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Association between The Use of Bisphosphonates and The Development of Osteonecrosis of The Maxillary Bones: Literature Review

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ABSTRACT

Currently, it is known that patients who use bisphosphonates exhibit a considerable risk of developing osteonecrosis of the jawbones. In this context, it is emphasized that the dental surgeon must be able to attend to this type of patient and consequently all the associated implications. The present study aimed to evaluate the association between the use of bisphosphonates and the development of osteonecrosis of the maxillary bones. For the development of this bibliographic review, a search was performed on the platforms: PubMed, SciELO, MedLine, and Google Scholar. Only articles that addressed the theme of the present study were included. According to the literature consulted, it is concluded that most cases of osteonecrosis of the maxillary bones are associated with invasive surgical procedures, such as extractions or implants, however periodontal, pericoronal, and periapical infections are also risk factors, stressing the importance of knowledge of dentists facing these complications that can be avoided or minimized with correct preoperative and postoperative planning.

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INTRODUCTION

Bisphosphonates are drugs widely used in the treatment of diseases related to bone metabolism, being the drugs of the first choice in the treatment of osteoporosis, Paget's disease, and bone metastases. These drugs act in the metabolism of osteoclasts and osteoblasts, which results in a decrease in bone remodeling, exhibiting inhibitory effects on inflammation mediators (Carvalho, 2008; Greenber, 2008).

This group of drugs exhibits low intestinal absorption in humans due to their lipophilic properties, which hinder their transport through the epithelial barrier. In addition, the charge and volume of the bisphosphonate molecules limit their penetration into the cell membrane, which can elucidate the low absorption in the intestine (from 1% to 7%) (Greenber, 2008).

Once absorbed, bisphosphonates have a high affinity for bone minerals, binding to calcium in hydroxyapatite crystals, with a variable half-life in the skeleton that can reach up to 10 years. The remainder absorbed not bound to the bone is rapidly excreted unchanged (Rodan, 1996; Toussaint, 2009). Currently, it is known that patients who use bisphosphonates exhibit a considerable risk of developing osteonecrosis of the jawbones. In this context, it is emphasized that the dental surgeon must be able to attend to this type of patient and consequently all the associated implications (Carvalho, 2008; Greenber, 2008). The present study aimed to evaluate the association between the use of bisphosphonates and the development of osteonecrosis of the maxillary bones.

MATERIALS AND METHODS

For the development of this bibliographic review, a search was performed on the platforms: PubMed, SciELO, MedLine, and Google Scholar, to collect information about the use of bisphosphonates and the risks of developing osteonecrosis of the maxillary bones. Only articles that addressed the theme of the present study were included.

Literature review

Bisphosphonates are, by definition, stable and synthetic analogs of pyrophosphate, composed of two phosphate groups (PO3), but with a central carbon in place of oxygen and two side chains.

This class of drugs decreases bone resorption because they induce osteoclastic apoptosis and thereby end up inhibiting mature osteoclasts. Bone metabolism has two activities, which are deposition and resorption. In the deposition, osteoblasts synthesize a matrix that undergoes primary mineralization and a long process of secondary mineralization. In bone resorption, osteoclasts, which consist of bone mineral dissolution and catabolism of bone matrix components (Brozoski, 2012).

This class of drugs has an important role in the treatment of several disorders that affect bone tissue, they are indicated mainly in the treatment of osteoporosis, in addition to Paget's disease and childhood osteogenesis imperfecta, in patients with hypercalcemia associated with multiple myelomas and also tumors solids with bone metastasis, such as breast, prostate and lung cancer, for example (Rodan, 1996).

Bisphosphonates may or may not have nitrogen in their side chain, being classified as nitrogenous or non-nitrogenous. The nitrogen bisphosphonate class acts within osteoclasts after they are absorbed from the hydroxyapatite crystals. The osteoclast is deactivated intracellularly via the isoprenoid pathway. The nitrogen-free bisphosphonate class, on the other hand, acts differently and is not as potent, as it does not bond so effectively to hydroxyapatite crystals. Among the most commonly used nitrogenous bisphosphonates, pamidronate and zoledronate stand out, both are maintained for long periods in the bone matrix and are strongly related to osteonecrosis of the jaws (Carvalho, 2018). The main characteristics of the available bisphosphonates are shown in Table 1.

Table No. 1: Characteristics of available bisphosphonates.

