Bisphosphonates-related osteonecrosis of the jaws

João Ferreira dos **SANTOS**[1], Bruno Feital **FUSARO**[2], Antônio Carlos Costa **BENTO JÚNIOR**[3], Leonardo Coelho Lima **SALGADO**[3], Andressa Antunes Prado de **FRANÇA**[4]

Introduction: *osteonecrosis of the jaws associated with the use of bisphosphonates has been a relevant subject matter addressed by dental clinics in the current century. The medication has been widely used and, for this reason, dental surgeons have faced the need to deepen their knowledge on such a theme, particularly because necrotic lesions associated with the use of bisphosphonates negatively affect patients' quality of life while also lead to their significant morbidity. Thus, knowing about the disease, its epidemiology, as well as risk rates and patients' management has been rendered necessary.* **Objective:** *the present study's general aim was to search the literature for relevant information on the pathology and medication by means of a literature review.* **Methods:** *an electronic search was conducted in EBSCO and MEDLINE databases for articles published between 1996 and 2014. Original articles and literature reviews providing the grounds for the development of the subject matter of choice were selected.* **Results:** *a total of 22 articles met the established criteria. While the research was being conducted, other medications associated with the disease were also found. Those medications are reported in this study as well.* **Conclusions:** *as a result of bisphosphonates use, bone tissue has its resorption capacity decreased, thus increasing the potential for lack of healing and consequent necrosis. Additionally, the action exerted by the medications is evinced, as they inhibit soft tissue cells and blood vessels proliferation. Finally, the importance of adequate patient management regarding the use of drugs for subjecting patients to surgical procedures is shown.* **Keywords:** *Osteonecrosis. Osteoclasts. Bone.*

[1]Student of the Specialization Course in Implant Dentistry, Estácio de Sá University - Juiz de Fora / MG.
[2]Coordinator of the Specialization Course in Implant Dentistry, Estácio de Sá University - Juiz de Fora / MG.
[3]Professor of the Specialization Course in Implant Dentistry, Estácio de Sá University - Juiz de Fora / MG.
[4]Professor of Medicine, Governador Ozanam Coelho College.

How to cite: Santos JF, Fusaro BF, Bento Júnior, ACC, Salgado LCL, França AAP. Bisphosphonates-related osteonecrosis of the jaws. Dental Press Implantol. 2015 July-Sept;9(3):101-9.
DOI: http://dx.doi.org/10.14436/2358-2553.9.3.101-109.oar

Submitted: May 03, 2015 - **Revised and accepted:** July 26, 2015

Contact address: João Ferreira dos Santos
Rua São Sebastião 508, Centro, Coimbra/MG - CEP: 36.550-000 - E-mail: jfsantos11@yahoo.com.br

» The authors report no commercial, proprietary or financial interest in the products or companies described in this article.

INTRODUCTION

Bisphosphonates are synthetic nonhydrolyzable compounds of which molecular structures are similar to those of inorganic pyrophosphate (P-C-P and P-O-P, respectively), an endogenous bone mineralization inhibitor. Bisphosphonates act against calcium resorption in bones, as they inhibit the action of osteoclasts.[1,2]

Therefore, they are largely used in Endocrinology, Oncology, Orthopedics and Dentistry to treat resorption diseases, including osteoporosis, Paget disease, malignant hypercalcemia, bone metastases and osteolytic lesions of multiple myeloma.[3] Osteonecrosis of the jaws associated with the use of bisphosphonates (OMJ) consists of bone exposure and/or necrosis in the maxillofacial region. It lasts for at least eight weeks in patients exposed to bisphosphonates not subjected to radiotherapy.[4] The pathology was first identified by Marx[5] in 2003 as a painful bone exposure lesion with negative response to conventional surgical and clinical treatment and, most of the times (77.7%), associated with previous dental surgical procedures. There are a few cases in which lesions are not related to surgical procedures.[5]

Those lesions negatively affect patients' quality of life and lead them to significant morbidity; thus, management strategies for patients with OMJ or at risk of being affected by lesions were established by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2007.[6] An agreement on this subject matter was also published. From that time onwards, knowledge on the theme has increased and changes on the published agreement were made between 2009 and 2014.

