Emerging Concepts in the Management and Treatment of Osteonecrosis of the Jaw

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KEYWORDS
- Osteonecrosis • BRONJ • Jaw necrosis • Bisphosphonates • Bone remodeling • Antiresorptive treatment

KEY POINTS
- Bisphosphonate-related osteonecrosis of the jaw is now a well-recognized entity that is associated with several risk factors that are identified across several disciplines in medicine and dentistry.
- Although osteonecrosis of the jaw (ONJ) has been well described in the literature, the pathogenesis of this disease process remains poorly understood.
- Standardization of diagnostic criteria and nomenclature for this clinical entity is important to facilitate future clinical and epidemiologic research.
- The goal of treatment of patients at risk of developing ONJ, or for those who have active disease, is preservation of quality of life by controlling pain, managing infection, and preventing the development of new areas of necrosis.

Since the first description of bone necrosis in patients receiving bisphosphonate therapy in 2004, there have been multiple retrospective, prospective, and case-control studies that have served to characterize the diagnosis, associated risk factors, and treatment of this new complication. Although bisphosphonate-related ONJ was not well recognized 10 years ago, it is at present associated with several risk factors that are identified across several disciplines in medicine and dentistry. With this level of broad-based recognition, new clinical and basic science research initiatives have begun and are likely to elucidate the etiopathogenesis of this disease process, significantly improving the level of disease management and prevention.

PATHOGENESIS
Despite the fact that ONJ has been well described in the literature, the pathogenesis of this disease process remains poorly understood. Four major hypotheses have been proposed to explain the etiology of the disease process, including bone remodeling suppression (osteoclast mediated), disturbances in bone vascularity (antiangiogenesis), local mucosal toxicity, and genetic factors. The most popular and researched hypothesis focuses on the profound inhibition of osteoclast function associated with these drugs. Bisphosphonate-mediated suppression of bone remodeling is thought to have a greater effect in the jaw, where baseline bone turnover rates are typically much higher than at other skeletal sites.

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This position is supported by several studies that have demonstrated bone necrosis isolated to the alveolar component of the jaw in animal models exposed to bisphosphonates.\textsuperscript{1-3}

The finding that nonbisphosphonate osteoclast inhibitors may be associated with osteonecrosis also supports this hypothesis. Denosumab (Prolia, Xgeva) is a novel antiresorptive agent and a fully humanized antibody against RANKL. It is a profound inhibitor of osteoclast function and bone remodeling. These agents do not bind to bone, and their affects on bone remodeling are reversible within 6 months of treatment cessation. Recent case reports\textsuperscript{4-6} as well as reports from large-scale clinical trials\textsuperscript{7} have shown that ONJ occurs in patients treated with denosumab. These findings strongly suggest that potent remodeling suppression in the form of osteoclast inhibition, a common feature of both denosumab and the bisphosphonates, is likely a key factor in the pathogenesis of ONJ (Fig. 1).

Defects of angiogenesis have also been considered as a mechanism for ONJ. This idea has been fueled by reports of bisphosphonate-induced inhibition of angiogenesis in culture and animal tumor models.\textsuperscript{8,9} These findings, however, are tempered by other animal studies in which bisphosphonates had no effect on angiogenesis associated with endochondral ossification\textsuperscript{10} and findings of normal vasculature in regions of bisphosphonate-induced matrix necrosis.\textsuperscript{1}

Direct mucosal toxicity from high bisphosphonate concentrations in the bone has been considered as the primary event for jawbone exposure and necrosis.\textsuperscript{11} This idea is based on culture data in which high concentrations of bisphosphonates were found to be toxic to oral mucosal cells. In the clinical setting, such an effect would occur only if the oral mucosa were subject to high concentrations of bisphosphonate for a prolonged period. This situation can theorectically occur at surgical sites or regions of inflammation where there is a local reduction in the pH, which facilitates the release of bisphosphonate from the bone.\textsuperscript{12} The clinical scenario where ONJ presents spontaneously in the nondentate region of the jaw, however, does not fit this hypothesis well.

The fact that only a small subset of patients exposed to bisphosphonates develop jaw necrosis has led some investigators to consider certain pharmacogenetic factors as well.\textsuperscript{13,14} In particular, Sarasquete\textsuperscript{15} noted certain genetic irregularities (ie, single nucleotide polymorphisms) in the cytochrome P450-2C gene in patients with multiple myeloma and ONJ. Patients who were homozygous for the T allele had a 12.7-fold increased risk of developing ONJ. The link to ONJ formation is thought to be related to alterations in bone vascularity and arachidonic acid metabolism, both of which are controlled by this gene.

