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Review Article

Dental complications and management of patients on bisphosphonate therapy: A review article

Sandeep Kalra^a, Veena Jain^{b,*}^a Research Officer, Department of Prosthodontics, Center for Dental Education and Research, All India Institute of Medical Sciences (AIIMS), New Delhi 110029, India^b Additional Professor, Department of Prosthodontics, Center for Dental Education and Research, All India Institute of Medical Sciences (AIIMS), New Delhi 110029, India

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ABSTRACT

Bisphosphonates are group of drugs that inhibit bone resorption and are used to treat a range of pathologies including Paget's disease, osteoporosis, multiple myeloma and metastasis associated with breast or prostate cancer. The most common complication in patients on bisphosphonate therapy is osteonecrosis of jaw (ONJ) which can occur after any surgical dental procedure and the risk for the development of osteonecrosis of jaw is higher in patients receiving intravenous bisphosphonate therapy than in patients receiving oral bisphosphonate therapy. Typical presentation is in the form of non-extraction socket, presence of exposed bone, gingival swelling or purulent discharge, when local debridement and antibiotics are ineffective.

At present, there is no effective treatment for bisphosphonate induced osteonecrosis, so prevention is extremely important. Maximum precautions should be taken in patients who are at the risk of development of ONJ especially when any dental surgical procedure like extractions, retrograde apicoectomies, periodontal surgery and implant placement is contemplated. Dentists and oral or maxillofacial surgeon must keep up to date with the latest approaches or guidelines to prevention and the risk factors, particularly when treating patients who are on bisphosphonates, or who will be taking bisphosphonates.

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1. Introduction

Bisphosphonates are the group of drugs that inhibit bone resorption and are used to treat metabolic diseases like osteoporosis, Paget's disease, hypercalcaemia of malignancy and multiple myeloma.¹ The nuclear structure of bisphosphonates consists of 2 phosphate group joined by single carbon atom.²

There are 2 types of bisphosphonates: nitrogen containing and non-nitrogen containing. Those containing nitrogen in their structure are more potent and accumulate in maximum concentration in the matrix and osteoclasts.³

There are two modes of administration of bisphosphonates: intravenously (IV) and orally. There is lot of difference in potency with both modes as with oral administration only

* Corresponding author. Tel.: +91 (0) 9868187441.

E-mail address: jainveena1@gmail.com (V. Jain).

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1% of the dose is absorbed by gastrointestinal tract whereas with IV mode more than 50% of the dose administered is bio available, which makes IV dose more potent.^{4,5} Intravenous bisphosphonates are used to reduce bone pain, Paget's disease, hypercalcaemia of malignancy, myeloma. Oral bisphosphonates are mainly used for treatment of osteoporosis, osteogenesis imperfecta.

The main mechanism of their action is explained by the fact that bisphosphonates have a high affinity for bone minerals and bind strongly to hydroxyapatite resulting in selective uptake to the target organ and high local concentration in bone, particularly at the sites of active bone remodelling. They act by inhibiting the osteoclast differentiation, reducing their activity, and inducing osteoclast apoptosis.⁶

Although bisphosphonates have been proved beneficial for many metabolic bone diseases but due to their action on osteoclast, they impair bone healing and remodelling and this has resulted in increased risk of development of osteonecrosis of jaw (ONJ) following surgical dental procedures like extraction or implant placement.⁷ The basic mechanism of development of osteonecrosis is that due to osteoclastic inhibition necrotic bone cannot be resorbed by the osteoclast during normal course of healing and the necrotic bone which remains, affects the blood supply to the area. So, the ONJ becomes the major dental complication in patients on bisphosphonate therapy. The risk of developing ONJ increases with the duration the patient has been taking the drugs. The patients receiving IV bisphosphonates are at more risk for development of ONJ than those getting oral bisphosphonates.⁸ So it becomes important to identify the patients who are, or will be placed on bisphosphonate therapy so that appropriate precautions or management can be done prior to any dental procedure.

