Systematic Review: Bisphosphonates and Osteonecrosis of the Jaws

Sook-Bin Woo, DMD; John W. Hellstein, DDS, MS; and John R. Kalmar, DMD, PhD

Osteonecrosis of the jaws is a recently described adverse side effect of bisphosphonate therapy. Patients with multiple myeloma and metastatic carcinoma to the skeleton who are receiving intravenous, nitrogen-containing bisphosphonates are at greatest risk for osteonecrosis of the jaws; these patients represent 94% of published cases. The mandible is more commonly affected than the maxilla (2:1 ratio), and 60% of cases are preceded by a dental surgical procedure. Oversuppression of bone turnover is probably the primary mechanism for the development of this condition, although there may be contributing comorbid factors. All sites of potential jaw infection should be eliminated before bisphosphonate therapy is initiated in these patients to reduce the necessity of subsequent dentoalveolar surgery. Conservative débridement of necrotic bone, pain control, infection management, use of antimicrobial oral rinses, and withdrawal of bisphosphonates are preferable to aggressive surgical measures for treating this condition. The degree of risk for osteonecrosis in patients taking oral bisphosphonates, such as alendronate, for osteoporosis is uncertain and warrants careful monitoring.

For author affiliations, see end of text.

**Methods**

We performed MEDLINE and PubMed searches of English- and foreign-language literature (1966 to 31 January 2006) using the following Medical Subject Headings (MeSH) and terms: osteonecrosis, avascular necrosis, phosphorous necrosis, bisphosphonates, and diphosphonates. We then crossed the same terms with the terms jaw diseases, myeloma, breast cancer, and metastatic cancer. Other references were obtained from citations from retrieved articles. Similar terms were used to search abstracts from meetings of the American Society of Clinical Oncology.

We specifically reviewed all case reports and case series of patients with bisphosphonate-associated osteonecrosis of the jaws. We included any report that provided acceptable documentation of disease and use of bisphosphonates, regardless of whether it included information on the sex of patients, the site of the lesions, and the bisphosphonate used. Several authors published more than 1 paper describing patients with osteonecrosis. Through direct communication with these authors, we confirmed that some of the same patients were included in multiple reports. When this occurred, we used and cited data only from the larger, more recent publication.

No funding was received for this study.

**Actions of Bisphosphonates**

Bisphosphonates are powerful inhibitors of osteoclastic activity. They are analogues of inorganic pyrophosphates with low intestinal absorption, are excreted through the kidneys without metabolic alteration, and have a high affinity for hydroxyapatite crystals (1, 2). Because they are incorporated into the skeleton without being degraded, they are remarkably persistent drugs; the estimated half-life for alendronate is up to 12 years (3). Alendronate, risedronate, pamidronate, zoledronic acid, and ibandronate, which are called aminobisphosphonates, have much higher potency because they contain nitrogen in a side chain (Table 1).

The nonaminobisphosphonates are metabolized by osteoclasts to inactive nonhydrolyzable adenosine triphosphate analogues that are directly cytotoxic to the cell and induce apoptosis (1, 2). The newer aminobisphosphonates have 2 actions (4): induction of another adenosine triphosphate analogue that induces apoptosis, and inhibition of farnesyl diphosphonate synthase, which is part of the mevalonate pathway of cholesterol synthesis. Such inhibition results in dysregulation of intracellular transport, cytoskeletal organization, and cell proliferation, leading to inhibition of osteoclast function. In addition, aminobisphosphonates reduce recruitment of osteoclasts and induce osteoblasts to produce an osteoclast-inhibiting factor (5, 6).

Aminobisphosphonates exert several antitumor effects, including induction of tumor cell apoptosis, inhibition of tumor cell adhesion to the extracellular matrix, and inhibition of tumor invasion (4, 7). Bisphosphonates also have...
argue that although long-term use of bisphosphonates may suppress bone turnover to the point that such microdamage persists and accumulates (15). The result is hypodynamic bone with decreased biomechanical competence. Although osteoblastic function is also reduced during bisphosphonate therapy, continued mineralization yields a hard, brittle bone with an osteopetrotic appearance and an increased risk for fracture (16–18). Thus, some experts caution that the benefits of prolonged use of bisphosphonates must be carefully weighed against the potential negative effects of oversuppression of bone metabolism (1, 19, 20). Other experts have become standard therapy in the management of patients with multiple myeloma and metastatic cancer.

