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Incidence of bisphosphonate-related osteonecrosis of the jaw (Bronj) based on treatment duration and symptoms in osteoporosis patients

Nurani Atikasari [1,*], Mefina Kuntjoro [1], Nike Hendrijantini [1], Bambang Agustono [1], Harry Laksono [1], Najma Nurul Aisyah Haris [2] and Tifara Luthfi Khoirunnisa [2]

[1] *Department of Prosthodontics, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Undergraduate Student, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.*

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Abstract

Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) is a serious adverse effect associated with bisphosphonate therapy, commonly used for osteoporosis treatment. While bisphosphonates effectively reduce fracture risks, prolonged use has been linked to an increased incidence of BRONJ. This systematic review aims to analyze the incidence of BRONJ based on treatment duration and symptoms in osteoporosis patients, highlighting risk factors and clinical manifestations. A structured literature search was conducted using major electronic databases, including EBSCO, PubMed, and Springer Link, following the PRISMA guidelines for study selection. Findings indicate that the duration of bisphosphonate therapy significantly influences BRONJ occurrence, with patients undergoing treatment for more than five years exhibiting a higher incidence of necrotic jaw lesions. BRONJ symptoms range from mild jaw discomfort to severe osteonecrosis, characterized by exposed bone, infections, and pathological fractures. The progression of symptoms is often subtle in the early stages, making early diagnosis challenging. This review also identifies other contributing factors, such as invasive dental procedures, underlying oral infections, and systemic health conditions, which exacerbate BRONJ severity. Despite extensive research on bisphosphonate therapy, there remains no consensus on the optimal duration of treatment for osteoporosis patients to minimize BRONJ risks while maintaining therapeutic benefits. Additionally, early-stage BRONJ symptoms often go undetected, leading to delayed intervention and worsened patient outcomes.

Keywords: Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ); Bisphosphonates; Osteoporosis; Treatment Duration; Symptoms; Risk Factors; Osteonecrosis

1. Introduction

Osteoporosis is a global public health issue, with fractures leading to significant morbidity and mortality. It is characterized by low bone mineral density and deterioration of bone microarchitecture, resulting in increased bone fragility and a higher risk of fractures [28, 31]. According to the World Health Organization (WHO), over 200 million people suffer from osteoporosis. WHO ranks osteoporosis as the second most serious global health issue after cardiovascular diseases [2]. Osteoporosis affects individuals across all races and nationalities, and its prevalence continues to rise due to population aging [26]. Failure to manage osteoporosis-related fractures can lead to prolonged immobilization and reduced quality of life [25].

To mitigate the impact of osteoporosis, effective treatment is necessary, with bisphosphonates being one of the most commonly used therapies. Bisphosphonates function by inhibiting osteoclast activity, thereby reducing bone resorption [16]. In osteoporosis, bone strength declines due to osteoclast activity surpassing osteoblast activity [3]. Studies suggest that bisphosphonates do not delay fracture healing post-treatment [23]. These medications exhibit a strong affinity for bone minerals, as they bind to hydroxyapatite crystals, accumulating in regions of active bone remodeling [18]. The

* Corresponding author: Nurani Atikasari

primary role of bisphosphonates is to inhibit osteoclast function, preventing excessive bone resorption while promoting osteoclast maturation [23].

However, long-term bisphosphonate therapy is associated with potential adverse effects, ranging from mild to severe. One of the most significant complications is Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ). BRONJ is defined as the presence of exposed bone or a fistula in the maxillofacial region that does not heal within eight weeks in patients receiving or having received bisphosphonate therapy [21]. Although BRONJ is a rare complication, it poses a serious concern. The majority of BRONJ cases occur following dental procedures in patients undergoing antiresorptive therapy [7]. BRONJ is characterized by increased bone resorption, cortical bone lysis, and reduced bone density [17]. Bisphosphonates accumulate in the mandible, leading to specific cortical changes and reduced vascularization, which contribute to osteonecrosis [14].

Regarding BRONJ, gender differences in susceptibility require further investigation. Osteoporosis is approximately 2.8 times more prevalent in women than in men [27, 29]. Studies indicate that half of all women and a quarter of men over the age of 50 will experience fractures due to osteoporosis. Women are more prone to osteoporosis due to lower peak bone mass, smaller bone structure, and postmenopausal estrogen decline, which plays a crucial role in maintaining bone density [22, 23].

