CASE REPORT

# Osteonecrosis of the jaw after oral bisphosphonate for osteoporosis

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**Bisphosphonates are a common treatment for osteoporosis. Osteonecrosis of the jaw has been associated with the use of bisphosphonates, usually when they have been used parenterally to treat malignancies. Cases associated with oral bisphosphonate as a treatment for osteoporosis are less frequent. We describe two patients exhibiting the clinical manifestations of bisphosphonate-associated osteonecrosis of the jaw. A brief review of the literature on the incidence, possible risk factors, and practice guidelines is also presented.**

## Introduction

Since an association between osteonecrosis of the jaw (ONJ) and the use of bisphosphonate was first reported in 2003,[1] more case series reporting similar findings, usually in patients undergoing parenteral treatment for malignancies, have emerged. Osteonecrosis of the jaw associated with use of oral bisphosphonate for the treatment of osteoporosis is much less frequently reported.[2,3] The American Society for Bone and Mineral Research defines bisphosphonate-associated ONJ as "an area of exposed bone in the maxillofacial region that has not healed within 8 weeks after identification by a healthcare provider in a patient who is receiving or has been exposed to a bisphosphonate and has not had radiation therapy to the craniofacial region".[4] We report two cases of ONJ after treatment with oral bisphosphonate for osteoporosis.

## Case reports

### Case 1

A 70-year-old woman presented in February 2008 with an 11-month history of jaw pain, unrelieved by wound curettage, after a left lower wisdom tooth extraction. She had been taking oral risedronate, 5 mg daily, after fracturing L2 and L3, for 4 years. On presentation, she had mild left facial swelling and an unhealed socket at tooth 38. Panoramic and periapical dental X-rays (Fig 1a) showed osteolysis in the left mandibular alveolus. Contrast computed tomography (CT) of the mandible (Fig 1b) showed a bony defect and sequestrum in the left mandible. The risedronate was stopped immediately. On exploration, sequestrum formation was noted at the site of the left mandibular osteonecrosis around the socket of tooth 38. Sequestrectomy was performed, followed by a long course of oral

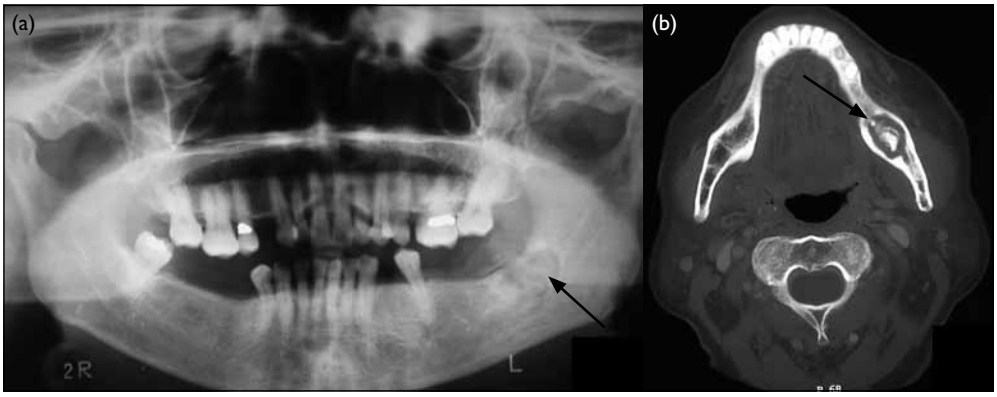


FIG 1. (a) Preoperative panoramic dental X-ray showing an ill-defined radiopacity surrounded by a rim of radiolucency (arrow) superior to the left inferior dentoalveolar canal suggestive of sclerotic changes and sequestrum formation. (b) Contrast computed tomographic scan of the mandible taken 1 year after wisdom tooth removal leaving an unhealed socket. A bony defect of about 19 x 12 mm in size was found in the left mandible near the angle, suggestive of a destructive process with surrounding sclerotic changes and sequestrum formation (arrow). It is also associated with enhancing inflammatory changes in the anterior aspect. No gross abscess cavity was detected in the soft tissue

**Key words**
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## 治療骨質疏鬆症的口服雙膦酸鹽類藥物導致頜骨壞死

雙膦酸鹽類藥物是治療骨質疏鬆症經常處方的藥物。據報告，使用雙膦酸鹽類藥物，尤以注射方式治療癌症跟頜骨壞死呈相關，但以口服治療引發的頜骨壞死病例則較為少見。本文報告兩名與雙膦酸鹽類藥物治療有關的頜骨壞死病人的臨床表現，也簡要回顧有關其發病率、可能的危險因素和治理指引的文獻。