This article focuses on presenting the incidence of osteonecrosis of jaw after surgical dental procedure in patients under bisphosphonate therapy and the management of such patients.

2. Complications in patients on bisphosphonate therapy

The most common complication in patients on bisphosphonate therapy is osteonecrosis of jaw which occurs after any surgical dental procedure. Although, spontaneous cases of osteonecrosis have been reported but in majority of cases (68.8%), patients had a history of dental disease or treatment.⁸ According to the information currently available, risk for developing bisphosphonate associated osteonecrosis of jaw is higher in patients on IV bisphosphonate therapy than the patients on oral bisphosphonates as orally they are poorly absorbed.^{8,9}

2.1. Pathophysiology of osteonecrosis

As stated earlier bisphosphonates have high affinity for bone minerals and bind strongly to hydroxyapatite which results in high concentration at the site of active bone remodelling. They further act to induce osteoclast apoptosis.⁶ The mode of their action depends on the type of bisphosphonate

administered. Non-nitrogen containing bisphosphonates act by interacting with ATP in osteoclast forming ATP analogues that induces osteoclast apoptosis. Nitrogen containing bisphosphonates inhibit farnesyl pyrophosphate synthase (FPPS), a key enzyme in mevalonic acid pathway, in osteoclast which prevents the production of proteins essential for their survival and function. Inhibition of this enzyme also leads to accumulation of isopentyl disphosphonate (IPP) which is incorporated into an analogue of ATP that can induce osteoclast apoptosis. So due to their action on the osteoclast the bone healing and remodelling is affected in the area that has been traumatized or surgically treated. This leads to non-resorption of the necrotic bone which further affects the blood supply of that area leading to osteonecrosis of jaw.¹⁰

Now since the jaws have a greater blood supply than other bones and a faster turnover rate related to their daily activity and presence of teeth, bisphosphonates are highly concentrated in jaws.¹¹ Due to chronic invasive dental disease and treatments, thin mucosa over bone, this anatomic concentration of bisphosphonates causes this condition to be manifested exclusively in jaws.

2.2. Clinical presentation of bisphosphonate associated osteonecrosis of jaw

Osteonecrosis of jaw is also known as avascular necrosis of bone or osteochondritis dissecans. It leads to bone pain, loss of bone function and bone destruction resulting in impairment of blood supply. It usually presents as area of exposed bone along with soft tissue swelling, purulent discharge, loosening of teeth and the lesion do not respond to local debridement and antibiotics.^{12,13} Lesion develops around sharp bony area or previous surgical site including extraction, retrograde apicoectomies, periodontal surgery and dental implant surgery. There also may be feeling of numbness, heaviness or dyesthesia of jaw. However, lesion may remain asymptomatic for weeks or months. Occasionally, pain in jaws may be the only symptom without any evidence of radiological abnormality. The lesion may also become secondary infected with actinomycetes.¹⁴

2.3. Risk factors for bisphosphonate induced osteonecrosis of jaw (ONJ)

2.3.1. Bisphosphonate exposure

Risk of developing osteonecrosis with intake of bisphosphonate depends upon the individual bisphosphonate potency, the mode of administration and the cumulative dose.^{15,16}

Among various bisphosphonates IV administered are more potent than orally administered bisphosphonates. In IV administered bisphosphonates, Zoledronate is the most potent bisphosphonate because of its high mineral binding affinity and FPPS enzyme inhibition whereas pamidronate is less potent.^{17–20} Orally administered bisphosphonates include etidronate, risedronate, tiludronate, alendronate. Most cases of bisphosphonate induced ONJ have been reported with alendronic acid which is also used most widely worldwide.

The cumulative dose of bisphosphonate is also considered to be an important factor in development of ONJ and is determined by the dose, frequency of administration, duration of therapy and half life of drug.

2.3.2. History of dental disease

A history of dental disease, including invasive dental procedures, dental trauma and periodontal disease are important risk factors for development of ONJ in association with bisphosphonates.