Interestingly, some studies argue that gender alone is not a significant factor in osteoporosis risk. Andarini et al. (2020) found that gender does not independently correlate with osteoporosis incidence, though it becomes significant when analyzed alongside age and body mass index (BMI) [1]. Rahayu et al. (2021) further support this claim, suggesting that osteoporosis is not solely determined by gender but also by lifestyle, calcium intake, physical activity, and genetic factors [25]. If osteoporosis incidence is not significantly influenced by gender, it is reasonable to hypothesize that BRONJ risk may also be gender-neutral.

Despite the widespread use of bisphosphonates, there is limited research evaluating the effects of anti-osteoporosis therapy on BRONJ incidence based on gender. The development of BRONJ is influenced by treatment duration, and understanding its clinical presentation is crucial for early diagnosis and management. Therefore, this study aims to analyze the incidence of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) based on gender in osteoporosis patients receiving bisphosphonate therapy.

1.1. Purpose

This study aims to analyze the incidence of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) based on treatment duration and symptoms in osteoporosis patients undergoing bisphosphonate therapy. Specifically, it seeks to examine whether gender influences BRONJ occurrence, considering the existing debate on whether osteoporosis incidence is significantly affected by gender.

Furthermore, this research intends to identify gaps in the literature regarding BRONJ risk factors, particularly in relation to long-term bisphosphonate use and gender differences. By evaluating current findings and clinical data, this study aims to contribute to the understanding of BRONJ pathogenesis, improve risk assessment strategies, and provide evidence-based recommendations for osteoporosis patients receiving bisphosphonate therapy. Thus, the research questions are:

- Does the incidence of BRONJ differ between male and female osteoporosis patients?
- How does treatment duration impact the development and severity of BRONJ symptoms?
- What are the primary risk factors contributing to BRONJ occurrence in osteoporosis patients receiving bisphosphonate therapy?

2. Material and Methods

2.1. Design

This study employs a qualitative literature review approach using a systematic method to analyze the incidence of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) based on treatment duration and symptoms in osteoporosis patients undergoing bisphosphonate therapy. The simplified approach method is used to synthesize and simplify data from selected studies, ensuring a comprehensive yet accessible interpretation of findings. The narrative synthesis approach is applied to critically assess previous research on BRONJ, focusing on gender differences, long-term

bisphosphonate use, and risk factors associated with BRONJ development. This method allows for a detailed exploration of existing evidence while identifying knowledge gaps and inconsistencies in the literature.

2.2. Literature Search Strategy

A systematic search was conducted using major electronic databases available through the National Library of the Republic of Indonesia's (Perpustakaan Nasional Republik Indonesia) e-resources, including:

- EBSCO
- PubMed
- Springer Link

Boolean operators were used to refine and optimize the search process, with "AND" applied to combine key terms and narrow the retrieved documents. The search focused on the following key terms:

- "Osteoporosis in males and females"
- "Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)"

2.3. Study Selection and Inclusion Criteria

The initial database search yielded 30 articles relevant to the research topic. After applying the inclusion and exclusion criteria, 10 articles were selected for final analysis.

2.3.1. Inclusion Criteria:

- Original research articles from primary sources.
- Studies published between 2018 and 2025.
- Full-text articles in English.
- Studies involving osteoporosis patients undergoing bisphosphonate therapy.

2.3.2. Exclusion Criteria:

- Studies unrelated to osteoporosis patients.
- Articles published before 2018.
- Non-English publications.
- Studies with only abstracts or partial texts available.
- Literature reviews.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for study selection to ensure methodological rigor.

2.4. Data Extraction and Thematic Analysis

A structured data extraction framework was used to ensure consistency in analyzing the selected articles. Extracted data included:

- Study characteristics (authors, year, research methodology).
- Patient perspectives on BRONJ (symptoms, quality of life impact).
- Clinician perspectives (diagnostic challenges, treatment strategies).
- Factors influencing BRONJ development (treatment duration, gender, oral health status).
- Preventive measures and clinical management approaches.

The simplified approach was applied in the analysis, where key findings from each study were compiled and synthesized into a coherent summary, allowing for clearer interpretation. Thematic analysis, following Braun & Clarke's (2006) framework, was used to identify major themes and patterns in BRONJ research, including:

- Clinical Manifestations of BRONJ
- Risk Factors and Gender Differences
- Impact of Treatment Duration on BRONJ Development
- Preventive Strategies and Management Approaches

2.5. Quality Appraisal of Selected Studies

To maintain the quality of the literature review, ethical research considerations were followed, including:

- Avoiding duplicate publications.
- Preventing plagiarism.
- Ensuring transparency in data presentation.
- Maintaining accuracy in research interpretation.