All these studies provide a much greater understanding of this disease process and certainly provide a clearer direction to which future research should be directed. The degree to which any of these theories, working in concert or individually, can completely explain the development of this drug-mediated bone necrosis remains to be determined more fully. Considering the aforementioned studies, ONJ can be accurately predicted based on specific risk factors such as the presence of jaw inflammation (trauma or infection), a genetic marker, and antiresorptive bone therapy.

**CLINICAL PRESENTATION AND DIAGNOSIS**

Standardization of diagnostic criteria and nomenclature for this clinical entity is important to facilitate future clinical and epidemiologic research. In addition, a uniform definition for ONJ serves to distinguish this new clinical entity from other delayed intraoral healing conditions. Various organizations have proposed clinical definitions for ONJ, all of which are analogous to each other; this has resulted in some degree of confusion. This condition has been referred to in the literature by several acronyms, including BRONJ (bisphosphonate-related osteonecrosis of the jaw), BRON (bisphosphonate-related osteonecrosis), BON (bisphosphonate osteonecrosis), BAONJ (bisphosphonate associated osteonecrosis of the jaw), and simply ONJ.

The American Association of Oral and Maxillofacial Surgeons (AAOMS) established a working definition for BRONJ, which has remained unchanged since it was first defined in 2006. The tenets of the diagnosis include (1) an exposure

![Fig. 1. Spontaneous exposure of necrotic left palatal bone (stage 1) in a patient receiving denosumab for the treatment of metastatic lung cancer. The patient had no history of bisphosphonate exposure.](image-url)
history to bisphosphonates, (2) exposed bone within the oral cavity, and (3) no history of prior radiation therapy to the jaws. The emergence of jaw necrosis in bisphosphonate-naive patients receiving RANKL inhibitors,4–7 however, may necessitate a modification of these criteria in the near future. The ADA later introduced the more generic term ARAONJ (antiresorptive associated osteonecrosis of the jaw) to include those new cases of necrosis associated with monoclonal therapy. Despite the variations in nomenclature, the clinical finding of exposed, necrotic bone remains the consistent hallmark of the diagnosis, and therefore physical examination is the most effective method of establishing the diagnosis of jaw necrosis.

The differential diagnosis of ONJ should exclude other common clinical conditions including, but not limited to, alveolar osteitis, sinusitis, gingivitis/peridontitis, periapical pathology, and temporomandibular joint disorders. In those rare situations in which exposed bone is present in patients exposed to bisphosphonates and radiation therapy to the jaw, osteoradionecrosis should be strongly considered. Although bone inflammation and infection are typically present in patients with advanced ONJ, this is a secondary event. The exposed bone and surrounding soft tissue become secondarily infected, presenting a clinical scenario that is similar to osteomyelitis. The histologic analysis of these bone specimens, however, rarely demonstrates the criteria required to establish a diagnosis of acute or chronic osteomyelitis. Analyses of the physical properties of the resected necrotic bone have also failed to demonstrate any unique features that would serve as a reliable biomarker for this disease process.16,17

The patient history and clinical examination remain the most sensitive diagnostic tools for this condition. Areas of exposed and necrotic bone may remain asymptomatic for weeks, months, or even years. These lesions are most frequently symptomatic when the surrounding tissues become inflamed or there is clinical evidence of exposed bone. Signs and symptoms that may occur before the development of clinically detectable osteonecrosis include pain, tooth mobility, mucosal swelling, erythema, and ulceration. These symptoms may occur spontaneously or, more commonly, at the site of prior dentoalveolar surgery. Most case series have described this complication at regions of previous dental surgery (ie, extraction sites); exposed bone, however, has also been reported in patients with no history of trauma or in edentulous regions of the jaw. Intraoral and extraoral fistulae may develop when necrotic jawbone becomes secondarily infected. Some patients may also present with complaints of altered sensation in the affected area as the neurovascular bundle becomes compressed from the inflamed surrounding bone. Chronic maxillary sinusitis secondary to osteonecrosis with or without an oral-antral fistula can be the presenting symptom in patients with maxillary bone involvement.