A number of studies have identified dental extractions as significant risk factors. Other dental procedures that have been implicated in development of ONJ include bony exostosis, intubation induced trauma and dental implants.^{11,21} The use of dentures and the presence of inflammatory dental disease such as periodontal disease, dental abscesses and poor dental hygiene have also been identified as risk factors.^{19,21,22}

2.3.3. Jaw anatomy

ONJ occurs twice as frequently in mandible than in maxilla and areas with thin mucosa such as torus mandibularis and mylohyoid ridge.^{11,18,23}

2.3.4. Malignant disease

Duration of malignant disease, duration of bone metastasis and type of cancer may be associated with increased risk of ONJ development.²¹ ONJ predominantly occurs in breast cancer, multiple myeloma and prostate cancer.²⁴

2.3.5. Concomitant treatment

Patients on additional chemotherapy and corticosteroids which is common in such patients are at higher risk for developing ONJ.^{23,25}

2.3.6. Age, sex and race

Old patients and female patients are at increased risk of developing ONJ. Caucasians patients may be at higher risk of developing ONJ.²³

2.3.7. Genetic factors

Single nucleotide polymorphism of the cytochrome P450 CYP2C8 gene have been identified as a possible risk factor for the development of ONJ in multiple myeloma patient receiving Zolendronate and pamidronate treatment.²⁶ Matrix metalloproteinase 2 has also been hypothesized as candidate gene for an increased risk of bisphosphonate induced ONJ.²⁷

2.3.8. Smoking

Smoking is also possible risk factor for developing ONJ in patients on bisphosphonate therapy.^{21,28}

2.3.9. Co-morbid condition

Low haemoglobin levels,²³ low serum calcium and secondary hyperparathyroidism,²⁹ renal dialysis,²³ diabetes³⁰ and obesity²⁸ are possible risk factors for ONJ in cancer patients. Other co-morbid conditions like hypertension, hyperlipidaemia, hypercholesterolaemia, rheumatoid arthritis and diabetes may possibly contribute to risk of developing factors ONJ in patients receiving bisphosphonates for non-cancer indications.³¹

3. Management of patients on bisphosphonate therapy

The action of bisphosphonate that is of concern to dentist is that they destroy osteoclast and without osteoclast there cannot be bone healing which is very important for surgical dental procedures like extraction or implant placement. So management of patients on bisphosphonate therapy prior to any surgical procedure becomes important.

3.1. Guidelines for management of patient on bisphosphonate therapy (preventive measures)^{11,12,32,33}

1. All patients should be asked about the current or past use of bisphosphonate drugs and the mode of administration because IV bisphosphonate have a longer half life and patients on IV mode are at more risk for development of ONJ than patients on oral bisphosphonate.
2. Patients yet to start with bisphosphonate therapy should be first examined for requirement of any surgical dental procedures prior to the therapy, if the risk factors allows. Hopeless teeth should be removed. Subgingival scaling should be performed. Poorly fitting dentures should be replaced to avoid soft tissue trauma. Comprehensive treatment should be performed to minimize the need for future dental treatment.
3. For patients who have already started with the therapy, any elective procedures should be avoided if possible to avoid the risk of bisphosphonate induced osteonecrosis of jaw. Root canal treatment should be done rather than dental extraction when possible.
4. Patient should be routinely examined radio graphically for osteonecrosis and baseline data should be recorded for the patient. Certain laboratory test may help to monitor markers of bone turnover and can help in diagnosis and risk assessment of developing bisphosphonate associated osteonecrosis. Bisphosphonates reduces the level of CTx (C-telopeptides) which are fragment of collagen released during remodelling and skeleton turnover. So by assessing the serum CTx levels risk assessment can be done³⁴ (Table 1).
4. Patients should be educated about the importance of good oral hygiene, regular dental check-ups and also about the symptoms of osteonecrosis of jaw so that patient can report early if the symptoms develop.
5. Patients in which dental extractions are unavoidable should be first consulted with the prescriber of bisphosphonate therapy for possible temporary

Table 1 – CTx serum value and risk factors for osteonecrosis.