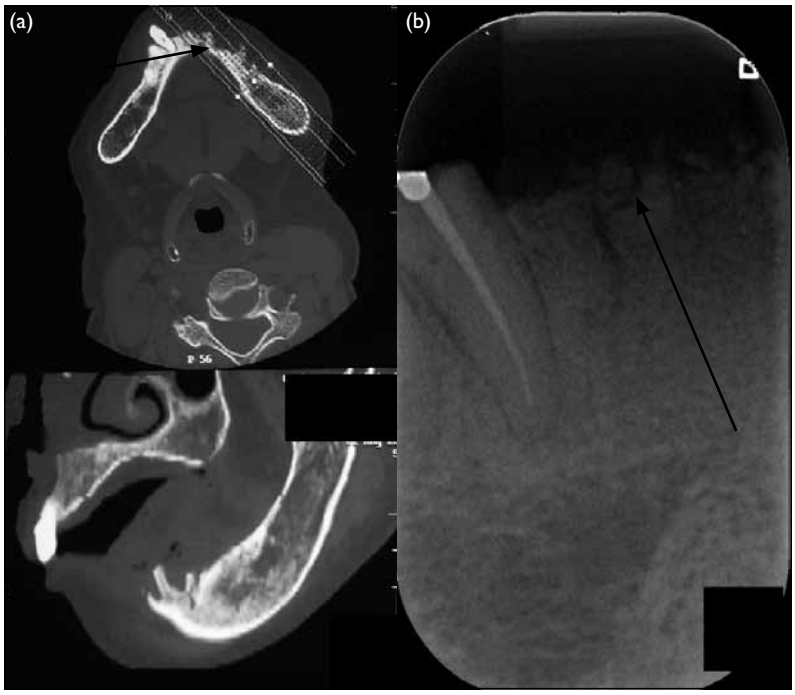


FIG 2. (a) Contrast computed tomographic scan of the mandible taken when an unhealed extraction socket in the left anterior mandible was noted. Some cavities with missing teeth (arrow) were noted in the body of the left mandible. Mild sclerotic changes were noted. No cortical disruption or fragmentation was noted. No destruction of trabeculations was noted. There was no radiological evidence of osteonecrosis. (b) The periapical dental X-ray of the alveolus of the anterior mandible shows non-specific sclerotic change and sequestrum formation at the alveolar ridge (arrow), which presented clinically as exposed bone

antibiotics. Good oral wound healing was achieved, indicated by granulation tissue at the tooth socket 38. A panoramic dental X-ray showed no increase in the size of the bony defect. When reviewed 5 months postoperatively the patient had a good edentulous ridge in the tooth socket 38 region.

### Case 2

A 78-year-old woman presented in July 2007 with a wound that had failed to heal for 2 years, despite curettage, after having teeth 32-34 extracted by a private dentist. She had been on oral alendronate 70 mg weekly for osteoporosis for 3 years. On presentation, she was found to have a buccal sinus discharging pus at the tooth 33 alveolus. A contrast CT of the mandible found no evidence of osteonecrosis (Fig 2a). The tooth 33 region of her left mandibular alveolus was resected. A histopathological examination found osteomyelitis and actinomyces colonies in the left mandibular alveolus, so she was given a 6-month course of antibiotics. On follow-up 2 weeks postoperatively, the wound was healing well and a good ridge was found at the tooth 34 alveolus resection site. An X-ray showed good periapical bone remodelling in the tooth 33-34 region. One year after the alveolar resection she underwent lower jaw rehabilitation with removable partial dentures prescribed by a private dentist. She was referred to us again complaining of pain in the edentulous ridge of the anterior mandible. A physical examination revealed an exposed bone chip at the lower anterior alveolus with sclerotic changes evident in the periapical dental X-ray (Fig 2b). It was suspected that the exposed dentoalveolus was a result of bisphosphonate-induced osteonecrosis. Her oral alendronate was stopped. The necrotic bone in the anterior mandible was surgically removed and the wound healed well. She was reviewed 3 months postoperatively and was found to have recovered well and was using dentures modified by a private dentist.

## Discussion

Osteoporosis is a major public health problem because of its high cumulative fracture risk and the potentially disastrous consequences. Bisphosphonates are a common treatment for osteoporosis. The above two cases illustrate the clinical manifestations of bisphosphonate-associated ONJ. Both had exposed bone with infection and the affected areas did not heal within 8 weeks.

