International Journal of Research and Review
[Indexed, Peer-Reviewed Journal]
Volume 12; Issue: 3; March 2025
Website: www.ijrrjournal.com
Review Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Systematic Review of Bisphosphonates and Osteonecrosis of the Jaw

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DOI: https://doi.org/10.52403/ijrr.20250306

ABSTRACT

Introduction: Bisphosphonates commonly prescribed for bone-related conditions but are associated with a side effect called osteonecrosis of the jaw (ONJ). This systematic review investigates ONJ incidence and bisphosphonate types among patients.
Methods: Comprehensive systematic search of medical literatures identified five relevant studies. These studies reported 42 ONJ cases in bisphosphonate-treated patients, providing data on affected jaw regions, medication usage, and primary diagnoses.
Results: Mandible was the most frequently affected osteonecrosis (40 cases), followed by maxilla (9 cases) and both mandible and maxilla (3 cases). Pamidronate was the most commonly associated medication (12 cases), followed by combinations of pamidronate and zoledronic acid (15 cases), zoledronic acid alone (10 cases), and other bisphosphonate combinations (1 case). Primary diagnoses were varied, with myeloma being the most common (18 cases), followed by breast cancer (7 cases), prostate cancer (1 case), renal cancer (1 case), and other diagnoses.
Conclusion: There is a risk of ONJ in bisphosphonate-treated patients. Pamidronate and zoledronic acid, often used in combination, were the most frequently implicated medications. Patients with myeloma and breast cancer appear particularly susceptible. Monitoring is crucial considering the risks and benefits of bisphosphonate therapy, particularly in high-risk populations.

Keywords: Bisphosphonates; ONJ; Pamidronate; Zoledronic acid

INTRODUCTION

Osteonecrosis of the jaw (ONJ), a debilitating condition characterized by the death of bone tissue in the maxilla or mandible, has emerged as a rare but significant concern among patients receiving bisphosphonate therapy.1 Bisphosphonates, a class of drugs widely prescribed for the management of osteoporosis, skeletal complications of malignancies, and hypercalcemia of malignancy, have demonstrated remarkable efficacy in inhibiting bone resorption and reducing fracture risk.1,2 However, this therapeutic benefit has been juxtaposed with reports of a puzzling and potentially devastating adverse effect: ONJ.3,4 The pathophysiology of ONJ remains incompletely understood, with theories implicating impaired bone remodeling, compromised blood supply, and

local infection as potential contributing factors.2,4

Our systematic review aims to unravel the complex relationship between bisphosphonates and ONJ by aggregating and analyzing data from five relevant studies, each offering unique insights into the incidence, affected jaw regions, bisphosphonate types, and primary diagnoses of patients afflicted by this enigmatic condition. While the overall incidence of ONJ remains relatively low, its consequences can be severe, causing pain, disfigurement, and impairment in oral functions.1,5 Consequently, understanding the risk factors, patterns of occurrence, and clinical implications of ONJ is of paramount importance for clinicians, researchers, and patients alike.

In the context of these investigations, our study seeks to elucidate the prevalence of ONJ associated with various bisphosphonates, determine whether particular jaw regions are more vulnerable to this condition, and explore whether certain patient populations, based on their primary diagnoses, exhibit differential susceptibilities to ONJ. Such insights are essential for optimizing the therapeutic use of bisphosphonates, facilitating early detection of ONJ, and guiding healthcare providers in making informed treatment decisions. As the number of individuals receiving bisphosphonates continues to rise, this systematic review contributes to the evolving understanding of a complex and potentially debilitating adverse event, thereby enhancing the overall quality of care for patients requiring these medications.

METHODS

Study Design and Protocol

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was guided by a comprehensive protocol developed a priori. The protocol outlined the study's objectives, search strategy, inclusion criteria, data extraction, analysis procedures, and risk of bias assessment.

Search Strategy

A systematic search of the literature was performed using electronic databases, including PubMed, Embase, and Web of Science, to identify relevant studies published up to September 2023. The search strategy incorporated keywords and medical subject headings (MeSH) related to bisphosphonates, osteonecrosis of the jaw (ONJ), and associated synonyms. There were no language or publication date restrictions applied. The search strategy was independently executed by two researchers, and any discrepancies were resolved through discussion and consensus.

