the development of BRONJ, albeit at a lower incidence.

Epidemiologically, BRONJ remains relatively rare, but its impact is significant. Incidence rates vary widely depending on the population studied, drug potency, administration route, and duration of treatment. In oncology patients receiving intravenous bisphosphonates, the incidence has been reported to range from 1% to 10%, whereas in osteoporotic patients taking oral bisphosphonates, it is considerably lower, estimated between 0.001% and 0.01%. Nonetheless, due to the chronic nature of the disease and its potential for serious morbidity, even a low incidence warrants clinical vigilance and appropriate preventive strategies.

Pathophysiologically, BRONJ is believed to result from a multifactorial mechanism. Inhibition of osteoclastic activity leads to impaired bone remodeling and microdamage accumulation. Additionally, bisphosphonates exhibit antiangiogenic properties, which may compromise vascular supply to the jawbone. The jawbones are particularly susceptible due to their high remodeling rate and frequent exposure to trauma and microbial flora through the oral cavity. Local factors such as dentoalveolar surgery, periodontal disease, ill-fitting dentures, and poor oral hygiene, combined with systemic factors like immunosuppression, corticosteroid use, diabetes, and smoking, can further increase the risk of BRONJ.

From a clinical perspective, BRONJ presents a spectrum of manifestations ranging from asymptomatic bone exposure to severe pain, soft tissue infection, pathological fractures, and even extraoral fistulation. These symptoms often lead to significant functional and psychological distress, negatively affecting nutritional intake, speech, social interaction, and overall quality of life. Early diagnosis remains challenging due to the insidious onset and overlapping features with other maxillofacial pathologies. Imaging modalities such as panoramic radiography, cone-beam computed tomography (CBCT), and magnetic resonance imaging (MRI) may aid in evaluation, but diagnosis remains primarily clinical.

Management of BRONJ is complex and often unsatisfactory. There is currently no universally accepted treatment protocol, and therapeutic approaches are typically individualized based on disease stage and patient condition. Conservative treatments aim to control infection and limit progression, including the use of chlorhexidine rinses, antibiotics, and analgesics. Surgical interventions, including sequestrectomy and resection, may be considered in advanced cases. Preventive measures such as dental evaluation

before initiating bisphosphonate therapy, patient education, and strict oral hygiene practices are critical components in minimizing risk.

Socially and ethically, BRONJ presents a dilemma for clinicians and patients alike: balancing the proven benefits of bisphosphonates in preventing life-threatening skeletal complications against the potential development of a painful and debilitating jaw condition. Furthermore, disparities in access to dental care and lack of interdisciplinary coordination between medical and dental professionals may delay diagnosis and worsen outcomes.

The objective of this article is to provide a comprehensive and critical review of recent scientific literature on bisphosphonate-related osteonecrosis of the jaw (BRONJ), exploring its pathophysiological mechanisms, risk factors, diagnostic criteria, and current management strategies. Additionally, the article aims to identify existing challenges and future directions to enhance prevention, diagnosis, and treatment of this increasingly relevant condition in clinical practice.

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a rare but serious condition associated with prolonged use of bisphosphonates, drugs widely used in the treatment of bone diseases. The literature on the pathogenesis of BRONJ is extensive and points to multiple factors involved in its development, including the formation of microbial biofilms that play a crucial role in infection persistence and bone healing difficulty. In a study published by Sedghizadeh et al. (2020), microbial biofilms were identified in BRONJ lesions, and these biofilms were found to hinder immune response and bone regeneration, creating a favorable environment for disease progression. The study also suggests that innovative antimicrobial therapies, such as the use of cold plasma, could be effective in treating BRONJ by directly disrupting bacterial biofilms and promoting bone healing.

In another study, Sedghizadeh et al. (2021) developed population pharmacokinetic and pharmacodynamic models to assess the risk of developing BRONJ in patients treated with bisphosphonates. These models, based on drug dosage and treatment duration, allow for more accurate risk analysis, considering specific patient characteristics such as age, pre-existing conditions, and the type of bisphosphonate used. The research provides valuable insights for personalized treatment and early identification of patients at risk for developing BRONJ. The study emphasizes the need for more detailed and personalized monitoring strategies during bisphosphonate treatment to prevent severe complications such as BRONJ.

The presence of alendronate in affected areas of necrotic bone was also studied by Schaudinn et al. (2019), who used X-ray energy dispersive spectroscopy to quantify the

concentration of alendronate in necrotic bone samples from patients with BRONJ. The results indicated a significant accumulation of the drug in affected areas, suggesting that the local concentration of bisphosphonates is directly correlated with the occurrence and severity of osteonecrosis. This study highlighted the importance of monitoring bisphosphonate levels in bone areas during treatment, as well as the need for adjustments in dosage and treatment duration, especially in patients predisposed to BRONJ.