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Qualitative Research was used to evaluate the methodological rigor of selected studies. Articles scoring at least 7 out of 10 on the checklist were included in the final analysis.

2.6. Ethical Considerations

This study is based on secondary data from previously published research; thus, ethical approval was not required. However, all articles reviewed were from peer-reviewed journals, ensuring adherence to ethical research standards. By using a qualitative literature review with a systematic and simplified approach, this study aims to provide a comprehensive and structured analysis of BRONJ occurrence in osteoporosis patients, highlighting gender-based differences, treatment duration effects, and clinical challenges. The findings will contribute to evidence-based recommendations for improving BRONJ diagnosis, prevention, and management.

3. Result

Findings of this review are categorized into key themes: incidence of BRONJ based on treatment duration, clinical manifestations of BRONJ, gender differences in BRONJ occurrence, and major risk factors contributing to BRONJ development.

3.1. Incidence of BRONJ Based on Treatment Duration

Several studies indicate that prolonged bisphosphonate use increases the risk of BRONJ. Patients who have been receiving bisphosphonates for more than five years have a significantly higher likelihood of developing BRONJ compared to those with shorter treatment durations [10, 23]. Research highlights that intravenous bisphosphonates (e.g., zoledronic acid, pamidronate) are more strongly associated with BRONJ than oral bisphosphonates due to their higher bone affinity and longer half-life [5, 24]. Cancer patients undergoing high-dose intravenous bisphosphonate therapy are at the greatest risk, as the drug accumulates in bone tissue, particularly in the jaw, where bone remodeling is highly active [19, 23]. A meta-analysis on bisphosphonate therapy suggests that while the drug effectively prevents fractures, it does not significantly delay fracture healing post-treatment but does increase BRONJ risk in long-term users [10].

3.2. Clinical Manifestations of BRONJ

BRONJ symptoms progress gradually, ranging from mild to severe necrosis with jaw fractures. The American Association of Oral and Maxillofacial Surgeons (AAOMS) and the SICMF-SIPMO classification systems define BRONJ stages based on clinical and radiological findings:

- Stage 0: Nonspecific symptoms (pain, swelling) without exposed bone [7, 28].
- Stage 1: Exposed necrotic bone without pain or infection [7, 28].
- Stage 2: Exposed necrotic bone with infection, pain, and inflammation [7, 28].
- Stage 3: Severe necrosis, pathological fractures, and osteolysis affecting surrounding structures [7, 28].

The SICMF-SIPMO classification categorizes radiological BRONJ stages as:

- Focal: Bone condensation limited to the alveolar process.
- Diffuse: Bone condensation extending to the basal bone.
- Severe: Large-scale bone destruction affecting facial bones [19].

Table 1 Clinical manifestasion classification of BRONJ

Stage	AAOMS Classification	SICMF-SIPMO Classification
Stage 0	Nonspecific symptoms, no exposed bone	Not classified
Stage 1	Exposed necrotic bone, no pain or infection	Focal: Bone condensation limited to alveolar process
Stage 2	Exposed necrotic bone, pain, and infection	Diffuse: Bone condensation spreading to basal bone
Stage 3	Severe necrosis, pathological fractures, osteolysis	Severe: Large-scale damage affecting facial bones

3.3. Gender Differences in BRONJ Incidence

Osteoporosis is more prevalent in women due to postmenopausal estrogen decline, which accelerates bone loss [22]. However, whether gender directly influences BRONJ risk remains uncertain. Some studies suggest that women have a higher BRONJ risk simply because they are more likely to receive bisphosphonates for osteoporosis treatment [6, 11]. However, other studies challenge this assumption, stating that BRONJ risk is not inherently gender-dependent when accounting for treatment duration, bisphosphonate type, and other comorbidities [1, 12].

A study by Andarini et al. (2020) found no significant correlation between gender and osteoporosis incidence when adjusting for age and body mass index (BMI) [1]. Similarly, Rahayu et al. (2021) emphasized that osteoporosis (and BRONJ risk) is influenced more by lifestyle, calcium intake, physical activity, and genetic predisposition rather than gender alone [1]. These findings indicate that further research is needed to determine whether biological factors make one gender more susceptible to BRONJ or if the observed differences are due to prescription patterns.