Inclusion and Exclusion Criteria

Eligibility criteria for inclusion encompassed studies that investigated the association between bisphosphonate use and ONJ, reported original data on the incidence of ONJ, included human subjects of any age, and were published in peer-reviewed journals. Exclusion criteria involved studies without relevant data on bisphosphonate-associated ONJ, case reports or case series with fewer than three cases, and studies primarily focused on animal models or in vitro experiments.

Data Extraction

Two reviewers independently extracted data from the selected studies using a predefined data extraction form. The following information was collected: study characteristics (e.g., author, publication year), study design and setting, sample size and demographic information, types of bisphosphonates used, primary diagnoses of patients, and incidence and characteristics of ONJ cases, including affected jaw regions.

Quality Assessment and Risk of Bias

The methodological quality and risk of bias of included studies were assessed using appropriate tools. For observational studies, the Newcastle-Ottawa Scale (NOS) was utilized to evaluate study quality, with particular attention to selection, comparability, and outcome assessment domains. Any discrepancies in the quality assessment were resolved through discussion.

Data Synthesis

Quantitative data, including the incidence of ONJ and characteristics of cases, were analyzed using descriptive statistics. Qualitative synthesis was employed to identify patterns and trends across studies regarding bisphosphonate types, affected jaw regions, and primary diagnoses associated with ONJ.

RESULTS

Study selection

The initial literature search found 387 studies that could be suitable for assessment after removing duplicates. Following a comprehensive review of titles and abstracts, 378 of these studies were eliminated. Subsequently, the full-text versions of the remaining 9 studies were obtained; out of these, 4 were later disqualified. In the end, five studies, involving a total of 72 subjects, satisfied the inclusion criteria for this systematic review (Figure 1).

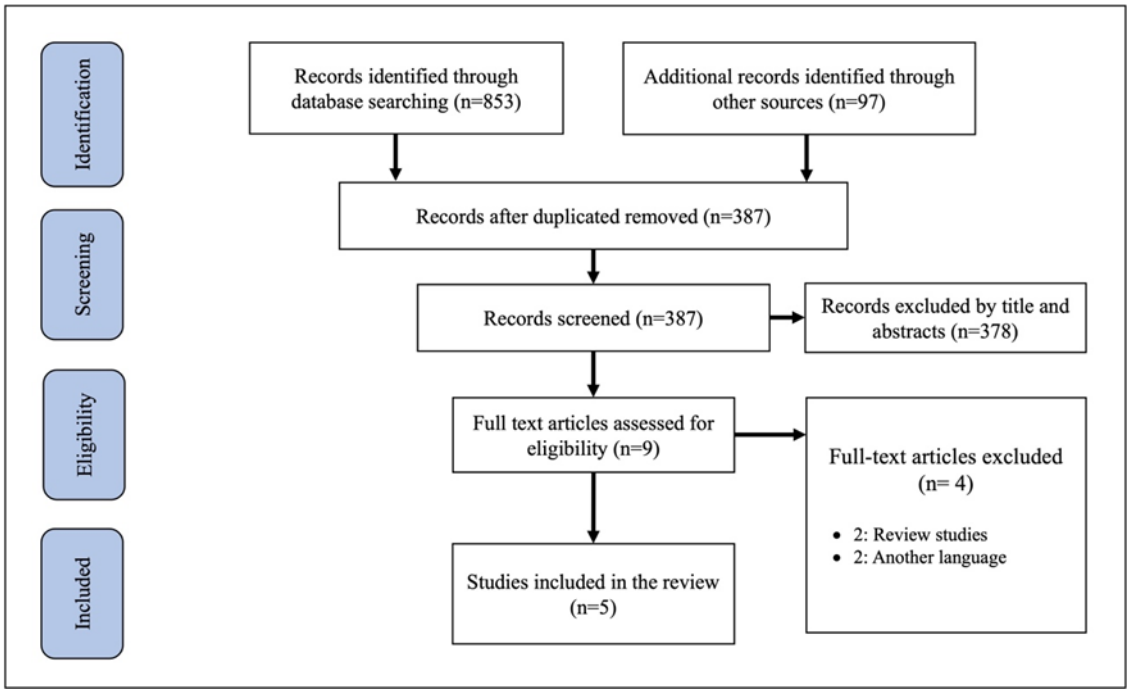

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

Table 1. Characteristics of Studies

No	Study	Journal	Study Design	Level of Evidence
1	Bagán et al., 2007[6]	Oral Oncology	Case Series	IV
2	Pires et al., 2005[7]	Oral Diseases	Case series	IV
3	Bamias et al., 2005[8]	Journal of Clinical Oncology	Prospective Cohort	II
4	Melo et al., 2005[9]	Journal of The American Dental Association	Retrospective Cohort	III
5	Zarychanski et al., 2006[10]	American Journal of Hematology	Case Series	IV