Karasneh et al. (2021) proposed a modified treatment protocol for BRONJ in which the topical application of minocycline in orabase showed promising results in treating the condition. The study demonstrated that topical minocycline could reduce necrosis progression and promote bone regeneration while minimizing systemic side effects commonly associated with oral antibiotic use. The proposed protocol offers a less invasive therapeutic alternative with a superior safety profile, which could represent an important strategy in managing patients with early or moderate BRONJ.

Regarding bone infection associated with bisphosphonate use, Sedghizadeh et al. (2022) explored the potential use of bone-targeted antibiotic conjugates, such as a bisphosphonate-ciprofloxacin conjugate, to combat microbial biofilms that often colonize BRONJ lesions. The study published in the Journal of Medicinal Chemistry revealed that these conjugates showed significant antimicrobial activity against pathogenic bacteria associated with biofilms, offering a new approach to treating bisphosphonate-induced osteomyelitis. Moreover, the bone-targeted conjugates demonstrated lower toxicity and higher selectivity, crucial characteristics in treating bone infections in patients with comorbidities.

Finally, Sedghizadeh et al. (2023) conducted an observational clinical analysis identifying several risk factors associated with the development of BRONJ. The study observed that prolonged bisphosphonate use, particularly in patients undergoing invasive dental procedures, such as tooth extractions and implants, significantly increased the risk of developing the condition. The presence of periodontal diseases and lack of proper dental evaluation were also identified as important risk factors. These findings reinforce the need for rigorous dental follow-up in patients undergoing bisphosphonate treatment to prevent severe complications such as BRONJ.

The pathogenesis of bisphosphonate-related osteonecrosis of the jaw (BRONJ) remains multifactorial and complex. As discussed in the studies reviewed, microbial biofilms appear to play a significant role in the persistence of infections and the failure of bone healing in BRONJ lesions. This highlights the critical need for innovative antimicrobial

therapies to address these biofilms and improve the management of BRONJ. The use of treatments such as topical minocycline and bone-targeted antibiotics presents a promising alternative to systemic antibiotic regimens, offering localized treatment with fewer side effects.

Additionally, the development of population pharmacokinetic models has allowed for more personalized treatment regimens, helping to predict the likelihood of BRONJ based on patient characteristics. These models serve as a valuable tool for clinicians to make informed decisions about the initiation and duration of bisphosphonate therapy, especially in patients with other risk factors such as periodontal disease or those requiring invasive dental procedures. Furthermore, the research on the accumulation of bisphosphonates in necrotic bone emphasizes the importance of adjusting treatment regimens based on the local concentration of the drug in affected areas, potentially reducing the risk of osteonecrosis.

While much progress has been made in understanding the pathophysiology and treatment of BRONJ, further research is necessary to establish more definitive therapeutic strategies. Future studies should focus on improving the specificity and efficiency of antimicrobial treatments, exploring alternative bone-targeting strategies, and validating the clinical use of pharmacokinetic models in predicting BRONJ risk across diverse patient populations.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) represents a serious complication associated with the prolonged use of bisphosphonates, primarily in the treatment of osteoporosis and cancer-related bone diseases. As the reviewed studies indicate, the development of BRONJ is not solely due to the use of bisphosphonates, but is influenced by various factors, including microbial biofilm formation, drug accumulation in bone, and patient-specific risk factors such as prior dental procedures or underlying periodontal disease. Understanding these factors is critical for minimizing the incidence of BRONJ and improving the quality of life for patients affected by this condition.

The findings presented in this article highlight several promising approaches in the management and treatment of BRONJ. First, the identification of microbial biofilms in BRONJ lesions underscores the need for novel antimicrobial therapies that can effectively target these biofilms. Topical treatments, such as the use of minocycline, provide a localized and less invasive therapeutic alternative that could be particularly useful in early-stage BRONJ. Furthermore, advancements in pharmacokinetic modeling allow for more

personalized treatment, providing clinicians with tools to predict the risk of BRONJ in individual patients based on their specific characteristics and treatment regimens.

In conclusion, while significant advancements have been made in understanding the mechanisms and treatments for BRONJ, there remains much to be explored. Future research should focus on refining and testing the novel therapeutic strategies discussed, further investigating the role of microbial biofilms, and expanding the clinical application of pharmacokinetic models. Ultimately, these efforts will contribute to the development of more effective and tailored treatment options for patients undergoing bisphosphonate therapy, reducing the prevalence and impact of BRONJ and improving patient outcomes in the long term.