Since then, methods used to assess patients at risk have been established in addition to criteria for assessing lesions and proper treatment modalities.[4] Based on the importance of the matter and its relationship with dental surgery, it is paramount to emphasize the importance of the present literature review on osteonecrosis of the jaws associated with the use of bisphosphonates.

MATERIAL AND METHODS

The present study was carried out as an electronic search in EBSCO and MEDLINE databases, including studies published between 1996 and 2014. Search strategy was conducted based on the following terms: bisphosphonates, osteonecrosis of the jaw and bisphosphonate-related osteonecrosis of the jaw. A total of 22 original articles and literature reviews were selected, based on the inclusion criterion of high relevance for the understanding of the medications studied and the overall picture of the disease.

Firstly, important topics on osteonecrosis of the jaws associated with the use of bisphosphonates were selected. Subsequently, articles addressing each theme were selected. The number of citations of each article in renowned dental journals was a selection criterion. Selected articles had a minimum of 20 citations each.

Finally, in order to restrict the number of references, articles with similar content were excluded, according to date of publication thus, keeping the most recent papers.

RESULTS

A total of 21 articles met the selection criteria and provided the grounds for the present literature review.

DISCUSSION

Bisphosphonates are synthetic compounds analogous to inorganic pyrophosphate (an important endogenous bone mineralization inhibitor) capable of preventing bone resorption. Due to that feature, they are used in Endocrinology, Oncology, Orthopedics and Dentistry to treat resorption diseases, namely: osteoporosis, Paget disease, malignant bone tumors and multiple myeloma.[1,2,3] Bisphosphonates molecular structure is similar to that of pyrophosphate; however, while the latter has a P-O-P structure (central oxygen), the former has a P-C-P structure (central carbon). Pyrophosphates and bisphosphonates molecular structures allow the former to become hydrolyzed while preventing the latter from becoming hydrolyzed.[1] Additionally, their tridimensional structure grants both pyrophosphates and bisphosphonates the capacity of bonding to divalent metal ions, among which the Ca^{2+} present in bone structure.[1]

Because bisphosphonates have some affinity to calcium ions, after they have been administered, they aim at calcified tissues (due to demanding bone remodeling, the jaws become a target) and can be found in three to four times higher concentrations in bone resorption sites than in bone formation sites.[5,7,8] They have two side chains, and the presence or absence of nitrogen in one of the two chains groups this drug into two different groups: nitrogenous bisphosphonates (more potent) and non-nitrogenous bisphosphonates (less potent).[2] Bisphosphonates molecular structures are shown in Figure 1.

This class of compounds acts mainly over adult osteoclasts and precursor cells of osteoclasts; however, it also acts over other structures, such as vascular endothelial growth factor (VRGF) and keratocytes.[1,8,9,10]

As for the action of the two groups of bisphosphonates over osteoclasts, each one of them acts in a different manner: when found in the cytoplasm, non-nitrogenous bisphosphonates build-up as nonhydrolyzable adenosine triphosphate (ATP) analogues, thus killing the cell by inhibition of ATP-dependent enzymes; nitrogenous bisphosphonates, on the other hand, act by inhibiting farnesyl diphosphate synthase (FDPS), an enzyme in the mevalonate pathway, changing a chain of enzymes responsible for cellular metabolism and cytoskeleton formation, thus hindering the formation and maintenance of osteoclasts ruffled borders (active), directly restraining bone resorption and killing the cell by apoptosis.[2,8] The medications also

