

#### LEARNING OBJECTIVES

- Discuss the etiology and pathogenesis of osteonecrosis of the jaws
- Describe risk factors and clinical features of bisphosphonate-related osteonecrosis of the jaws
- Review patient education issues regarding dental care and the importance of maintaining oral health while taking bisphosphonates

# Managing the adverse effects of bisphosphonate therapy on the jaw

Bisphosphonates are used to correct bone loss from osteoporosis and osteopenia and treat multiple myeloma. However, their mechanism of action can lead to a devastating oral condition.

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More than 100 years ago, unexplainable, non-healing bone exposures were seen on the jaws of phosphate miners and match workers in the United States and Great Britain. At that time, the condition was diagnosed as an occupational industrial disease called phossy jaw. The daily exposure to phosphate was postulated to cause an accumulation of the compound in the jaw, eventually leading to bone necrosis.<sup>1</sup>

Today, a similar pattern of exposed, nonhealing bone is being seen in patients taking bisphosphonates (Figure 1). This phenomenon is referred to as *bisphosphonate-related osteonecrosis of the jaws* (BRONJ). Osteonecrosis is bone death resulting from poor blood supply to an area of bone. However, no universal definition of BRONJ has been established to date, making the diagnosis and determining the actual prevalence of the disease difficult.<sup>2</sup>

#### ETIOLOGY AND PATHOPHYSIOLOGY

Bisphosphonates, which are related to pyrophosphate compounds, have an affinity for sites with high bone turnover. They were first introduced in the 1980s as treatment for Paget's disease of bone. Currently, IV bisphosphonates are used to treat hypercalcemia of malignancy and skeletal-related events associated with bone metastases of solid tumors, such as breast cancer, prostate cancer, and lung cancer, and to manage lytic lesions in patients with multiple myeloma.<sup>3</sup> Additionally, oral bisphosphonates are prescribed as treatment for osteoporosis and osteopenia.

Normal bone remodeling is balanced by osteoblast and osteoclast activity. Osteoblasts cause bone formation and osteoclasts cause bone resorption. A fine balance between

osteoblast and osteoclast activity allows for normal bone formation and necessary maintenance of optimal bone mineral density (BMD). Bisphosphonates bind to osteoclasts, causing a reduction in their recruitment, life span, and activity. When osteoclast activity is reduced, less bone is resorbed and subsequently less bone is remodeled. In patients taking bisphosphonates, osteoclast activity is inhibited for many years because bisphosphonate metabolites accumulate in the bone matrix and prolong bioactivity. Thus, even when the drugs (such as alendronate sodium) are discontinued, the influence on osteoclastic activity can remain in effect for 10 years or longer.



**FIGURE 1.** A patch of exposed necrotic bone on the lower jaw

Photo courtesy of Thomas A. Chiodo, DMD

**The upper and lower jaws** are comprised of two types of bone: alveolar and basal bone. These bones are more susceptible to BRONJ because they have unique characteristics. For instance, alveolar bone resides in the tooth-bearing segments of the upper and lower jaws. Its functions are to support and to maintain dentition. Alveolar bone is the only bone exposed to the outside environment. Its remodeling rate is 10 times faster than the remodeling rate of the tibial bone; as a result the jaw bones have a greater uptake of bisphosphonates, which causes the metabolite to readily accumulate at higher concentrations.<sup>1,4</sup> In patients with osteoporosis, the accumulation of bisphosphonates in the bone eventually causes hypermineralization, thus increasing BMD. This process helps to increase BMD in the lumbar spine and axial skeleton, areas often affected by osteoporosis and osteopenia; however, it can go awry in the maxilla and mandible.

For example, a tooth extraction leaves a large residual void that is exposed to the outside environment. Healing involves the formation and stabilization of a blood clot and progression through the natural phases of bone healing that include osteoid deposition, mineralization, and remodeling. The bone of the jaw must progress through the natural healing phases, including remodeling through balanced osteoblast and osteoclast activity. Bisphosphonate-induced suppression of osteoclast activity disrupts that balance and leaves nonhealing bone exposed, which leads to osteonecrosis.