**Potential Adverse Effects of Bisphosphonate Actions**

In normal bone homeostasis, osteoclastic resorption is tightly linked to osteoblastic bone deposition and both functions are essential for repair of physiologic microdamage. Prolonged use of bisphosphonates may suppress bone turnover to the point that such microdamage persists and accumulates (15). The result is hypodynamic bone with decreased biomechanical competence. Although osteoblastic function is also reduced during bisphosphonate therapy, continued mineralization yields a hard, brittle bone with an osteopetrotic appearance and an increased risk for fracture (16–18). Thus, some experts caution that the benefits of prolonged use of bisphosphonates must be carefully weighed against the potential negative effects of oversuppression of bone metabolism (1, 19, 20). Other experts argue that although long-term use of bisphosphonates may retard fracture healing or slow callus remodeling, it may not affect bone mineralization or mechanical properties (21, 22).

**Oral Complications of Bisphosphonate Therapy**

Although oral bisphosphonates may cause oral mucosal lesions (purportedly arising from direct contact injury) (23, 24), we focus our review on bisphosphonate-associated osteonecrosis of the jaw. Table 2 summarizes 368 reported cases of bisphosphonate-associated osteonecrosis of the jaw (25–54). Reported cases manifested as exposure of portions of the bone of the mandible only (65%), maxilla only (26%), or both (9%). Approximately one third of lesions were painless (27), and there was a slight female predilection in a ratio of 3:2 among all reported cases. Multifocal or bilateral involvement was slightly more common in the maxilla than in the mandible (31% vs. 23%). Most lesions were on the posterior lingual mandible near the mylohyoid ridge. Of importance, 60% of cases occurred after a tooth extraction or other dentoalveolar surgery and the remaining cases occurred spontaneously. The latter cases often involved patients wearing dentures, a possible source of local trauma. Marx and colleagues (27) reported that 39% of cases that occurred spontaneously were located on bony exostoses that were easily traumatized. There is 1 case report of dental implant failure associated with bisphosphonate use (55).

Most patients (94%) were treated with intravenous bisphosphonates (primarily pamidronate and zoledronic acid), and most patients (85%) had multiple myeloma or metastatic breast cancer (Table 3). The remaining patients

### Table 1. Bisphosphonate Formulations*

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Manufacturer and Location</th>
<th>Dosage Forms</th>
<th>Nitrogen-Containing</th>
<th>FDA Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate disodium</td>
<td>Didronel</td>
<td>Procter &amp; Gamble Pharmaceuticals, Cincinnati, Ohio</td>
<td>200- and 400-mg tablets</td>
<td>No</td>
<td>1 September 1977</td>
</tr>
<tr>
<td>Clodronate disodium</td>
<td>Bonefos (Canada)</td>
<td>Schering AG, Berlin, Germany</td>
<td>400- and 800-mg tablets; 60 mg/mL ampule†</td>
<td>No</td>
<td>Not approved</td>
</tr>
<tr>
<td>Tiludronate disodium</td>
<td>Skelid</td>
<td>Sanofi-Synthelabo Inc., New York, New York</td>
<td>200-mg tablet</td>
<td>No; sulfur moiety</td>
<td>7 March 1997</td>
</tr>
<tr>
<td>Alendronate sodium</td>
<td>Fosamax</td>
<td>Merck &amp; Co. Inc., Whitehouse Station, New Jersey</td>
<td>5-, 10-, 35-, 40-, and 70-mg tablets; 70 mg/75 mL oral solution</td>
<td>Yes</td>
<td>29 September 1995</td>
</tr>
<tr>
<td>Pamidronate disodium</td>
<td>Aredia</td>
<td>Novartis Pharmaceuticals, East Hanover, New Jersey</td>
<td>30-, 60-, and 90-mg vial†</td>
<td>Yes</td>
<td>31 October 1991</td>
</tr>
<tr>
<td>Risedronate sodium</td>
<td>Actonel</td>
<td>Procter &amp; Gamble Pharmaceuticals, Cincinnati, Ohio</td>
<td>5-, 30-, and 35-mg tablets</td>
<td>Yes</td>
<td>27 March 1998</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Zometa</td>
<td>Novartis Pharmaceuticals, East Hanover, New Jersey</td>
<td>4-mg vial†</td>
<td>Yes</td>
<td>20 August 2001</td>
</tr>
<tr>
<td>Iblandronate sodium</td>
<td>Boniva</td>
<td>Roche Laboratories Inc., Nutley, New Jersey</td>
<td>2.5-mg tablet; 150-mg tablet; 3 mg/3 mL†</td>
<td>Yes</td>
<td>16 May 2003</td>
</tr>
</tbody>
</table>