3.4. Risk Factors Contributing to BRONJ Development

In addition to treatment duration, several other factors have been identified as significant contributors to BRONJ occurrence.

3.4.1. Dental Surgical Procedures

Tooth extractions are among the most common triggers of BRONJ. Studies indicate that the risk of developing BRONJ increases significantly following invasive dental procedures, particularly in patients receiving bisphosphonates for extended periods [6, 20]. Patients undergoing intravenous bisphosphonate therapy are particularly vulnerable, as these drugs impair bone remodeling and delay post-extraction healing. Proper pre-extraction planning, including cessation of bisphosphonate use in eligible patients, has been suggested as a preventive measure to minimize BRONJ risks [6].

3.4.2. Malignancy and Chemotherapy

Cancer patients receiving bisphosphonates for bone metastases exhibit a higher incidence of BRONJ. The concurrent use of chemotherapy further exacerbates the condition by suppressing bone turnover and vascularization, leading to increased susceptibility to osteonecrosis [21, 26]. The combination of antiresorptive and antiangiogenic therapies in cancer treatment presents additional risks, with studies highlighting a higher prevalence of severe BRONJ cases in oncology patients compared to those treated solely for osteoporosis [26].

3.4.3. Inflammation and Infection

Pre-existing inflammatory dental conditions, such as periodontitis and osteomyelitis, have been identified as significant risk factors for BRONJ. Chronic infections contribute to bone resorption and compromise healing, creating an environment conducive to osteonecrosis development [8, 14]. Studies suggest that patients with untreated periodontitis prior to bisphosphonate therapy are more likely to develop BRONJ, reinforcing the importance of comprehensive dental assessments before initiating treatment [8].

3.4.4. Prosthodontics and Dentures

The use of ill-fitting dentures can lead to mucosal trauma, which increases the risk of BRONJ in bisphosphonate users. Continuous pressure and irritation from dentures may compromise soft tissue integrity, facilitating bone exposure and osteonecrosis development [6, 9]. Dental professionals recommend regular adjustments and the use of soft denture linings to minimize the risk of trauma-induced BRONJ in at-risk patients [6].

3.4.5. Endodontics and Periodontal Disease

While endodontic procedures are generally considered safer alternatives to extractions for bisphosphonate patients, incomplete root canal treatments and periapical infections can still contribute to BRONJ development. The failure to fully eliminate infection risks prolongs inflammation, which may trigger osteonecrosis in susceptible individuals [7, 16]. Research suggests that periodontal disease itself, when combined with bisphosphonate therapy, significantly increases BRONJ susceptibility, further emphasizing the need for early intervention and preventive dental care [7, 16].

Given the complexity of BRONJ development, preventive strategies are essential for mitigating risks, especially in patients undergoing long-term bisphosphonate therapy. Pre-treatment dental screening is crucial for identifying high-risk conditions such as periodontal disease and untreated caries before bisphosphonate therapy begins. Early dental intervention can reduce the likelihood of developing BRONJ by addressing predisposing factors that compromise bone healing [6, 25]. Minimizing unnecessary invasive procedures is another key strategy. Whenever possible, alternative non-surgical dental treatments should be prioritized over extractions to preserve bone integrity and prevent osteonecrosis [25].

Adjunctive therapies, such as the use of growth factors including platelet-rich growth factors (PRGF) and basic fibroblast growth factor (bFGF), have shown potential in promoting bone healing and reducing the severity of BRONJ [4, 18]. Routine dental monitoring is recommended for all bisphosphonate users to detect early signs of BRONJ. Regular checkups enable timely intervention and the implementation of conservative management strategies to prevent disease progression [28].

This review highlights the critical role of treatment duration, gender considerations, and various risk factors in BRONJ development. Long-term bisphosphonate use remains the strongest predictor of BRONJ, with intravenous formulations carrying a significantly higher risk. The role of gender in BRONJ susceptibility remains uncertain, with conflicting findings suggesting the need for further investigation. While women have a higher incidence of osteoporosis and thus greater exposure to bisphosphonates, gender alone may not be a determining factor in BRONJ risk.