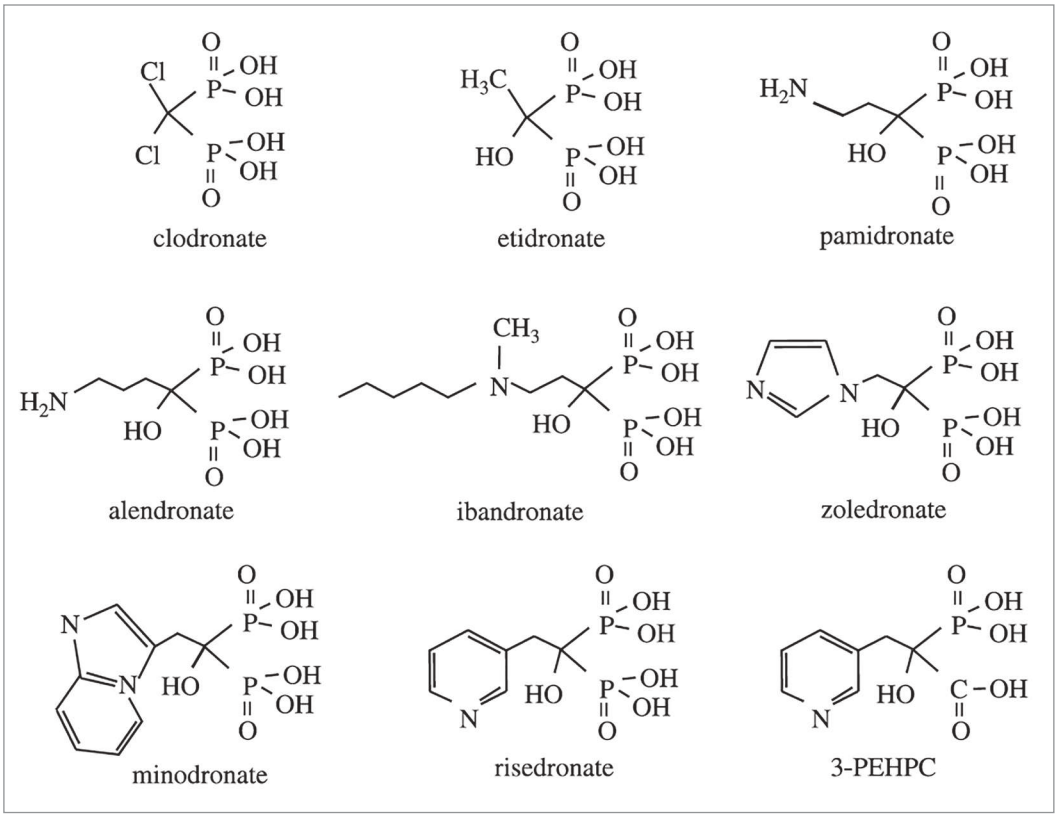

Figure 1. Structures of bisphosphonates groups one and two, according to Roelofs et al,[2] and 3-PEHPC phosphonocarboxylates analogue (a bisphosphonate-derivative capable of inhibiting Rab geranylgeranyl transferase, an enzyme in the mevalonate pathway using isoprenoid lipids).

act by inhibiting vascular neoformation by VEGF inhibition.[9] They also act over oral mucosa soft tissues, thus inhibiting cell proliferation.[10]

Finally, bisphosphonates are administered orally and parenterally. When administered orally, less potent bisphosphonates are used against osteoporosis and Paget disease (e.g. alendronate and etidronate). When administered intravenously, more potent bisphosphonates are used against bone tumors (e.g., zoledronate and pamidronate).[4] Table 1 shows the most commonly used bisphosphonates, their commercial brands, therapeutic indications, presence or not of a nitrogenous compound, usual dosage, administration and power.

Osteonecrosis of the jaws has been often studied. It is caused by a number of local and systemic factors:[11]

- **Local factors:** infectious and inflammatory events, bone tumors, mechanical trauma, radiotherapy, exposure to chemical

substances (arsenic-derivatives, liquid substances for endodontic treatment) and the use of electric scalpel during bone surgery.

- **Systemic factors:** osteoporosis, AIDS, autoimmune diseases, hypothyroidism, alcoholism, drug addiction, hyperlipidemia, hemodialysis and long-term use of corticosteroids.