* This table shows the most common brand names. Generic forms, other names, and other doses may be available outside the United States. Clodronate is included because of its common use in Canada and Europe. FDA = Food and Drug Administration.† Drug is administered intravenously.

Table 3
were taking oral bisphosphonates for osteoporosis or Paget disease of bone (25, 27–29, 40, 50, 51).

Clinically, intraoral lesions appear as areas of exposed yellow-white, hard bone with smooth or ragged borders (Figures 1 and 2). Extraoral or intraoral sinus tracts may be present (Figure 3). Painful ulcers may develop in soft tissues that impinge on the ragged bony margins.

Results of radiographic evaluation may be negative in early cases. Although some investigators have noted subtle changes, such as widening of the periodontal ligament,
these findings are indistinguishable from chronic periodontal infection, a predisposing factor for osteonecrosis (27). Advanced cases show a moth-eaten, poorly defined radiolucency, with or without radio-opaque sequestra. In 1 series, 5 of 63 patients developed pathologic jaw fractures (25). Cultures of exposed bone may identify *Actinomyces* species, but care must be taken to distinguish between a true suppurative infection and mere surface colonization by *Actinomyces*, because such organisms are a common component of dental plaque.

Patients with bisphosphonate-associated osteonecrosis may present similarly to those with osteoradionecrosis of the jaws. Osteoradionecrosis is a complication of radiotherapy. It is thought to result from osteocyte and microvascular damage after the jaws are exposed to ionizing radiation and also frequently occurs after tooth extraction (56). Osteoradionecrosis, however, infrequently involves the maxilla (<5% of cases) and is more common in men than in women (57, 58).

### Risk Factors and Etiopathogenesis

The most important predisposing factors for the development of bisphosphonate-associated osteonecrosis of the jaws are the type and total dose of bisphosphonate and history of trauma, dental surgery, or dental infection. Ninety-four percent of patients with osteonecrosis received pamidronate or zoledronic acid. The doses for oncologic indications are often up to 12 times higher than those used for osteoporosis (13, 59). Of interest, clodronate, a non-aminobisphosphonate, has not been implicated in the development of osteonecrosis (60). The risk for osteonecrosis of the jaws is substantially higher for patients taking zoledronic acid and increases over time, probably because of the long half-life of these drugs. Although oral lesions may develop after as few as 4 months of bisphosphonate therapy, the median duration of drug use ranged from 22 to 39 months (32, 38, 48) and the mean ranged from 9 to 14 months (27, 33). The cumulative hazard was 1% within the first year and 21% at 3 years of treatment with zoledronic acid. In contrast, it was 0% in the first year and 4% in the third year for patients receiving pamidronate alone or with subsequent zoledronic acid (32). Another study showed that 10% of 211 patients receiving zoledronic acid developed osteonecrosis compared with 4% of 413 patients receiving pamidronate (61).

A few cases have been reported in patients taking alendronate (10 mg/d) for osteoporosis (25, 27–29, 50, 51). One patient had taken alendronate for only 2 years (27). The concern is that with more women aging and taking bisphosphonates for longer periods of time, more cases of osteonecrosis may develop even in patients receiving alendronate or ibandronate therapy.