Of 368 cases of ONJ reported in the literature,[5] only 15 (4.1%) had received oral bisphosphonates for osteoporosis. Another review found that the estimated risk of ONJ in patients treated with oral bisphosphonates for osteoporosis was between 1 in 10 000 and less than 1 in 100 000 patient-treatment years.[3] This very low risk assessment has been supported by two recent population-based prevalence studies. A German study of 780 000 people with osteoporosis found only three cases of ONJ, yielding a risk of less than 1 in 100 000 patient-treatment years.[6] An Australian study identified 36 cases of ONJ in people with osteoporosis, giving an overall risk ranging between 0.01 and 0.04%, rising to between 0.09 and 0.34% after dental extraction. The total dose of oral alendronate at the onset of ONJ was 9060 (±7269) mg.[7]

Two series have reviewed the clinical features of ONJ in osteoporotic patients treated with

bisphosphonates. In one series of 26 cases,[2] the most commonly affected site was the mandible (16 cases), followed by the maxilla (6 cases). Of 15 patients with a history of invasive dental treatment, 80% had undergone dental surgery or experienced dental trauma at the site of the ONJ. In another review of 11 cases,[3] the ONJ was triggered by dental surgery in nine and by ill-fitting dentures in two. Of nine patients with follow-up periods of 6 months or more, the ONJ healed completely in three, partially healed in four and not at all in two. Heavy smokers were the most recalcitrant subjects. In a recent systematic review of ONJ and bisphosphonates being used by people who do not have cancer,[8] 85 patients whose osteoporosis was being managed with bisphosphonates had been diagnosed with ONJ. The mean age was 68.7 (standard deviation, 9.4) years and 90.6% were female. The duration of use of the bisphosphonates was more than 1 year in 93.5% and more than 5 years in 38.7%. Most were taking oral bisphosphonates. Among patients providing clinical information, co-morbidities or concomitant medications were very common. Over 92% (49/53) had a dental procedure before the onset of ONJ; 71% (17/24) had been taking one or more concomitant medication known to affect bone turnover (10 patients were on steroids); 26% reported periodontitis, gingivitis or poor oral health, 21% had rheumatoid arthritis or lupus, and 15.8% had diabetes or impaired glucose function. These features suggest that ONJ may be due to a combination of factors affecting the jaw that, when combined with bisphosphonate, increase the risk of ONJ.

A clear causal relationship between oral bisphosphonate and ONJ has yet to be established. Oversuppression of bone turnover is probably the primary mechanism for the development of ONJ[5] as it makes the bone susceptible to necrosis when there is increased demand for bone repair from trauma or infection. The dosage and duration of bisphosphonate use probably determines the occurrence and the extent of the ONJ. Furthermore, bisphosphonates exhibit toxicity to epithelial cells[9] and antiangiogenic effects.[10] It has also been suggested that bisphosphonates have an inhibitory effect on oral mucosal cell wound healing in animal models.[11] It is not known whether infection represents a primary or secondary event in the development of ONJ. Perhaps the most important risk factors are invasive oral treatments involving bone exposure (eg tooth extraction, subgingival curettage, periapical and periodontal surgery), trauma (eg from ill-fitting dentures), and poor oral hygiene.[12] All these can lead to oral mucosal lesions and can trigger ONJ in the presence of the above contributing factors. Other risk factors include age over 60 years, use of steroids or other medications affecting bone turnover, and use of bisphosphonate for more than 1 year.[8]

Despite its low prevalence, the potential risk of ONJ occurring after the use of oral bisphosphonate for osteoporosis should not be neglected. Stopping smoking, limiting alcohol intake, and maintaining good oral hygiene with or without regular dental cleaning should be emphasised. According to the Canadian consensus practice guidelines,[13] patients receiving oral or intravenous bisphosphonates do not require a dental examination prior to initiating therapy in the presence of appropriate dental care and good oral hygiene. Nonetheless, in an Australian study, over 95% of patients on bisphosphonates who were referred for an oral health check had advanced periodontal disease.[14] Therefore, patients who are on bisphosphonates and are not receiving regular dental care would benefit from a comprehensive oral examination by a dentist either before, or soon after, commencement of the therapy. All sites of potential jaw infection should be eliminated before commencing bisphosphonate therapy to reduce the necessity of subsequent dentoalveolar surgery.[5] As there is no validated diagnostic technique available for determining which patients are at increased risk of developing ONJ, an oral health programme consisting of sound oral hygiene practices and regular dental care is considered the optimal approach by the American Dental Association.[15] Discontinuation of bisphosphonate treatment may not eliminate or reduce the risk of ONJ in those patients requiring dental surgery.[15]

Osteoporosis poses an increased risk of fractures, which lead to significant pain, morbidity, functional disability and dependence, and mortality. In our opinion, the significant positive benefits of bisphosphonates offered to patients with osteoporosis outweigh the relatively small risk of developing ONJ. Nevertheless, prescribing clinicians should understand and recognise this clinical entity and fully explain all the benefits and risks of bisphosphonate therapy to their patients.

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