Bioavailability of the oral form of bisphosphonates differs from that of the IV form. Oral bisphosphonates are poorly absorbed into the blood stream from the GI tract compared with direct serum induction. IV administration bypasses gastric absorption; therefore, uptake is up to 10 times faster. The difference in the absorption rates could make 6 to 12 months of IV therapy equivalent to 3 to 5 years of oral therapy.<sup>1</sup> Therefore, the incidence of BRONJ is higher in patients on IV therapy than it is in patients on oral therapy.

#### PREVALENCE OF BRONJ

Data on BRONJ are limited to retrospective studies with small sample sizes. The estimated cumulative incidence of IV therapy-associated BRONJ is 0.8% to 12%.<sup>3</sup> During the past

3 years, a number of researchers have studied the relationship between bisphosphonates and osteonecrosis of the jaw. Most of these reports and case studies focused on patients with multiple myeloma or metastatic breast cancer who were receiving high doses of IV bisphosphonate.<sup>1,5,6</sup>

The prevalence of BRONJ in patients on oral bisphosphonate therapy appears to be very small (0%-0.04%).<sup>6</sup> Only a few reports focused on patients receiving oral bisphosphonates as treatment for osteoporosis, Paget's disease of bone, or other skeletal disorders. Spontaneous occurrences of osteonecrosis of the jaw reported to bisphosphonate manufacturers indicate a rate of approximately one event per

**“Discontinuing bisphosphonate therapy may not eliminate or reduce the risk of developing osteonecrosis of the jaws.”**

100,000 patient-years of exposure to oral bisphosphonates.<sup>7</sup> However, this data should be interpreted with some caution, as the reports are not adjudicated and much of the information required to classify the cases properly is unavailable.<sup>2</sup>

The clinical efficacy of oral bisphosphonates for the treatment of osteopenia and osteoporosis is well-established, and millions of prescriptions for oral bisphosphonates are dispensed in the United States annually.<sup>8</sup> Although the incidence of BRONJ is low in patients taking oral bisphosphonates, these patients are still at risk. Therefore, clinicians must be able to recognize the clinical signs of BRONJ and begin management of this disease in a timely fashion.

#### CONCOMITANT RISK FACTORS

Bisphosphonates are implicated as the main factor in the development of BRONJ. However, concomitant factors have been identified as well (Table 1).

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#### KEY POINTS

- Normal bone remodeling is balanced by osteoblast and osteoclast activity. Osteoblasts cause bone formation and osteoclasts cause bone resorption. A fine balance between osteoblast and osteoclast activity allows for normal bone metabolism and necessary maintenance of optimal bone mineral density.
- In patients taking bisphosphonates, osteoclast activity is inhibited for many years because bisphosphonate metabolites accumulate in the bone matrix and prolong bioactivity. Thus, even when the drugs are discontinued, the influence on osteoclastic activity can remain in effect for more than 10 years.
- The risk of BRONJ is significantly greater for patients receiving IV bisphosphonate therapy compared with the risk for patients receiving oral bisphosphonate therapy. The estimated cumulative incidence of IV therapy-associated BRONJ is 0.8% to 12%. The prevalence of BRONJ in patients on oral bisphosphonate therapy appears to be very small (0%-0.04%).
- Patient should undergo a comprehensive oral examination; and any treatment needed, including extraction of any unsalvageable teeth, should be provided before initiation of IV or oral bisphosphonate therapy. In patients already on bisphosphonate therapy, invasive dental procedures should not be delayed until optimal periodontal health is achieved but should proceed conservatively with concurrent antibiotic coverage.