It has been observed that lesions are found more commonly in the mandible than in the maxilla (2:1 ratio). They are also more prevalent in areas with thin mucosa overlying bone prominences such as tori, exostoses, and the mylohyoid ridge.18–20 The size of the affected area is variable and ranges from a nonhealing extraction site to exposure and necrosis of large sections of jawbone. The area of exposed bone is typically surrounded by inflamed erythematous soft tissue. Purulent discharge at the site of exposed bone is present when these sites become secondarily infected. Microbial cultures from areas of exposed bone usually show normal oral microbes and therefore are not always helpful. In cases in which there is extensive soft-tissue involvement, however, microbial culture data may define comorbid oral infections that may facilitate the selection of an appropriate antibiotic regimen.

A clinical staging system developed by Ruggiero and colleagues19 and adopted by the AAOMS in 200621 and updated in 200922 has served to categorize patients with ONJ, direct rational treatment guidelines, and collect data to assess the prognosis and treatment outcome in patients who have used either intravenous (IV) or oral bisphosphonates (Table 1). Patients with no evidence of exposed or necrotic bone are considered to be “at risk” if they have been exposed to either IV or oral bisphosphonates. The potency of the bisphosphonate used, the duration of exposure, and dentoalveolar surgery seem to be the main determinants in assessing the risk of developing ONJ. Patients with stage 1 disease have exposed bone but are asymptomatic. There is no evidence of significant adjacent or regional soft-tissue inflammatory swelling or infection. Patients may have symptoms of pain before the development of radiographic changes suspicious for osteonecrosis or clinical evidence of exposed bone. Stage 2 disease is characterized by exposed bone with associated pain, adjacent or regional soft-tissue inflammatory swelling, or secondary infection. Patients with stage 3 disease have exposed bone associated with pain, adjacent or regional soft-tissue inflammatory swelling, or secondary infection in addition to a pathologic fracture, an extraoral fistula, or radiographic evidence of osteolysis extending to the inferior border of the mandible or sinus floor (Fig. 2).
Since the publication of the initial treatment guidelines in 2006, reports of nonspecific signs and symptoms such as pain, abscess formation, altered sensory function, or osteosclerosis have emerged in patients with a bisphosphonate exposure history but no clinical evidence of necrosis. In an effort to determine whether or not these findings represent a precursor for clinical disease, the updated AAOMS position paper has included these patients in a new stage 0 category. The degree to which patients with stage 0 disease progress to overt ONJ remains to be determined and represents an important area for future investigation. Recent reports in the European literature have described a variant of ONJ in which there is bone pain with no exposed bone. Greater than 50% of these patients developed exposed bone at these sites within 5 months.

Multiple risk factors including drug-related issues (potency and duration of exposure), local risk factors (dentoalveolar surgery), local anatomy, concomitant oral and systemic disease, demographic factors, and genetic factors have all been considered for this complication. Only 3 risk factors, however, have remained constant throughout most clinical studies. In most ONJ cases reported to date, recent dentoalveolar trauma was the most prevalent and consistent of these risk factors. The duration of bisphosphonate therapy also seems strongly related to the likelihood of developing necrosis, with longer treatment regimens associated with a greater risk of developing disease. In addition, the more potent IV bisphosphonates that are administered on a monthly schedule such as zoledronic acid and pamidronate are significantly more problematic as compared with other preparations.

Efforts to establish risk assessment by measuring fluctuations in bone turnover markers are problematic and remain controversial. The rationale for this approach is based on the knowledge that markers for bone remodeling increase within months after withdrawal of oral bisphosphonate medications, thereby suggesting that osteoclastic function and bone remodeling was normalizing. These markers, however, are a reflection of total bone turnover throughout the skeleton and are not specific to the maxilla or mandible where it is suspected that the bone turnover rate may be more severely depressed from prolonged bisphosphonate exposure. From a more practical perspective, using bone turnover markers to predict disease progression would be ideal. Unfortunately, however, bone turnover markers lack sufficient sensitivity and specificity to achieve this goal. Efforts to develop new markers that are specific to the jaw have been largely unsuccessful.

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
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<tbody>
<tr>
<td>At-risk category</td>
<td>No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates</td>
</tr>
<tr>
<td>Stage 0</td>
<td>Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection</td>
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<tr>
<td>Stage 2</td>
<td>Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border or sinus floor</td>
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markers to estimate the level of bone turnover suppression is only meaningful when compared with baseline pretreatment levels, and these are rarely obtained in clinical practice. In addition, using bone resorption marker levels to assess ONJ risk can be misleading for the small cohort of patients who develop osteoporosis despite normal baseline levels of bone resorption markers.