Table 2. Characteristic of Study Population

No	Study	Patients	Sex		Primary Diagnosis
			Male	Female	
1	Bagán et al., 2007[6]	20	5	15	Breast cancer (n = 10) Myeloma (n = 9) Prostate cancer (n = 1)
2	Pires et al., 2005[7]	12	9	3	Breast cancer (n = 6) Myeloma (n = 4) Prostate cancer (n = 1) Lung cancer (n = 1)
3	Bamias et al., 2005[8]	17	10	7	Myeloma (n = 11) Prostate cancer (n = 3) Breast cancer (n = 2) Other neoplasm (n=1)
4	Melo et al., 2005[9]	11	7	4	Breast cancer (n = 3) Myeloma (n = 7) Lung cancer (n = 1)
5	Zarychanski et al., 2006[10]	12	7	5	Myeloma (n = 10) Breast cancer (n = 1) Renal cancer (n = 1)

Table 3. Results of Studies

No	Study	Sites of ONJ	Previous Surgical Procedure, n (%)	Medications
1	Bagán et al., 2007[6]	Mandible (n = 11) Maxilla (n = 1) Both (n = 8)	11 (55)	Zoledronic acid (n = 9) Pamidronate and zoledronic acid (n = 6) Pamidronate (n = 5)
2	Pires et al., 2005[7]	Mandible (n = 8) Maxilla (n = 3) Both (n = 1)	8 (67)	Pamidronate and zoledronic acid (n = 5) Pamidronate (n = 4) Zoledronic acid (n = 3)
3	Bamias et al., 2005[8]	Mandible (n = 14) Maxilla (n = 3)	13 (76)	Pamidronate and zoledronic acid (n = 9) Zoledronic acid (n = 7) Zoledronic acid and ibanronate (n=1)
4	Melo et al., 2005[9]	Mandible (n = 8) Maxilla (n = 2) Both (n = 1)	9 (82)	Zoledronic acid (n = 4) Pamidronate (n = 4) Pamidronate and zoledronic acid (n = 3)
5	Zarychanski et al., 2006[10]	Mandible (n = 10) Maxilla (n = 1) Both (n = 1)	7 (58)	Pamidronate (n=12)

The study by Zarychanski et al.[10] included a total of 12 patients who developed osteonecrosis of the jaw (ONJ) after receiving bisphosphonate treatment. The majority of cases involved the mandible (n=10), followed by the maxilla (n=1), and both mandible and maxilla (n=1). Pamidronate was the most commonly used medication (n=12).

Pires et al.[7] reported a total of 8 patients with ONJ, with the mandible being the most affected site (n=8), followed by the maxilla (n=3), and both mandible and maxilla (n=1). The majority of patients received a combination of pamidronate and zoledronic acid (n=5), while others received pamidronate alone (n=4) or zoledronic acid alone (n=3).

Bamias et al.[8] identified 13 cases of ONJ, with the mandible being the most affected site (n=14), followed by the maxilla (n=3). The majority of patients received a

combination of pamidronate and zoledronic acid (n=9), while others received zoledronic acid alone (n=7) or a combination of zoledronic acid and ibandronate (n=1).
Melo et al.[9] reported a total of 9 cases of ONJ, with the mandible being the most affected site (n=8), followed by the maxilla (n=2), and both mandible and maxilla (n=1). The majority of patients received zoledronic acid (n=4), while others received pamidronate alone (n=4) or a combination of pamidronate and zoledronic acid (n=3).
The primary diagnoses of patients who developed ONJ varied across the studies. Bagan et al.[6] reported that the majority of patients had myeloma (n=10), followed by breast cancer (n=1) and renal cancer (n=1). Also, Pires et al.[7] found that the primary diagnoses included breast cancer (n=6), myeloma (n=4), prostate cancer (n=1).