**TABLE 1. Risk factors for BRONJ**

<b>Concomitant oral disease</b>
Dental abscess
Inflammatory dental disease
Periodontal abscess
<b>Demographic factors</b>
Age
Alcohol use
Cancer (most commonly multiple myeloma)
Diabetes
Smoking
<b>Drug-related factors</b>
Chemotherapeutic drugs
Corticosteroid therapy
Duration of bisphosphonate therapy
Potency of the bisphosphonate
Route of administration used for bisphosphonate therapy
<b>Local anatomy</b>
Mylohyoid ridge
Torus mandibularis
Torus palatinus
<b>Local events</b>
Dental implant placement
Dentoalveolar surgery
Extraction
Periapical surgery
Periodontal surgery/osseous injury
<small>Key: BRONJ, bisphosphonate-related osteonecrosis of the jaws. Data from American Association of Oral and Maxillofacial Surgeons.<sup>3</sup></small>

**Duration of therapy** seems to play a direct role in the development of BRONJ. The risk of developing BRONJ increases in relation to the length of time the patient is on bisphosphonate therapy. Research to date suggests that the risk of developing BRONJ is negligible when bisphosphonates are taken for less than 3 years.<sup>1,3,9</sup>

**Dentoalveolar surgery** includes but is not limited to extractions, dental implant placement, periapical surgery, and periodontal surgery involving osseous injury.<sup>3</sup> Studies suggest patients on IV bisphosphonate therapy who undergo dentoalveolar surgery are at least 7 times more likely to develop BRONJ.<sup>10</sup> In addition, patients with inflammatory

dental disease, such as periodontal or dental abscesses, who are taking bisphosphonates have a 7-fold increased risk of developing BRONJ.<sup>11</sup>

**Systemic and demographic factors** thought to be concomitant risk factors for disease include diabetes mellitus, smoking, alcohol use, and poor oral hygiene.<sup>3</sup> Additionally, the risk of BRONJ increases by 9% with each passing decade in patients undergoing IV bisphosphonate therapy for multiple myeloma.<sup>10</sup>

**Torus mandibularis/palatinus** can also lead to an increased risk of BRONJ because the projections are frequently traumatized and have a thin mucosal covering.<sup>3</sup> The mylohyoid ridge is also susceptible to BRONJ.

### SIGNS AND SYMPTOMS

BRONJ is often difficult to recognize in its early stages because the disease may be asymptomatic for many weeks or months. The symptoms can mimic dental or periodontal disease, and infection may not be present. Typically, a patient may seek care because of oral pain. Many times the area of exposed bone is underneath a denture or oral appliance and is identified during a routine oral examination.

Symptoms can occur spontaneously but more commonly manifest after a tooth extraction or other oral surgical procedure. Exposed bone can cause trauma to the buccal mucosa or tongue (**Figure 2**) if it consistently rubs against the necrotic bone. Symptoms typically go unnoticed; therefore, obtaining a thorough history during routine physical examination is essential. If the patient is on bisphosphonate therapy, the duration of treatment should be ascertained and a thorough oral examination performed. This diagnosis can be made only through vigorous monitoring for early signs of exposed bone.

### MAKING THE DIAGNOSIS

Clinical diagnosis is usually made by visualizing exposed bone in the maxillofacial area that has failed to heal after 8 weeks of appropriate treatment (**Figure 3**). After BRONJ is diagnosed, panoramic radiography should be performed. Radiography can demonstrate osteolytic lesions; however, distinguishing an osteolytic lesion from a malignancy is difficult. The border between the lesion and surrounding healthy tissue is also difficult to clearly define on a radiograph.<sup>12</sup> Therefore, panoramic radiography should be followed up with CT of the mandible. CT detects alterations, periosteal reactions, and soft tissue alterations inside the bone and delineates the extent of the disease.<sup>12</sup>

Some researchers have suggested that clinicians should check serum levels of C-terminal cross-linking telopeptide (CTX) of type I collagen and urinary N-telopeptide (NTX) of type I collagen before starting any new dental procedures.<sup>13</sup> CTX and NTX are collagen breakdown products and are considered to be markers for bone resorption. Low levels of these markers may suggest decreased bone turnover, potentially identifying a patient who is at greater risk for BRONJ. However, research on these markers is

inconclusive and limited. Thus, no firm recommendations have been established regarding the use of these markers to detect the risk for BRONJ.