The radiographic features of ONJ are nonspecific. Plain film radiography does not typically demonstrate any abnormality in the early stages of the disease because of the limited degree of decalcification that is present. Findings on plain film imaging, however, such as localized or diffuse osteosclerosis or a thickening of the lamina dura (components of stage 0), may be predictors for future sites of exposed, necrotic bone. Little or no ossification at a previous extraction site may also represent an early radiographic sign. The findings on computed tomography (CT) are also nonspecific, but this modality is significantly more sensitive to changes in bone mineralization and is therefore more likely to demonstrate areas of focal sclerosis, thickened lamina dura, early sequestrum formation, and presence of reactive periosteal bone (Fig. 3). The CT images have also proved to be more accurate in delineating the extent of disease, which is helpful for surgical treatment planning.35,36 The utility of nuclear bone scanning in patients at risk of ONJ has received growing attention after reports of increased tracer uptake in regions of the jaws that subsequently developed necrosis.37,38 Although nuclear imaging has limited value in patients with existing disease, its usefulness as a predictive tool in those patients with preclinical disease (stage 0) seems to have some level of potential benefit and therefore requires continued evaluation.

**TREATMENT AND PREVENTION**

The management of patients with ONJ remains challenging because surgical and medical interventions may not eradicate this process. The goal of treatment of patients at risk of developing ONJ, or for those who have active disease, is preservation of quality of life by controlling pain, managing infection, and preventing the development of new areas of necrosis. This treatment has to be balanced with the oncologic management of the patient with osteolytic metastases and the risk of pathologic fracture in the patient with osteoporosis.

Patients at risk of developing ONJ benefit from preventive dental care directed at minimizing the likelihood of extraction and optimizing the level of dental health. The time-tested dental care protocols instituted to prevent osteoradionecrosis in irradiated patients with cancer serve as appropriate models for patients at high risk for ONJ.

The treatment approach for patients with stage 1 disease has remained primarily nonsurgical because these patients are not infected or symptomatic. In most patients with stage 1 disease, the exposed bone eventually matures into a defined sequestrum that can easily be removed. Because infection and pain is typical in patients with stage 2 disease, these patients benefit from local and systemic antibiotic therapy. These patients likewise develop sequestra, which in most cases are managed with local debridement. In patients with stage 3 disease, the extensive nature of the necrosis and infection usually dictate early surgical treatment (segmental resection or marginal resection) for control of the infection and pain (Fig. 4).

For those few patients who require surgical resection with a continuity defect, the reconstruction has been challenging. Although there have been reports of immediate reconstruction with vascularized bone grafts, most surgeons are hesitant to proceed with such a procedure because of the uncertain viability of the remaining bone.39 Alternatively, the mandibular defect can be bridged and stabilized with a reconstruction plate (that could include the condylar head if necessary) and soft-tissue flap. The use of bone morphogenic protein within a sponge carrier has been described for immediate reconstruction of continuity defects in patients with ONJ.40 This method may represent a viable alternative to autogenous bone grafting.
techniques in this unique patient population. In the author’s experience, immediate reconstruction of maxillectomy defects with an alloplastic obturator has worked well and quickly restored function. Reports from some institutions suggest that early surgical treatment, regardless of disease stage, is associated with a good level of cure and disease control, indicating that surgical treatment may play a larger role in managing this complication in the near future.39,41–43

New approaches in the surgical and nonsurgical treatment of ONJ have emerged and may be of value. The use of hyperbaric oxygen (HBO) as an adjunct to nonsurgical therapy has been reported. In a randomized prospective study in which patients received HBO therapy in addition to other forms of care, the treatment group trended better in measurements of pain and quality-of-life score, but healing was only reported in 50% of patients.44

The use of platelet-rich plasma as an adjunct to local resection and primary closure was reported in a total of 5 cases at 2 separate institutions.45,46 In all instances, there was complete wound healing and resolution of pain. However, the small number of cases that were reported and the lack of controls mandate further study before recommending this technique.

In a small case study, simultaneous systemic pentoxifylline (improved microcirculation) and \( \alpha \)-tocopherol (antioxidant) administration has been reported to decrease pain and the size of the exposed bone.47 The rationale for this approach is based on other studies that demonstrated the efficacy of these drugs in the treatment of osteoradionecrosis.