In 2003, Marx[5] established a direct association between osteonecrosis and the use of bisphosphonates, when assessing 36 cases of painful bone exposure of the jaws in patients using pamidronate (Aredia) and zoledronate (Zometa). Out of those patients, 77.7% of cases were associated with previous dental surgical procedures. Marx also

Table 1. Bisphosphonates more commonly available on the American market in 2009. Adapted from Ruggiero et al,[4] 2009.

DRUG (brand name)	PRIMARY INDICATION	PRESENCE OF NITROGEN	DOSAGE	ROUTE OF ADMINISTRATION	RELATIVE POTENCY*
Etidronate (Didronel)	Paget's disease	No	300-750 mg/day for 6 months	Oral	1
Tiludronate (Skelid)	Paget's disease	No	400 mg/day for 3 months	Oral	50
Alendronate (Fosamax)	Osteoporosis	Yes	10 mg/day 70 mg/week	Oral	1000
Residronate (Actonel)	Osteoporosis	Yes	5 mg/day 35 mg/week	Oral	1000
Pamidronate (Aredia)	Osteoporosis	Yes	5 mg/day 35 mg/week	Oral Parenteral	1000
Pamidronate (Aredia	Bone metastasis	Yes	90 mg/ 3 months	Parenteral	1000-5000
Zoledronate (Zometa) (Reclast)	Bone metastasis Osteoporosis	Yes	4 mg/each 3 weeks	Parenteral	>10000

*Relative to etidronate.

mentions that, since the jaws are bones exposed to the outer environment due to the presence of teeth, and thereby exposed to all pathologies associated with them (periodontitis, pulpitis, dentoalveolar abscess), they end up being more frequently affected by necrosis.[5]

Once the association between medication and illness had been established, OMJ was conceptualized as a painful bone exposure in the maxillofacial region, lasting for at least eight weeks in patients exposed to bisphosphonates not subjected to radiotherapy. The pathology negatively affects patients' quality of life and lead them to significant morbidity.[4]

The incidence rate for this illness depends on the type of drug used, the pathology treated, invasive dental procedures previously carried out and medication administration. In patients under osteoporosis treatment, with alendronate being administered orally, the incidence rate ranges between 0.01% and 0.04% in cases without previous extraction and between 0.09% and 0.34% in patients subjected to surgery. As for patients with Paget disease, numbers range between 0.26% and 1.8% in individuals not subjected to surgery and between 2.1% and 13.5% in subjects with previous extraction. Finally, patients diagnosed with cancer receiving zoledronate or pamidronate parenterally have an illness incidence rate ranging between 0.88% and 1.15%, for those not subjected to surgery, and between 6.67% and 9.91% for those subjected to extraction.[12,13]

Due to being relevant to the day-to-day dental clinic, management strategies for patients at risk or affected by the disease have been established by the AAOMS.[4]

Since the disease is more commonly established in patients subjected to invasive dental procedures, assessment and invasive dental interventions must be carried out before bisphosphonate therapy performed parenterally, whenever patients' general health allows it. Additionally, whenever surgical intervention is to be carried out in patients undergoing bisphosphonate therapy orally for more than three years, treatment should be interrupted for three months before the invasive procedure and three months afterwards, always assessing whether patients' general health allows the drug use to be discontinued. Furthermore, it is important to highlight that the method available for bone remodeling assessment must be used: bone resorption biomarkers (CTx). Such an examination measures (in picograms per milliliter of blood – pg/ml) the serum concentration of CTx, which is a type I collagen degradation-derived molecule present in bone tissues. Values lower than 100 pg/ml suggest high risks of osteonecrosis development; whereas values between 100 and 150 pg/ml suggest an intermediate risk, and values higher than 150 pg/ml suggest low risks of osteonecrosis development.[4,14,15,16]

In 2009, Ruggiero et al[4] established a protocol for determining staging and treatment of patients at risk or affected

by the illness. Five different stages were determined, according to the intensity of illness:

- **Patients at risk:** asymptomatic, without evidence of necrotic bone and undergoing bisphosphonate treatment.
- **Stage 0:** patients with no evidence of necrotic bone, but with non-specified symptoms or with the presence of clinical and radiographic findings.
- **Stage 1:** exposed, necrotic bone in asymptomatic patients without infection.
- **Stage 2:** exposed, necrotic bone in patients with clinical evidence of infection.
- **Stage 3:** bone exposure and necrosis in patients with pain, infection and one or more of the following pathologies: bone exposure and necrosis beyond alveolar bone limits; pathogenic bone fracture; extraoral fistula; oroantral or oronasal communication; bone lysis affecting the lower ridge of the mandible or the maxillary sinus.