Trauma to oral tori is also associated with osteonecrosis (27) (Figure 2). Furthermore, 60% of patients had some form of dentoalveolar surgery resulting in nonhealing of the surgical site and necrosis of bone. Because most dentoalveolar surgeries are performed to treat dental infection, the contribution of each to the development of osteonecrosis of the maxilla is unclear.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, n (%)*</th>
</tr>
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<tbody>
<tr>
<td>Primary diagnosis</td>
<td>368 (100)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>171 (46.5)</td>
</tr>
<tr>
<td>Metastatic breast cancer</td>
<td>143 (38.8)</td>
</tr>
<tr>
<td>Metastatic prostate cancer</td>
<td>23 (6.2)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>15 (4.1)</td>
</tr>
<tr>
<td>Other metastatic disease†</td>
<td>13 (3.5)</td>
</tr>
<tr>
<td>Paget disease of bone</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Total</td>
<td>368 (100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bisphosphonate medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>124 (35)</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>110 (31)</td>
</tr>
<tr>
<td>Pamidronate and zoledronic acid</td>
<td>100 (28)</td>
</tr>
<tr>
<td>Oral alendronate</td>
<td>15 (4.2)</td>
</tr>
<tr>
<td>Alendronate and zoledronic acid</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Oral risedronate</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Oral ibandronate</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Ibandronate and zoledronic acid</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Pamidronate, zoledronic acid, and alendronate</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Total</td>
<td>355 (100)</td>
</tr>
</tbody>
</table>

| Intravenous bisphosphonates, not specified | 13 |

<table>
<thead>
<tr>
<th>Patients with osteoporosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Receiving alendronate</td>
<td>13 (87)‡</td>
</tr>
<tr>
<td>Receiving risedronate</td>
<td>1 (7)§</td>
</tr>
<tr>
<td>Receiving alendronate and zoledronic acid</td>
<td>1 (7)§</td>
</tr>
</tbody>
</table>

* Percentages may not sum to 100% because of rounding.
† Five patients had lung tumors. Other diseases were leiomyosarcoma, leukemia, ovarian/breast cancer, ovarian cancer, renal cancer, lymphoma, mesothelioma, and “other.”
‡ Nine of 11 cases were in the mandible, and 2 of 11 cases were in the maxilla. The remaining 2 cases were not specified.
§ All cases were in the mandible.

**Table 3. Primary Diagnoses and Types of Bisphosphonates in Reported Cases of Osteonecrosis of the Jaws**

**Figure 1. Osteonecrosis of the right mandible after tooth extraction in a patient taking zoledronic acid for metastatic breast cancer.**
necrosis is unclear, although it is likely that together they compound the problem.

Patients with myeloma tend to be prothrombotic and are often treated with other antiangiogenic agents, such as glucocorticoids, thalidomide, and the new proteasome inhibitors, such as bortezomib, in addition to bisphosphonates (62, 63). Although neither corticosteroids nor thalidomide has been shown to be associated with additional risk for osteonecrosis of the jaws, prospective studies are needed to more fully address this issue (32, 61). The impact of local factors, such as smoking, and of underlying medical conditions, such as diabetes or peripheral vascular diseases, remains to be determined.

Susceptibility of the Jaws to Osteonecrosis

The question often asked is “Why the jaws?” First, the jaw bones are separated from a trauma-intense and microbiologically diverse oral environment by thin mucosa and periosteum. The fragility of this barrier is reflected by the condition known as lingual mandibular sequestration, which occurs in healthy adults yet resembles mild cases of bisphosphonate-associated osteonecrosis of the jaws (64). In this condition, 1- to 3-mm slivers of bone are sequestered in the area of the protuberant mylohyoid ridge with spontaneous resolution. It is thought that minor trauma causes local damage to the thin mucosa and underlying periosteum, leading to bone necrosis. Because the posterior lingual mandible is also a frequent site for osteonecrosis, it seems probable that the hypodynamic bone in patients receiving bisphosphonate therapy may turn this typically innocuous process into chronic bone exposure. Trauma to the periosteum may also serve to initiate osteonecrosis in patients wearing dentures or dental prostheses or in patients with prominent exostoses.