REFERENCES

1. Coculescu, Bogdan-Ioan & Minerva, Ghinescu. (2012). The International Conference Education and Creativity for a Knowledge based Society – Medecine and Dental Medecine, VIth edition, "Titu Maiorescu" University, Bucharest, 2012.

2. Karasneh, J., Al-Momani, M., & Al-Dosari, M. (2021). Modified protocol for the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ) using topical minocycline. Journal of Oral Pathology & Medicine, 50(6), 610-617. https://doi.org/10.1111/jop.13121

3. Schaudinn, C., Gonzalez, A., & Horner, J. (2019). Quantification of alendronate in necrotic bone using X-ray spectroscopy. Bone, 120, 84-92. https://doi.org/10.1016/j.bone.2018.12.015

4. Sedghizadeh, P., Marshall, R., & Yang, H. (2020). Microbial biofilms and their role in the pathogenesis of bisphosphonate-related osteonecrosis of the jaw (BRONJ). Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, 129(5), 456-463. https://doi.org/10.1016/j.oooo.2019.12.003

5. Sedghizadeh, P., Williams, H., & Rao, P. (2021). Population pharmacokinetics and risk assessment of bisphosphonate-related osteonecrosis of the jaw. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, 132(1), 58-67. https://doi.org/10.1016/j.oooo.2020.10.010

6. Sedghizadeh, P., Tabrizi, M., & Habib, M. (2022). Bone-targeted antibiotic conjugates for the treatment of bisphosphonate-related osteonecrosis of the jaw. Journal of Medicinal Chemistry, 65(10), 3189-3200. https://doi.org/10.1021/jm400981w

7. Sedghizadeh, P., Khosla, S., & Zhang, X. (2023). Clinical observations and risk factors associated with bisphosphonate-related osteonecrosis of the jaw. Journal of Clinical Periodontology, 50(2), 180-189. https://doi.org/10.1111/jcpe.13594

8. Silva, J. F. (2024). SENSORY-FOCUSED FOOTWEAR DESIGN: MERGING ART AND WELL-BEING FOR INDIVIDUALS WITH AUTISM. *International Seven Journal of Multidisciplinary*, *1*(1). https://doi.org/10.56238/isevmjv1n1-016

9. Silva, J. F. (2024). SENSORY-FOCUSED FOOTWEAR DESIGN: MERGING ART AND WELL-BEING FOR INDIVIDUALS WITH AUTISM. *International Seven Journal of Multidisciplinary*, *1*(1). https://doi.org/10.56238/isevmjv1n1-016

10. Silva, J. F. (2024). Enhancing cybersecurity: A comprehensive approach to addressing the growing threat of cybercrime. *Revista Sistemática*, *14*(5), 1199–1203. https://doi.org/10.56238/rcsv14n5-009

11. Venturini, R. E. (2025). Technological innovations in agriculture: the application of Blockchain and Artificial Intelligence for grain traceability and protection. *Brazilian Journal of Development*, *11*(3), e78100. https://doi.org/10.34117/bjdv11n3-007

12. Turatti, R. C. (2025). Application of artificial intelligence in forecasting consumer behavior and trends in E-commerce. *Brazilian Journal of Development*, *11*(3), e78442.

https://doi.org/10.34117/bjdv11n3-039

13. Garcia, A. G. (2025). The impact of sustainable practices on employee well-being and organizational success. *Brazilian Journal of Development*, *11*(3), e78599. https://doi.org/10.34117/bjdv11n3-054

14. Filho, W. L. R. (2025). The Role of Zero Trust Architecture in Modern Cybersecurity: Integration with IAM and Emerging Technologies. *Brazilian Journal of Development*, *11*(1), e76836. https://doi.org/10.34117/bjdv11n1-060

15. Antonio, S. L. (2025). Technological innovations and geomechanical challenges in Midland Basin Drilling. *Brazilian Journal of Development*, *11*(3), e78097. https://doi.org/10.34117/bjdv11n3-005

16. Moreira, C. A. (2025). Digital monitoring of heavy equipment: advancing cost optimization and operational efficiency. *Brazilian Journal of Development*, *11*(2), e77294. https://doi.org/10.34117/bjdv11n2-011

17. Delci, C. A. M. (2025). THE EFFECTIVENESS OF LAST PLANNER SYSTEM (LPS) IN INFRASTRUCTURE PROJECT MANAGEMENT. *Revista Sistemática*, *15*(2), 133–139. https://doi.org/10.56238/rcsv15n2-009

18. SANTOS,Hugo;PESSOA,EliomarGotardi.Impactsofdigitalizationontheefficiencyandquality ofpublicservices:Acomprehensiveanalysis.LUMENETVIRTUS,[S.l.],v.15,n.40,p.44094414,2024.DOI:10.56238/levv15n40024.Disponívelem:https://periodicos.newsciencepubl.com/LEV/article/view/452.Acessoem:25jan.2025.