Treatment protocols for each stage of the disease have also been established:

- **Patients at risk:** no need for treatment, they need to be informed not only about the risks of developing OMJ, but also about the illness' signs and symptoms.
- **Stage 0:** therapy aimed at relieving symptoms, management of risk factors (caries and periodontal disease). Infection control with antibiotic therapy might be necessary.
- **Stage 1:** use of antimicrobial mouth wash (0.12% chlorhexidine).
- **Stage 2:** use of antimicrobial mouth wash associated with antibiotic therapy.
- **Stage 3:** debridement and bone resection at the affected site associated with stage 2 treatment, which might be long-term palliative care only, with resolution of acute infection and pain. Removal of bone sequestrum might be rendered necessary; however, without changing the non-affected bone. Extraction of symptomatic affected teeth at the necrotic site must be considered while assessing the potential risk of extraction aggravating the necrotic process.[4]

Antibiotic therapy attempts have been assessed. Separately, they do not show any significant difference regarding bacteria found at the lesion sites.[17]

A few extra procedures have also been proposed in the attempt to properly seal the lesions, with considerable relevance to the treatment of ill patients.

Lemound et al[18] included the use of the mylohyoid muscle fascia to recover mandibular lesions in patients at stages 1 or 2 established by Ruggiero et al[4] in 2009. After submitting 20 patients to surgery and clinical control for 19 months, the authors achieved a success rate of 90% (patients with lesion sealing;[18] on the other hand, Agrillo et al[19] proposed the use of ozone gas to reduce bacterial colonization at the surgical site after lesion debridement - surgical debridement, as proposed by Ruggiero et al[4] in 2009). Results revealed success in relieving pain previously caused to the patients (the authors' hypothesis associated ozone therapy with pain relief).

Franco et al,[20] in 2014, proposed hyaluronic acid and amino acid therapy at debridement or resection surgical sites to treat osteonecrotic lesions (as suggested by Ruggiero et al[4]).

After assessing the results, the authors found a success treatment rate (patients without recurring lesions) of 84,96%.[20] Last, but not least, the new boundaries of studies and researches on bone necrosis of the jaws, new medication against malignant tumors acting over the vascular endothelial growth factor (VRGF) as well as over osteoclasts should be highlighted. Antiangiogenic drugs, such as Sunitinib, Sorafenib, Bevacizumab and Sirolimus, in addition to Denosumab monoclonal antibody (used to treat bone tumors due to being antiresorptive) were described by Ruggiero et al[21] in 2014 on a document published by the American Association of Oral and Maxillofacial Surgeons (AAOMS). Therefore, the illness also includes cases of patients treated with the aforementioned drugs, thus having its name changed to osteonecrosis of the jaws associated with the use of medications.[21]

CONCLUSION

Despite the risks involved in the dental and surgical treatment of patients using bisphosphonates and other antitumoral drugs, such procedures are not contraindicated. Individual patients must have risk rates examined, while having them associated with the medication being used, treatment time, administration, potential for treatment interruption, general health conditions and diagnostic examination available (CTx). Should the association of the aforementioned factors suggest low risk of osteonecrosis, there is no reason why necessary surgical procedures or elective surgery, as it is the case in Implantodontics, should be avoided.