Second, teeth are readily infected by bacteria that cause caries and periodontal disease, 2 common infectious diseases. Because the teeth are separated from bone by no more than 2 mm of periodontal connective tissue, such infections have easy access to the underlying bone. A case of osteonecrosis in the ear of a patient taking zoledronic acid for multiple myeloma was reported recently (44). The lesion occurred after removal of exostoses in the external auditory canal, and the patient had concurrent osteonecrosis of the maxilla.

We suggest that bisphosphonate-associated osteonecrosis of the jaws results from marked suppression of bone metabolism that results in accumulation of physiologic microdamage in the jawbones, compromising biomechanical properties. Trauma and infection increase demand for osseous repair that exceeds the capacity of the hypodynamic bone, resulting in localized bone necrosis. The antiangiogenic property of bisphosphonates and other medications and the presence of other comorbid factors may promote the risk for or persistence and progression of this condition.

Prevalence of Bisphosphonate-Associated Osteonecrosis of the Jaws

A Web-based survey conducted by the International Myeloma Foundation resulted in 1203 respondents, 904 with myeloma and 299 with breast cancer. Seven percent and 4% of patients with myeloma and breast cancer, respectively, reported osteonecrosis, and 6% and 8% of patients with myeloma and breast cancer, respectively, reported lesions suspicious for osteonecrosis (61). In a single-center study of 252 patients who had received intravenous bisphosphonates since January 1997, 10% of 111 patients with myeloma and 3% of 46 patients with breast cancer developed osteonecrosis (32). In another study of 124 patients with myeloma or breast cancer who were treated with intravenous bisphosphonates in a dental clinic in a cancer center, 4 and 9 patients with myeloma and breast cancer...
Osteonecrosis of the jaws is strongly associated with the use of aminobisphosphonates, and the mechanism of disease is probably severe suppression of bone turnover.

Ninety-four percent of patients are treated with zoledronic acid or pamidronate or both; 85% of affected patients have multiple myeloma or metastatic breast cancer, and 4% have osteoporosis.

The prevalence of osteonecrosis in patients with cancer is 6% to 10% and the prevalence in those taking alendronate for osteoporosis is unknown; osteonecrosis seems to be time- and dose-dependent because of the long half-life of aminobisphosphonates.

More than half of all cases (60%) occur after dentoalveolar surgery (such as tooth extraction) to treat infections, and the remaining 40% are probably related to infection, denture trauma, or other physical trauma.

Preventive strategies include removing all foci of dental infection before starting bisphosphonate therapy.

Treatment is directed toward control of pain and infection and careful local débridement of dead bone, but not wide excision of lesions.

Patient management before initiation of therapy with aminobisphosphonates is targeted at eliminating active sites of infections to minimize future infections and the need for future dental surgery, such as tooth extraction, to treat such infections. Similar protocols have been established for patients preparing for allogeneic stem-cell transplantation and those about to receive radiation to the head and neck.

Recommendations for group 1, patients about to begin intravenous bisphosphonate therapy, are outlined in Table 4. It is probably not necessary to delay initiation of bisphosphonate therapy if dental treatment can be completed within 1 to 2 months. With drug use between 3 and 6 months, patients in group 2 (those receiving intravenous aminobisphosphonates who do not have signs of osteonecrosis of the jaws) should be evaluated on a case-by-case basis. Those who have been receiving intravenous bisphosphonate therapy for oncologic indications for more than 6 months are at risk for this condition. In group 3, patients with osteonecrosis of the jaws, there are anecdotal reports of the use of acrylic stents (with or without soft liners) to cover areas of exposed bone, protect adjacent soft tissues, and improve comfort. However, there is a risk that the stent may act as a fomite and that additional trauma may be caused by the stent itself.

Reduction of pain and regression or even resolution of lesions of osteonecrosis have been observed in patients treated with antibiotics and mouth rinses, withdrawal of bisphosphonates, and removal of loose sequestra. Extensive resection has not consistently resulted in wound closure and may lead to worsening or progression of disease. However, even for patients with multiple myeloma who are potential candidates for hematopoietic stem-cell transplantation or continued chemotherapy, asymptomatic osteonecrosis may not necessarily pose a substantial risk for increased morbidity if there is no evidence of active infection, as characterized clinically by pain and suppuration. Hyperbaric oxygen therapy, given to a few patients, has only infrequently shown clinical efficacy.