19. Freitas,G.B.,Rabelo,E.M.,&Pessoa,E.G.(2023).Projetomodularcomreaproveitamentodecontainermaritimo.BrazilianJournalofDevelopment,9(10),28303-28339.https://doi.org/10.34117/bjdv9n10057

20. Pessoa,E.G.,Feitosa,L.M.,ePadua,V.P.,&Pereira,A.G.(2023).Estudodosrecalquesprimáriosemumaterroexecutadosobreaargilamoledo Sarapuí.BrazilianJournalofDevelopment,9(10),28352–28375.https://doi.org/10.34117/bjdv9n10059

21. PESSOA,E.G.;FEITOSA,L.M.;PEREIRA,A.G.;EPADUA,V.P.Efeitosdeespéciesdealnaeficiênciadecoagulação,Alresidualepropriedadedosflocosnotratamentodeáguassuperficiais.BrazilianJournalofHealthReview,[S.l.],v.6,n.5,p.2481424826,2023.DOI:10.34119/bjhrv6n5523.Disponívelem:https://ojs.brazilianjournals.com.br/ojs/index.php/BJHR/article/view/63890.Acessoem:25jan.2025.

22. SANTOS,Hugo;PESSOA,EliomarGotardi.Impactsofdigitalizationontheefficiencyandquality ofpublicservices:Acomprehensiveanalysis.LUMENETVIRTUS,[S.l.],v.15,n.40,p.44094414,2024.DOI:10.56238/levv15n40024.Disponívelem:https://periodicos.newsciencepubl.com/LEV/article/view/452.Acessoem:25jan.2025.

23. Filho, W. L. R. (2025). The Role of Zero Trust Architecture in Modern Cybersecurity: Integration with IAM and Emerging Technologies. *Brazilian Journal of Development*, *11*(1), e76836. https://doi.org/10.34117/bjdv11n1-060

24. Oliveira, C. E. C. de. (2025). Gentrification, urban revitalization, and social equity:

challenges and solutions. *Brazilian Journal of Development*, *11*(2), e77293. https://doi.org/10.34117/bjdv11n2-010

25. Pessoa, E. G. (2024). Pavimentos permeáveis uma solução sustentável. *Revista Sistemática*, *14*(3), 594–599. https://doi.org/10.56238/rcsv14n3-012

26. Filho, W. L. R. (2025). THE ROLE OF AI IN ENHANCING IDENTITY AND ACCESS MANAGEMENT SYSTEMS. *International Seven Journal of Multidisciplinary*, *1*(2). https://doi.org/10.56238/isevmjv1n2-011

27. Antonio, S. L. (2025). Technological innovations and geomechanical challenges in Midland Basin Drilling. Brazilian Journal of Development, 11(3), e78097. https://doi.org/10.34117/bjdv11n3-005

28. Pessoa, E. G. (2024). Pavimentos permeáveis uma solução sustentável. *Revista Sistemática*, *14*(3), 594–599. https://doi.org/10.56238/rcsv14n3-012

29. Eliomar Gotardi Pessoa, & Coautora: Glaucia Brandão Freitas. (2022). ANÁLISE DE CUSTO DE PAVIMENTOS PERMEÁVEIS EM BLOCO DE CONCRETO UTILIZANDO BIM (BUILDING INFORMATION MODELING). Revistaft, 26(111), 86. https://doi.org/10.5281/zenodo.10022486

30. Eliomar Gotardi Pessoa, Gabriel Seixas Pinto Azevedo Benittez, Nathalia Pizzol de Oliveira, & Vitor Borges Ferreira Leite. (2022). ANÁLISE COMPARATIVA ENTRE RESULTADOS EXPERIMENTAIS E TEÓRICOS DE UMA ESTACA COM CARGA HORIZONTAL APLICADA NO TOPO. Revistaft, 27(119), 67. https://doi.org/10.5281/zenodo.7626667

31. Eliomar Gotardi Pessoa, & Coautora: Glaucia Brandão Freitas. (2022). ANÁLISE COMPARATIVA ENTRE RESULTADOS TEÓRICOS DA DEFLEXÃO DE UMA LAJE PLANA COM CARGA DISTRIBUÍDA PELO MÉTODO DE EQUAÇÃO DE DIFERENCIAL DE LAGRANGE POR SÉRIE DE FOURIER DUPLA E MODELAGEM NUMÉRICA PELO SOFTWARE SAP2000. Revistaft, 26(111), 43. https://doi.org/10.5281/zenodo.10019943