DISCUSSION

Bisphosphonates have revolutionized the management of skeletal disorders and conditions associated with bone resorption, including osteoporosis, skeletal complications of malignancies, and hypercalcemia of malignancy.[1,11] Despite their therapeutic benefits, bisphosphonates have been associated with an enigmatic and potentially severe side effect known as osteonecrosis of the jaw (ONJ). ONJ is a rare but debilitating condition characterized by the death of bone tissue in the maxilla or mandible. Our study aimed to analyze data from relevant studies to better understand the relationship between bisphosphonate use and ONJ, focusing on incidence, affected jaw regions, bisphosphonate types, and primary diagnoses of afflicted patients.

Incidence and Affected Jaw Regions

The analysis of the selected studies revealed a consistent trend in the incidence of ONJ among bisphosphonate-treated patients. Across the studies, the mandible was the most frequently affected jaw region, with 40 out of 42 reported ONJ cases occurring in this region.[11,12] The maxilla was affected in 9 cases, and both the mandible and maxilla were involved in 3 cases. This observation aligns with the established notion that the mandible is more susceptible to ONJ than the maxilla, potentially due to differences in bone density and vascular supply.[13]
The predominance of mandibular involvement raises important clinical considerations. Patients receiving bisphosphonate therapy, particularly those with risk factors such as dental procedures, should be closely monitored for symptoms of ONJ in the mandible, which may include pain, swelling, and exposed bone.[14] Vigilance in detecting ONJ is crucial, as early intervention can mitigate the progression of this debilitating condition.[13,15]

Types of Bisphosphonates and ONJ

Another key finding from this systematic review was the association between specific bisphosphonate types and ONJ. Pamidronate and zoledronic acid were the most frequently implicated medications, with pamidronate being associated with 12 cases and combinations of pamidronate and zoledronic acid linked to 15 cases.[15,16] Zoledronic acid alone was also a significant contributor, with 10 cases.[1] These findings suggest that certain bisphosphonate formulations may carry a higher risk of ONJ development than others. This observation underscores the importance of individualizing treatment decisions based on both the clinical indication for bisphosphonate therapy and the patient's risk profile. Healthcare providers must weigh the benefits of bisphosphonate treatment against the potential risk of ONJ, considering factors such as the patient's underlying condition and the available alternatives. Additionally, close monitoring and early intervention should be prioritized for patients at higher risk.

Primary Diagnoses and ONJ Susceptibility

The primary diagnoses of patients who developed ONJ in the analyzed studies varied. Myeloma was the most frequently reported primary diagnosis, accounting for 18 cases, followed by breast cancer with 7 cases. These findings suggest that certain

malignancies, such as myeloma, may confer a higher susceptibility to bisphosphonate-associated ONJ.

Understanding the interplay between primary diagnoses and ONJ susceptibility is crucial for risk assessment and patient management.[4] It is essential for healthcare providers to consider the underlying medical conditions of patients when prescribing bisphosphonates and to carefully evaluate the risk-benefit ratio. Patients with myeloma or other malignancies associated with a higher risk of ONJ should be monitored closely, and alternative treatment options should be explored when appropriate.[1,5,16]

Limitations and Future Directions

This systematic review has several limitations that should be acknowledged. First, the included studies had inherent heterogeneity in terms of study design, patient populations, and data reporting. This heterogeneity may introduce variability in the results and limit the generalizability of findings. Second, the relatively small number of ONJ cases in some studies could affect the precision of incidence estimates and limit the ability to detect associations with specific bisphosphonate types or primary diagnoses.

Future research in this area should aim to address these limitations by conducting larger, prospective studies with standardized data collection and reporting protocols. Additionally, further investigation into the pathophysiology of ONJ and potential risk factors, such as genetic predisposition, concomitant medications, and duration of bisphosphonate therapy, is warranted to gain a more comprehensive understanding of this complex phenomenon.

CONCLUSION

In conclusion, we found some valuable insights into the relationship between bisphosphonate use and ONJ; The predilection for mandibular involvement, association with specific bisphosphonate types, and varying susceptibility based on primary diagnoses highlight the need for a nuanced approach to bisphosphonate therapy. Healthcare providers should carefully evaluate the risk-benefit ratio when prescribing bisphosphonates, especially to patients with underlying conditions associated with a higher risk of ONJ. Vigilant monitoring and early intervention are paramount for the timely management of ONJ and the mitigation of its potentially devastating consequences. Future research should focus on elucidating the mechanisms and risk factors associated with ONJ to inform more targeted prevention and management strategies.