REFERENCES

1. Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J, et al. Cellular and molecular mechanisms of action of bisphosphonates. Cancer. 2000 Jun 15;88(12 Suppl):2961-78.
2. Roelofs AJ, Thompson K, Gordon S, Rogers MJ. Molecular mechanisms of action of bisphosphonates: current status. Clin Cancer Res. 2006 Oct 15;12(20 Pt 2):6222s-30s.
3. Ruggiero SL, Drew SJ. Osteonecrosis of the jaws and bisphosphonate therapy. J Dent Res. 2007 Nov;86(11):1013-21.
4. Ruggiero S, Dodson T, Assael L, Landesberg R, Marx R, Mehrotra B. American association of oral and maxillofacial surgeons position paper on bisphosphonate: related osteonecrosis of the jaw - 2009 Update. Aust Endod J. 2009;35:119-30.
5. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003 Sep;61(9):1115-7.
6. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws. J Oral Maxillofac Surg. 2007;65(3):369-76.
7. Masarachia P, Weinreb M, Balena R, Rodan GA. Comparison of the distribution of 3H-alendronate and 3H-etidronate in rat and mouse bones. Bone. 1996 Sep;19(3):281-90.
8. Rogers MJ, Crockett JC, Coxon FP, Mönkkönen J. Biochemical and molecular mechanisms of action of bisphosphonates. Bone. 2011 Jul;49(1):34-41.
9. Santini D, Vincenzi B, Galluzzo S, Battistoni F, Rocci L, Venditti O, et al. Repeated intermittent low-dose therapy with zoledronic acid induces an early, sustained, and long-lasting decrease of peripheral vascular endothelial growth factor levels in cancer patients. Clin Cancer Res. 2007 Aug 1;13(15 Pt 1):4482-6.
10. Landesberg R, Cozin M, Cremers S, Woo V, Kousteni S, Sinha S, et al. Inhibition of oral mucosal cell wound healing by bisphosphonates. J Oral Maxillofac Surg. 2008 May;66(5):839-47.
11. Pompa G, Bignozzi I, Cristalli M, Quaranta A, Di Carlo S, Annibali S. Bisphosphonate and osteonecrosis of the jaw: the oral surgeon's perspective. Eur J Inflamm. 2012;10(1):11-23.
12. Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg. 2007 Mar;65(3):415-23.
13. Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol. 2012 May;23(5):1341-7.
14. Rosen HN, Moses AC, Garber J, Iloputaife ID, Ross DS, Lee SL, et al. Serum CTX: a new marker of bone resorption that shows treatment effect more often than other markers because of low coefficient of variability and large changes with bisphosphonate therapy. Calcif Tissue Int. 2000 Feb;66(2):100-3.
15. Marx RE, Cillo JE Jr, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg. 2007 Dec;65(12):2397-410.
16. Rissanen JP, Suominen MI, Peng Z, Halleen JM. Secreted tartrate-resistant acid phosphatase 5b is a Marker of osteoclast number in human osteoclast cultures and the rat ovariectomy model. Calcif Tissue Int. 2008 Feb;82(2):108-15. Epub 2007 Dec 15.
17. Ji X, Pushalkar S, Li Y, Glickman R, Fleisher K, Saxena D. Antibiotic effects on bacterial profile in osteonecrosis of the jaw. Oral Dis. 2012 Jan;18(1):85-95.
18. Lemound J, Eckardt A, Kokemüller H, von See C, Voss PJ, Tavassol F, et al. Bisphosphonate-associated osteonecrosis of the mandible: reliable soft tissue reconstruction using a local myofascial flap. Clin Oral Investig. 2012 Aug;16(4):1143-52.
19. Agrillo A, Ramieri V, Riccardi E, Quarato D, Rinna C, Genaro P, et al. Bisphosphonate-related osteonecrosis of the jaw (BRONJ): 5 year experience in the treatment of 131 cases with ozone therapy. Eur Rev Med Pharmacol Sci. 2012;16(12):1741-7.
20. Franco S, Miccoli S, Limongelli L, Tempesta A, Favia G, Maiorano E, et al. New dimensional staging of bisphosphonate-related osteonecrosis of the jaw allowing a guided surgical treatment protocol: long-term follow-up of 266 lesions in neoplastic and osteoporotic patients from the university of bari. Int J Dent. 2014;2014:935657.
21. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg. 2014 Oct;72(10):1938-56.