Generic	Nitrogenated	Recommendation	Use
Elhydronate	Not	Paget	Intravenous
Tiludronate	Not	Paget	Oral
Clodronate	Not	Neoplasms	Intravenous /Oral
Pamidronato	Yes	Paget/Neoplasms	Intravenous
Alendronate	Yes	Osteoporosis/Paget	Oral
Ibandronate	Yes	Osteoporosis	Intravenous /Oral
Risedronate	Yes	Osteoporosis	Oral
Zoledronate	Yes	Paget/Neoplasms	Intravenous

Source: Authors.

Despite their range of benefits, bisphosphonates have side effects, one of the main effects being osteonecrosis, which presents as painful bone exposure in the maxilla and mandible. The first report in the literature was made by Marx in 2003. After that, several authors have been documenting and discussing this adverse effect, called Bisphosphonate-Related Osteonecrosis of the Jaw, defined as areas of exposed bone in the maxillofacial region that do not heal within eight weeks, in an individual who has been or is being treated with bisphosphonates (Yoo, 2010). Osteonecrosis is an oral lesion whose main characteristic is bone exposure initiated by the alveolar bone and can extend to the lower border of a mandibular branch, to the zygomatic, or the maxillary sinus wall. It presents radiographically with radiolucent zones and also with decreased bone density (Sampaio, 2010; Brozoski, 2012).

This action happens because the bones of the maxilla and mandible have a greater predisposition to osteonecrosis, as these bones receive a greater blood supply to the other bones, and a faster remodeling rate to the teeth, this being the main reason for the greater number of bisphosphonates to be concentrated in its structure, and thus the invasive and rehabilitative procedures practiced in that place with bone exposure end up favoring microbial contamination (Ruggiero, 2006; Brozoski, 2012).

The diagnosis is made based on the association of imaging tests with the clinical examination and the report presented by the patient, biopsy is not recommended in these cases, as this procedure can aggravate the condition. The first signs and symptoms described are deep bone pain and dental mobility unrelated to periodontal diseases, dental trauma, or other injuries, such as swelling, erythema, ulceration, and sinus fistula. The amount of bone exposed is very variable in its dimensions. It starts with a point exposure that can remain or progress to higher exposure. Radiographically analyzing it, it is possible to observe thickening of the hard lamina and an increase in the periodontal ligament in the alveolar bone, thus being the starting point of osteonecrosis (Brozoki, 2012).

The use of the CTX test (collagen carboxyterminal telopeptide) is a method to define the risk of developing osteonecrosis of the jaws in patients undergoing therapy with bisphosphonates. This test is defined as a bone resorption marker, which consists of assessing the dosage of C-terminal tetrapeptide in the bloodstream. At serum CTX levels, less than 150pg / ml, the bisphosphonate suspension, approved by the physician, must be carried out for at least three months for this serum level to increase, and thus the patient can be submitted to implant surgery. That is, to start any surgical procedure, the CTX must be greater than 150 pg/ml, decreasing the risk of developing osteonecrosis of the jaws. Since dental implant therapy is considered an invasive procedure, the onset of osteonecrosis can occur in these patients and impair the positive result of oral rehabilitation due to bone changes. It is recommended that patients using bisphosphonates should be informed about the risks and benefits of its use (Rigo, 2017).

The main objectives of the treatment of osteonecrosis of the maxillary bones are to eliminate pain, control infection, and minimize the progression of bone necrosis and this implies the dependence of each clinical case presented by each patient, considering that it presents different clinical stages and the treatments proposed by AAOMS for each stage are shown in Table 2.

Table No. 2: Definition of the clinical stage of osteonecrosis of the jaws and treatment proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS) for each stage.

Phase	Clinical presentation	Conduct
At-risk	No bone exposure	Patient orientation
1	Asymptomatic bone exposure with small soft tissue inflammation.	Patient guidance, mouthwashes with antibacterial solutions, and careful monitoring.
2	Exposed bone with pain, inflammation, or infection of adjacent soft tissue.	Patient guidance, mouthwash with antibacterial solutions, antibiotic therapy, superficial bone debridement, careful monitoring.
3	Bone exposed with pain, inflammation, or infection of adjacent soft tissue, which may present osteolysis, pathological fractures, and extraoral fistulas.	Patient guidance, mouthwash with antibacterial solutions, palliative surgery.

Source: Authors.

CONCLUSION

According to the literature consulted, it is concluded that most cases of osteonecrosis of the maxillary bones are associated with invasive surgical procedures, such as extractions or implants, however periodontal, pericoronal, and periapical infections are also risk factors, stressing the importance of knowledge of dentists facing these complications that can be avoided or minimized with correct preoperative and postoperative planning.

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