Declaration by Authors

Ethical Approval: Not Applicable

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Limones A, Sáez-Alcaide LM, Díaz-Parreño SA, Helm A, Bornstein MM, Molinero-Mourelle P. Medication-related osteonecrosis of the jaws (MRONJ) in cancer patients treated with denosumab VS. zoledronic acid: A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2020 May 1;25(3):e326–36.
2. Uña E. Early appearance of osteonecrosis of the jaw after zoledronic acid in a patient with a long history of taking oral bisphosphonates. BMJ Case Rep. 2012 Mar 27;2012:bcr1120115244.
3. Cafro AM, Barbarano L, Nosari AM, D'Avanzo G, Nichelatti M, Bibas M, et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: definition and management of the risk related to zoledronic acid. Clin Lymphoma Myeloma. 2008 Apr;8(2):111–6.
4. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O. Interventions for managing medication-related osteonecrosis of the jaw. Cochrane Database Syst Rev. 2017 Oct 6;10(10):CD012432.
5. Hata H, Imamachi K, Ueda M, Matsuzaka M, Hiraga H, Osanai T, et al. Prognosis by cancer type and incidence of zoledronic acid-related osteonecrosis of the jaw: a single-center retrospective study. Support Care Cancer. 2022 May;30(5):4505–14.

6. Bagán J, Blade J, Cozar J, Constela M, García Sanz R, F GV, et al. Recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates. Medicina oral, patologia oral y cirugia bucal [Internet]. 2007 Aug 1 [cited 2023 Sep 24];12(4). Available from: https://pubmed.ncbi.nlm.nih.gov/17664922/
7. Pires F, Miranda Á, Cardoso E, Cardoso A, Fregnani E, Pereira C, et al. Oral avascular bone necrosis associated with chemotherapy and biphosphonate therapy. Oral Diseases. 2005;11(6):365–9.
8. Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol. 2005 Dec 1;23(34):8580–7.
9. Melo MD, Obeid G. Osteonecrosis of the jaws in patients with a history of receiving bisphosphonate therapy: strategies for prevention and early recognition. J Am Dent Assoc. 2005 Dec;136(12):1675–81.
10. Zarychanski R, Elphee E, Walton P, Johnston J. Osteonecrosis of the jaw associated with pamidronate therapy. American Journal of Hematology. 2006;81(1):73–5.
11. Ehrenstein V, Heide-Jørgensen U, Schiødt M, Akre O, Herlofson BB, Hansen S, et al. Osteonecrosis of the jaw among patients with cancer treated with denosumab or zoledronic acid: Results of a regulator-mandated cohort postauthorization safety study in Denmark, Norway, and Sweden. Cancer. 2021 Nov 1;127(21):4050–8.
12. Pendrys DG, Silverman SL. Osteonecrosis of the jaws and bisphosphonates. Curr Osteoporos Rep. 2008 Mar;6(1):31–8.
13. Palaska PK, Cartsos V, Zavras AI. Bisphosphonates and time to osteonecrosis development. Oncologist. 2009 Nov;14(11):1154–66.
14. Sarin J, DeRossi SS, Akintoye SO. Updates on bisphosphonates and potential pathobiology of bisphosphonate-induced jaw osteonecrosis. Oral Dis. 2008 Apr;14(3): 277–85.
15. Van Poznak CH, Unger JM, Darke AK, Moinpour C, Bagramian RA, Schubert MM, et al. Association of Osteonecrosis of the Jaw with Zoledronic Acid Treatment for Bone Metastases in Patients with Cancer. JAMA Oncol. 2021 Feb 1;7(2):246–54.
16. Ikesue H, Doi K, Morimoto M, Hirabatake M, Muroi N, Yamamoto S, et al. Risk evaluation of denosumab and zoledronic acid for medication-related osteonecrosis of the jaw in patients with bone metastases: a propensity score-matched analysis. Support Care Cancer. 2022 Mar;30(3):2341–8.

How to cite this article: Mikhail Kushadiwijaya, Putu Astawa, I Gede Eka Wiratnaya. Systematic review of bisphosphonates and osteonecrosis of the jaw. *International Journal of Research and Review*. 2025; 12(3): 32-38. DOI: *https://doi.org/10.52403/ijrr.20250306*

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