CTx serum value (pg/ml)	Risk for osteonecrosis
300–600 (normal)	None
150–299	None to minimal
101–149	Moderate
<100	High

Table 2 – Staging and management of osteonecrosis.

Stage	Characterized by	Treatment
Stage I	Asymptomatic detection of exposed bone without soft tissue infection	Managed conservatively. Daily irrigation, oral antimicrobials rinses (0.12% chlorhexidine rinses) Follow up every 3 months If patient is wearing dentures then they should be properly adjusted to avoid further trauma and should be removed in night
Stage II	Presence of symptoms around the area of exposed bone secondary to soft tissue swelling or bone infection	Culture directed antimicrobial therapy- long term Analgesics Minor bone debridement to reduce sharp edges
Stage III	Presence of pathological fracture Exposed bone associated with soft tissue infection, which is not manageable with antibiotics alone	Requires surgical debridement/resection to reduce volume of necrotic bone Analgesics Culture directed antibiotics-IV or oral Oral antimicrobial rinses

interruption of drug if beneficial. Extraction should be done as atraumatically as possible and flap raising should be avoided. Sterile technique has to be followed. Patient should be kept on chlorhexidine mouthwash twice daily for two months and postoperatively 2 month follow up should be done. In some cases it has been recommended to do root canal of the teeth followed by coronal amputation and leave the roots.³⁵

3.2. Management of patients who have developed ONJ

1. If ONJ is suspected then panoramic radiography is recommended to determine the extent of necrosis and the position of sequestrum or osteomyelitis.
2. Microbial cultures from the associated soft tissue swelling or purulent discharge should be done to identify any superinfection and the appropriate antimicrobial therapy.
3. Any additional dental trauma should be avoided as it may further delay wound healing.
4. ONJ should be properly characterized and staging should be done so that appropriate treatment can be done (Table 2).¹²

4. Dental implants and bisphosphonate therapy

Implant placement in patients on bisphosphonate therapy predisposes them to development of osteonecrosis of jaw. So prior to planning implants in such patients it is important to identify the type of bisphosphonate (oral or intravenous) they are taking. Various studies have been done to identify the incidence of osteonecrosis in patients on bisphosphonate therapy (Table 3):

From the various studies it has been seen that patients on oral bisphosphonate therapy do not always result in osteonecrosis of jaw but it also depends on the duration of the therapy. The American association of oral and maxillofacial surgeons do not contraindicate the dental implant placement in patients taking oral bisphosphonates for fewer than three years prior to surgery provide that they do not present with other risk factors such as medication with steroids or advance age. If the patient has been taking medicine for more than 3 years it has been recommended to stop the medicine for at least 3 months before carrying out any surgical procedure and once the healing is complete the drug can be taken.

Table 3 – Recent studies showed the incidence of osteonecrosis in patients on bisphosphonate therapy.

Author	Year	Sample	No. Of implants	Bisphosphonate therapy duration	Mode of administration	Incidence of osteonecrosis
Marx ¹¹	2005	119 cases of osteonecrosis in patients treated with oral bisphosphonates	—	3	Oral	4 cases of osteonecrosis deriving from implants
Jeffcoat ³⁶	2006	25 patients	102	25 (for 3 years on average)	Oral	No case of osteonecrosis
Wang ³⁷	2007	1	5	1 (for more than ten years)	Oral	1
Marx ³⁸	2007	30 cases of osteonecrosis in patients treated with oral bisphosphonates	—	30	Oral	2 deriving from implant placement
Fugazzotto ³⁹	2007	61	169	61 (3 year average)	Oral	Torus exposure around on post extraction implant which closed spontaneously after four weeks
Grant ⁴⁰	2008	115	468	89 (33 for more than 3 years)	Oral	None