**Differential diagnosis** Traumatic ulcer should be considered when an open mucosal lesion is present; however, these lesions usually heal with appropriate treatment. Osteomyelitis and malignancy are other considerations that are easily ruled out by appearance on CT scans. Clinicians should understand that other common clinical conditions that should not be confused with BRONJ may also manifest in patients either at risk for or with established BRONJ. These commonly misdiagnosed conditions include alveolar osteitis, sinusitis, gingivitis, caries, and temporomandibular joint disorders.<sup>3</sup>

### TREATMENT

Patients should undergo a comprehensive oral examination; and any treatment needed, including extraction of any unsalvageable teeth, should be performed before initiation of bisphosphonate therapy.<sup>6</sup> In patients already on bisphosphonate therapy, invasive dental procedures should not be delayed until optimal periodontal health is achieved but should proceed conservatively with concurrent antibiotic coverage.<sup>3,6</sup> The American Academy of Oral and Maxillofacial Surgeons (AAOMS) Task Force suggests discontinuing oral bisphosphonates from 3 months before an invasive procedure until 3 months after the last invasive dental surgery, if possible. This may lower the risk of BRONJ, although this theory is purely speculative at this point.

There is no treatment protocol for BRONJ. However, the following stages for directing treatment are proposed by the AAOMS:

- **At risk** No apparent exposed/necrotic bone in patients who have been treated with IV or oral bisphosphonates
- **Stage I** Exposed/necrotic bone found in patients who are asymptomatic and have no evidence of infection
- **Stage II** Exposed/necrotic bone found in patients with pain and clinical evidence of infection
- **Stage III** Exposed/necrotic bone found in patients with pain, infection, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border.<sup>3</sup>

Using this staging system, the recommended treatment strategy for patients with stage I disease is use of an oral antimicrobial rinse, such as chlorhexidine 0.12%. Surgical treatment is not indicated and prognosis for a full recovery is very good. Patients with stage II disease should use oral antimicrobial rinses in combination with antibiotic therapy. Antibiotics used are penicillin, metronidazole, clindamycin, doxycycline, erythromycin, or a quinolone. Surgical debridement or resection in combination with antibiotic therapy may offer long-term palliation with resolution of acute infection and pain for patients with stage III disease. Once BRONJ has been diagnosed, appropriate referral to an oral and maxillofacial surgeon for evaluation and treatment should be scheduled promptly.

**Patient education** is important for oral health, especially for patients who are being treated with bisphosphonates. All patients taking oral bisphosphonates should be educated about the risk for developing BRONJ, even though that risk is minimal. Patients should also be informed that an oral health program, consisting of good oral hygiene practices and regular dental care, may lower their risk of developing BRONJ.<sup>6</sup> Furthermore, patients should be told that discontinuing bisphosphonate therapy may not eliminate or reduce this risk. If they experience any problems in the oral cavity at any time during therapy or after discontinuing therapy, they should contact their health care provider immediately.<sup>6</sup>

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**FIGURE 2.** An ulceration on the ventral posterior tongue caused by rubbing against exposed necrotic bone



**FIGURE 3.** Exposed necrotic bone on lingual surface of the mandible in the molar area in a patient receiving radiation therapy for throat carcinoma

Photos courtesy of Thomas A. Chiodo, DMD

## CONCLUSION

The benefits of bisphosphonate drugs are indisputable. Without these medications, many people would suffer from the devastating effects of bone loss and even succumb to some cancers. However, bisphosphonates have potential side effects as well. PAs should be aware of the signs and symptoms of BRONJ. They should educate their patients about the risks of BRONJ with bisphosphonate therapy. When receiving these medications, patients should be monitored closely, especially if they use the IV form. Bisphosphonate therapy should be discontinued if its risks appear to potentially outweigh its benefits. **JAAPA**

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## DRUGS MENTIONED

Alendronate sodium (Fosamax, generics)	Erythromycin
Chlorhexidine (Peridex, Periogard, generics)	Metronidazole (Flagyl, Helidac Therapy, generics)
Clindamycin (Cleocin, generics)	Penicillin
Doxycycline	

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