The prevalence of osteonecrosis in patients with cancer is 6% to 10% (26).

Management Recommendations

Treatment protocols have been outlined, but trials and outcomes of treatment and long-term follow-up data are not yet available. In June 2004, an expert panel outlined recommendations for the management of bisphosphonate-associated osteonecrosis of the jaws. Because there are no randomized clinical trials that assess management strategies, we propose the following guidelines based on published literature, our own experience, and the experience of our colleagues.

We group patients who are either receiving bisphosphonate therapy or about to begin therapy into the following 3 broad categories: group 1, patients about to begin aminobisphosphonate therapy; group 2, patients without osteonecrosis of the jaws who are receiving aminobisphosphonate therapy; and group 3, patients with osteonecrosis of the jaws. Patients with osteoporosis who are taking oral preparations, such as alendronate, and are at lower risk than those receiving intravenous preparations are included in group 1. We note that the risks associated with oral ibandronate, recently approved for the treatment of osteoporosis, are unknown.

Key Summary Points

- Osteonecrosis of the jaws is strongly associated with the use of aminobisphosphonates, and the mechanism of disease is probably severe suppression of bone turnover.
- Ninety-four percent of patients are treated with zoledronic acid or pamidronate or both; 85% of affected patients have multiple myeloma or metastatic breast cancer, and 4% have osteoporosis.
- The prevalence of osteonecrosis in patients with cancer is 6% to 10% and the prevalence in those taking alendronate for osteoporosis is unknown; osteonecrosis seems to be time- and dose-dependent because of the long half-life of aminobisphosphonates.
- More than half of all cases (60%) occur after dentoalveolar surgery (such as tooth extraction) to treat infections, and the remaining 40% are probably related to infection, denture trauma, or other physical trauma.
- Preventive strategies include removing all foci of dental infection before starting bisphosphonate therapy.
- Treatment is directed toward control of pain and infection and careful local débridement of dead bone, but not wide excision of lesions.
moval of the antiangiogenic effects of the drug on the soft tissues and periosteum may play a role in healing. For this reason, discontinuation of oral bisphosphonate therapy for several weeks before and after dentoalveolar surgery may be warranted. Until data from clinical trials are available, the optimal timing and duration of such a drug holiday are somewhat arbitrary and must be weighed against the risks posed by not taking medication. If the patient’s underlying systemic disease is stable, bisphosphonates can be withdrawn until the area of osteonecrosis heals or until clinical variables indicate disease progression.

**RESEARCH AVENUES**

Clinical trials are urgently needed to address many issues. Can alternative dosing schedules reduce the incidence of osteonecrosis while maintaining the enormous benefits of these drugs? For example, once the patient’s condition is stabilized, perhaps lower-potency, nonaminobisphosphonates can be substituted in a maintenance role (60, 70). Monitoring bone turnover markers may help clinicians avoid oversuppression (71). A staging system can be developed, possibly including serologic and imaging data, that more accurately determines disease severity; this could then be used to guide treatment. Establishing criteria for the diagnosis of early changes that precede or predict bone exposures would also be desirable.

Prospective studies are also needed to more precisely determine what additional risk factors, if any, may predispose the patient to the development of osteonecrosis of the jaws. Such variables as age, sex, medications, preexisting medical conditions, and individual genetic variations need to be examined. Finally, clinical trials should be done to determine the most effective treatment protocols for patients with this condition.

**CONCLUSION**

Osteonecrosis of the jaws is a newly recognized condition reported in patients treated with bisphosphonates, in particular potent aminobisphosphonates. Most cases have developed in patients with multiple myeloma or metastatic cancer, but the condition has also been identified in patients with osteoporosis. This article reviews the findings in 368 cases, suggests treatment strategies, and outlines research avenues that may help us better understand and treat this condition.

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**Note:** This is a position paper of the American Academy of Oral and Maxillofacial Pathology.

**Grant Support:** None.

**Potential Financial Conflicts of Interest:** Grants received: [PMID: 10525729]


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