Recombinant human parathyroid hormone (PTH) (teriparatide, Forteo) is the only anabolic agent for bone approved for use in humans in the United States. Daily PTH injections stimulate enhanced bone formation through positive effects on osteoblast lifespan and direct stimulation of quiescent bone lining cells. In several case reports, the use of systemic low-dose PTH was successful in resolving an area of necrosis when other modalities of treatment had failed.48,49 In each case, when combined with other standard treatment strategies, PTH therapy resulted in a rapid resolution of the exposed bone. In a recent prospective, placebo-controlled study of 40 patients, low-dose systemic PTH in conjunction with vitamin D and oral calcium was associated with greater resolution of periodontal bone defects and accelerated intraoral osseous healing.50 Although systemic PTH is contraindicated in patients with osteolytic bone metastases, these promising findings may have real applicability for ONJ cases in the noncancer setting. If these agents can be delivered locally to the regions of necrosis, the concern about enhanced medullary cellular proliferation in the patient with cancer may be ameliorated.
RESEARCH EFFORTS

Since ONJ was first described,20,51 the importance of developing an adequate animal model to study the factors associated with its cause, presentation, and response to treatment have been realized. Experimental animal models for ONJ have been described within the past several years.52,53 The challenge for any animal researcher is to establish a model that would be analogous to the human condition in terms of bone healing and response to therapy. It must take into consideration that bone remodeling in humans and large animal species occurs intracortically as opposed to at the bone surface.

In mouse models, bone matrix necrosis and delayed extraction socket healing have been demonstrated in animals exposed to zoledronic acid. Several studies have also focused on the rat model, where exposed bone is noted in a large percentage of extraction sites in animals exposed to bisphosphonates.54–56 These results are certainly promising and may provide the groundwork for future experiments. A troubling issue for both rodent models, however, is that necrosis also developed in the control groups. The degree to which the findings from these rodent models can be applied to a higher vertebrate biologic system remains to be established.

ONJ has also been reported in a dog model, where animals that did not undergo surgery were exposed to various dosages of oral bisphosphonates during a 3-year period. Although there were no areas of exposed bone, large regions of matrix necrosis were identified only within the alveolar bone of the treatment group.1 Similar results were also seen in dogs treated with oral bisphosphonate for just 1 year.3 In experiments specifically aimed at understanding the interaction between dental extraction and bisphosphonate exposure in dogs, 1 of 6 animals treated with IV zoleodronic acid in doses and schedules comparable to those received by patients with cancer developed exposed, necrotic bone at the extraction sites.5 These findings in a dog model are encouraging and may develop into a valid animal model for this disease process. Identifying such a model will enable future studies to truly focus on the mechanism of this disease and establish the utility of preventive and management strategies.

FUTURE CHALLENGES

As one looks at the present understanding of this iatrogenic complication and projects it into the future, there are many questions and challenges that still remain. The emergence of biologic therapies (anti-RANK/RANKL antibodies) as an efficacious bone-targeted treatment of patients with cancer and osteoporosis creates a new set of potential challenges, because these drugs are also associated with the development of jaw necrosis. Although the reversible nature of this humanized antibody may prove to be uniquely beneficial in managing ONJ, those potential benefits have yet to be studied or realized.

Accurate predictors of disease also remain elusive. Although certain types of costly nuclear imaging may prove to have some predictive value for those patients at risk, it remains uncertain as to when or which patients should receive these invasive tests. As yearly zoledronic acid therapy (Reclast) becomes more popular, the ONJ risk assessment needs to be monitored and reassessed. Based on current studies, the risk of developing ONJ was very low through 3 years of yearly zoledronic acid treatment.57,58 These data need to be considered in comparison to conventional oral bisphosphonate therapy, however, where the risk of developing ONJ usually appears after more than 3 years of exposure. With regard to monthly IV bisphosphonate therapy for cancer, the risk of developing jaw necrosis has been well described, yet the degree and timing (if any) of risk reduction after cessation of therapy remains poorly understood. The variation that exists in the literature regarding how the cumulative dose loads are measured (ie, yes/no, total amount in milligrams, years/months, and total doses) complicates efforts to more precisely assess the exposure risk. This information is pivotal to achieving a better understanding of the exposure thresholds for IV (and oral) therapy so that patients and clinicians are more accurately informed of the progressive risks of these bone-targeted therapies.

The understanding of the etiopathogenesis of this process, although much improved during the past several years, is still lacking. The identification of a reliable animal model system will serve as a valuable experimental tool to assess the various theories of pathogenesis, associated risk factors, and the predictive value of diagnostic and treatment strategies.

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