5. Conclusion

Since the introduction of bisphosphonates they have been used to treat multiple bone disorders and cancers. In routine dental practice clinicians come across many patients who are receiving bisphosphonates as part of their therapy. Most commonly postmenopausal female patient who are receiving bisphosphonates as a treatment for osteoporosis which is very common for their age group, are encountered. These patients are at increased risk of developing ONJ when any dental treatment is done or patient is suffering from dental disease. So it becomes important to identify such patients and follow a suggested protocol to avoid complications. It is also important to identify various risk factors for the patient who might develop bisphosphonate induced ONJ prior to any dental procedure.

Conflicts of interest

All authors have none to declare.

REFERENCES

- Montoya-Carralero JM, Parra-Mino P, Ramírez-Fernández P, Morata-Murcia IM, Mompeán-Gambín Mdel C, Calvo-Guirado JL. Dental implants in patients treated with oral bisphosphonates: a bibliographic review. *Med Oral Patol Oral Cir Bucal*. 2010;15(1):e65–e69.
- Serra MP, Llorca CS, Donat FJ. Oral implants in patients receiving bisphosphonates: a review and update. *Med Oral Patol Oral Cir Bucal*. 2008;13:e755–e760.
- Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int*. 2008;19:733–759.
- Ezra A, Golomb G. Administration routes and delivery systems of bisphosphonates for the treatment of bone resorption. *Adv Drug Deliv Rev*. 2000;42:175–179.
- Berenson JR, Rosen L, Vesico R, et al. Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *J Clin Pharmacol*. 1997;37:285–290.
- Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc*. 2008;83:1032–1045.
- Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg*. 2004;62:527–534.
- King AE, Umland EM. Osteonecrosis of the jaw in patients receiving intravenous or oral bisphosphonates. *Pharmacotherapy*. 2008;28:667–677.
- Ruggiero SL. Bisphosphonate-related osteonecrosis of the jaws. *Compend Contin Educ Dent*. 2008;29:96–98. 100-102, 104-105.
- Russell RGG, Xia Z, Dunford JE, et al. Bisphosphonates. An update on mechanisms of action and how these relate to clinical efficacy. In: Zaidi M, ed. *Skeletal Biology and Medicine*. Ann N Y Acad Sci. 2007;1117:209–257.
- Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate induced exposed bone (osteonecrosis/osteoporosis) of the jaws: risk factors, recognition, prevention and treatment. *J Oral Maxillofac Surg*. 2005;63:1567–1575.
- Mehrotra B, Ruggiero SL. Bisphosphonate complications including osteonecrosis of the jaw. *Hematology Am Soc Hematol Educ Program*; 2006::356–360.
- Migliorati CA, Casiglia J, Jacobsen PL, Siegel MA, Woo S-K. Managing the care of patients with bisphosphonate-associated osteonecrosis. *J Am Dent Assoc*. 2005;136:1658–1668.
- Chun YH, Foster BL, Lukasavage PA. Bisphosphonate modulates cementoblast behaviour in vitro. *J Periodontol*. 2005;76:1890–1900.
- Badros A, Weikel D, Salama A, et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol*. 2006;24(6):945–952.
- Bannias A, Kastiris E, Bannia C, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol*. 2005;23:8580–8587.
- Dimopoulos M, Kastiris E, Amagnostopoulos A, et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Hematologica*. 2006;91:968–971.
- Woo SB, Hell Stein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaw. *Ann Intern Med*. 2006;144:753–761.
- Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. *N Engl J Med*. 2005;353:99–102.
- Corso A, Varettoni M, Zappasodi P, et al. A different schedule of zoledronic acid can reduce the risk of the osteonecrosis of the jaw in patients with multiple myeloma. *Leukemia*. 2007;21:1545–1548.
- Hoff AO, Toth BB, Altundag K, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res*. 2008;23:826–836.
- Kyrgidis A, Vahtsevanos K, Koloutsos G, et al. Bisphosphonate related osteonecrosis of the jaws: risk factors in breast cancer patients. A case control study. *J Clin Oncol*. 2008;26:4634–4638.
- Jadu F, Lee L, Pharoah M, Reece D, Wang L. A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients. *Ann Oncol*. 2007;18:2015–2019.
- Abu-Id MH, Warnke PH, Gottschalk J, et al. “Bis-phossy jaws”—high and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. *J Craniomaxillofac Surg*. 2008;36:95–103.
- Zervas K, Verrou E, Teleioudis Z, et al. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. *Br J Haematol*. 2006;134:620–623.
- Sarasquete ME, García-Sanz R, Marín L, et al. Bisphosphonate-related osteonecrosis of the jaw is associated with polymorphisms of the cytochrome P450 CYP2C8 in multiple myeloma: a genome-wide single nucleotide polymorphism analysis. *Blood*. 2008;112(7):2709–2712.
- Lehrer S, Montazem André, Ramanathan Lakshmi, et al. Bisphosphonate-Induced osteonecrosis of the jaws, bone markers, and a hypothesized candidate gene. *J Oral Maxillofac Surg*. 2009;67(1):159–161.
- Wessel JH, Dodson TB, Zavras AI. Zoledronate, smoking, and obesity are strong risk factors for osteonecrosis of the jaw: a case-control study. *J Oral Maxillofac Surg*. 2008;66:625–631.
- Ardine M, Generali D, Donadio M, et al. Could the long-term persistence of low serum calcium levels and high serum parathyroid hormone levels during bisphosphonate treatment predispose metastatic breast cancer patients to