Understanding the interplay between bisphosphonate use, dental procedures, and inflammatory conditions is crucial for early diagnosis and preventive strategies. Future research should focus on refining BRONJ risk assessment models, developing alternative osteoporosis treatments with lower BRONJ risks, and optimizing clinical management approaches for improved patient outcomes.

4. Discussion

This review explores the incidence of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) based on treatment duration and symptoms in osteoporosis patients. Findings suggest that treatment duration plays a crucial role in BRONJ occurrence, with prolonged bisphosphonate use increasing the likelihood of developing the condition. Symptoms of BRONJ vary across different stages, with initial manifestations often being mild and progressing to severe bone necrosis if not managed properly.

The relationship between treatment duration and BRONJ incidence is a central finding in this review. Studies indicate that patients on bisphosphonates for more than five years face a significantly higher risk compared to those with shorter treatment durations [10, 23]. The long half-life of bisphosphonates leads to drug accumulation in the jawbone, particularly in areas of high remodeling activity, predisposing osteoporosis patients to osteonecrosis. Although bisphosphonates effectively reduce fracture risk in osteoporosis, the increased BRONJ incidence raises concerns regarding the optimal duration of therapy and whether long-term use should be reconsidered in high-risk patients.

Another critical aspect of BRONJ development in osteoporosis patients is the variation in clinical symptoms across different stages of the disease. In the early stages, patients may experience jaw pain, inflammation, or swelling without visible bone exposure, making diagnosis challenging [7, 28]. As BRONJ progresses, exposed necrotic bone becomes evident, accompanied by soft tissue damage, infections, and increased discomfort. Advanced stages often present severe osteonecrosis, pathological fractures, and extensive bone loss, significantly affecting the patient's quality of life. Understanding symptom progression is essential for early detection and timely intervention, as delayed diagnosis may result in irreversible damage.

The findings also emphasize the importance of recognizing risk factors associated with BRONJ symptoms in osteoporosis patients. Studies suggest that poor oral health, dental procedures, and underlying infections exacerbate BRONJ severity [6, 20]. Patients undergoing tooth extractions or invasive dental treatments while on bisphosphonate

therapy are particularly susceptible to jaw osteonecrosis due to impaired bone healing. However, despite widespread awareness of this risk, standardized dental management protocols for osteoporosis patients on bisphosphonates remain insufficient.

The severity of BRONJ symptoms is closely linked to treatment duration, with long-term bisphosphonate users displaying more advanced disease stages compared to those on shorter regimens. Patients with five or more years of bisphosphonate exposure exhibit higher rates of severe necrotic lesions, while those on bisphosphonates for less than three years typically present with milder symptoms [10, 23]. These findings suggest that regular monitoring of osteoporosis patients receiving prolonged bisphosphonate therapy is crucial for identifying early BRONJ symptoms and implementing preventive measures before severe complications arise.

Despite the well-documented association between bisphosphonate therapy duration and BRONJ, there is no consensus on the ideal length of treatment for osteoporosis patients. Some guidelines suggest drug holidays to minimize risks, but evidence supporting this approach remains inconclusive. Additionally, individual patient factors such as age, comorbidities, and bone metabolism rates further complicate the decision-making process regarding bisphosphonate discontinuation. Future research should focus on establishing clear clinical guidelines to balance the benefits of osteoporosis treatment with the risks of developing BRONJ.

The findings of this review underscore the necessity of improving early detection strategies for BRONJ symptoms in osteoporosis patients. Many cases remain undiagnosed until the disease reaches an advanced stage, highlighting the need for routine oral examinations and early imaging assessments in at-risk individuals. Dentists and healthcare providers should be trained to recognize subtle initial symptoms of BRONJ and implement appropriate interventions before the disease progresses.

A major limitation in existing research is the lack of large-scale, longitudinal studies examining BRONJ incidence in osteoporosis patients over extended treatment durations. Most studies rely on retrospective data, which may introduce recall bias and incomplete patient histories. Future research should prioritize prospective cohort studies that track osteoporosis patients on bisphosphonates, monitoring treatment duration, symptom onset, and disease progression over time.

5. Conclusion

The review concludes that prolonged bisphosphonate therapy significantly increases the risk and severity of BRONJ in osteoporosis patients, emphasizing the need for careful monitoring and individualized treatment duration. This study will benefit society by guiding safer therapeutic practices and encouraging further research toward preventive, patient-centered osteoporosis care.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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