- undergo osteonecrosis of the jaw? *Ann Oncol*. 2006;17:1336–1337.
30. Khamaisi M, Regev E, Yarom N, et al. Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. *J Clin Endocrinol Metab*. 2007;92(3):1172–1175. Epub 2006 Dec 19.
 31. Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS. Factors associated with osteonecrosis of the jaw among bisphosphonate users. *Am J Med*. 2008;121:475–483.
 32. Damata K, Gralow J, Hoff A, et al. *Recommendation for Prevention, Diagnosis and Treatment of Osteonecrosis of Jaws (Expert Panel)*. Novartis Pharmaceuticals; 2004.
 33. Ruggiero S, Gralow J, Marx RE, et al. Practical guidelines for prevention, diagnosis and treatment of osteonecrosis of jaw in patient with cancer. *J Oncol Pract*. 2006;2:7–14.
 34. Greenspan SI, Rosen HN, Parker RA. Early changes in serum N-telopeptide and C-telopeptide cross linked collagen type I predict long term response to alendronate therapy in elderly women. *J Clin Endocrinol Metab*. 2000;85:3357–3540.
 35. American Association of Endodontists Position Statement. Endodontic implications of bisphosphonate-associated osteonecrosis of the jaws. Available at: <http://www.aae.org/dentalpro/guidelines.htm>. Accessed on 14.08.2006.
 36. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants*. 2006;21:349–353.
 37. Wang HL, Weber D, McCauley LK. Effect of long term oral bisphosphonates on implant wound healing: literature review and a case report. *J Periodontol*. 2007;78:584–594.
 38. Marx RE, Cillo Jr JE, Ulloa JJ. Oral bisphosphonate induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention and treatment. *J Oral Maxillofac Surg*. 2007;65:2397–2410.
 39. Fugazzoto PA, Lightwood WS, Jaffin R, Kumar A. Implant placement with or without simultaneous tooth extraction in patients taking oral bisphosphonates: postoperative healing, early follow-up, and the incidence of complications in two private practices. *J Periodontol*. 2007;78:1664–1669.
 40. Grant BT, Amenedo C, Freeman K, Kraut RA. Outcomes of placing dental implants in patients taking oral bisphosphonates: a review of 115 cases. *J Oral Maxillofac Surg*. 2008;66:223–230.