

Osteonecrosis associated with bisphosphonates and its relationship with dental implants - literature review

Osteonecrose associada a bifosfonatos e sua relação com a implantodontia – revisão de literatura

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ABSTRACT

Bisphosphonates are drugs used to treat diseases such as osteoporosis, Paget's disease, and bone metabolism changes that might be associated with neoplasms. These drugs have some side effects, one of them is a new complication of great interest to the dental class, namely, osteonecrosis of the jaws associated with bisphosphonates (OAB). How bisphosphonates develop such a disease is still unknown. However, the type of bisphosphonate, the treatment duration and the route of administration may have a direct relationship with the occurrence of OAB. Due to the care required by patients who use bisphosphonates and the risk of developing osteonecrosis after implant surgery, this study aims to conduct a literature review about the

context of bisphosphonates in implant dentistry, as well as their mechanism of action and most common complications. As this is a recently discovered disease, there is still no consensus on the installation of dental implants in patients who have taken or are taking bisphosphonates, therefore, communication between the dental surgeon and the patient's physician is vital, so that all preventive measures are taken always aiming at the patient's well-being.

Keywords: bisphosphonates, osteonecrosis, dental implants.

RESUMO

Os bifosfonatos são medicamentos utilizados para tratar doenças como osteoporose, doença de Paget, e nas alterações do metabolismo ósseo associados ou não a neoplasias. Esses medicamentos apresentam alguns efeitos colaterais, dentre eles uma nova complicação de bastante interesse para a classe odontológica, a osteonecrose dos maxilares associada a bifosfonatos (OAB). A forma pela qual os bifosfonatos desenvolvem tal doença ainda é desconhecida, porém, o tipo de bifosfonato, a duração do tratamento e a via de administração pode ter uma direta relação com a ocorrência de OAB. Devido aos cuidados com os pacientes que utilizam bifosfonatos e ao risco de desenvolverem osteonecrose após cirurgias para instalação de implantes, este trabalho teve por objetivo realizar uma revisão de literatura sobre o contexto dos bifosfonatos na implantodontia, bem como seu mecanismo de ação e suas complicações mais frequentes. Por se tratar de uma doença descoberta recentemente, ainda não existe um consenso sobre a instalação de implantes dentários em pacientes que fizeram ou fazem uso de bifosfonatos, devendo sempre haver uma comunicação entre o cirurgião dentista e o médico do paciente para que todas as medidas preventivas sejam tomadas, visando sempre o bem-estar do paciente.

Palavras-chave: bifosfonatos, osteonecrose, implantes dentários.

1 INTRODUCTION

Detailed preoperative planning is an important factor when performing osseointegrated dental implants and depends greatly on a thorough anamnesis, which analyses general health along with radio and tomographic examinations, aiming at establishing a suitable plan essentially based on the patient's bone and systemic conditions (GONÇALVES et al., 2020).

Predisposition to systemic diseases and other illnesses in patients that might require osseointegrated implants might reduce the chances of having a successful osseointegration. Some medication used to treat these systemic conditions might result in an unfavorable outcome, for example, the use of synthetic drugs such as the bisphosphonates (BFs) (MORAES et al., 2013).

BFs have been widely used since the 1960s to treat bone diseases such as osteoporosis, osteogenesis imperfecta, multiple myeloma, malignant hypercalcemia, Paget's disease, as well as bone metastasis caused by breast cancer, prostate, and lung cancer. BFs are powerful inhibitors of the osteoclast action. This medication acts bonding to hydroxyapatite crystals and

accumulates on the mineralized bone matrix for several years, promoting its apoptosis and, therefore, preventing bone loss (SALES and CONCEIÇÃO, 2020).

Among the side effects of this medication, the development of osteonecrosis of the jaw is the factor that provokes the greatest concern among dentists, since it is clinically characterized by bone necrosis and might present fever symptoms or be asymptomatic. Periodontal surgeries, tooth extraction, dental implant surgeries, badly fixed prosthesis, and local traumas, even if less serious might affect the periosteum, exposing bone tissue and, consequently, causing infection, which results in BF- associated osteonecrosis (LUCIANO and DOMINGUETE, 2018).

Patients affected by osteonecrosis might present the following clinical symptoms: pain, swelling, bleeding, purulent secretion, fistulas, and dental mobility. When radiographic examination is used, the findings include: poor healing of alveoli after tooth extraction, bone sequestration formation, and increased trabecular density (LEITE et al.,2015).

Taking all that into consideration, this study aimed to carry out a literature review about risk factors in dental implant surgeries in patients that use BFs and the occurrence of osteonecrosis in those patients.

2 MATERIAL AND METHODS

This literature review was carried out by surveying the online data bases PubMed, Scielo and Academic Google, using the following keywords in Portuguese: “bifosfonatos na odontologia”, “complicações devido ao uso de bifosfonatos na odontologia”, and “osteonecrose associada a bifosfonatos”. The English keywords employed were: “bisphosphonates in dentistry”, “complications due to the use of bisphosphonates in dentistry”, “bisphosphonate associated osteonecrosis”.

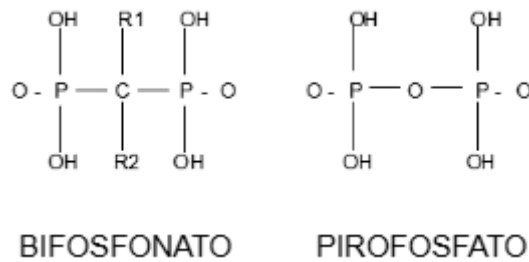
The articles included were those published between 2005 and 2021 in Portuguese and in English, clinical case descriptions, laboratory studies and literature reviews related to osteonecrosis. Papers published in idioms different from English or Portuguese and papers that did not discuss the relation between BFs and osteonecrosis were excluded. After analyzed, the data were cross checked and discussed to elaborate the work with conclusive data.

3 LITERATURE REVIEW

BFs are synthetic analogues of pyrophosphate, which is a natural bone resorption inhibitor. However, for going through fast enzymatic hydrolysis, pyrophosphates are not used as efficient therapeutic agents in the treatment of bone diseases, since they present an oxygen

central atom (P-O-P). BFs are more resistant drugs to the enzymatic degradation process, since the oxygen central atom in these compounds is substituted with a carbon atom (P-C-P) (Figure 1), this change provides BFs with a longer half-life, making them able to influence effectively the bone metabolism. (FERNANDES et al., 2005).

Figure 1: Biphosphonate and Pyrophosphate chemical structure.



Source: Scarpa et al., 2010.

BFs are classified into two groups: non nitrogenous and nitrogenous. The former includes etidronate, clodronate, and tiludronate, while some examples of the latter are: ibandronate sodium, alendronate sodium, pamidronate sodium, risedronate sodium, and zoledronate sodium (MOURÃO et al., 2013).

They act in dispute with adenosine triphosphate (ATP) in osteoclasts promoting the apoptosis process of these cells. Non nitrogenous BFs are metabolized faster and, therefore, their action potential is reduced. Nitrogenous BFs, in turn, induce the apoptosis process, inhibiting the action of the diphosphate farnesyl enzyme, which is essential to the isoprenoid lipid synthesis, interrupting the protein bond chain that is essential to the osteoclast function. For presenting nitrogen in their molecular structure, these drugs are not metabolized and tend to accumulate in the bone tissue acting for a long period and becoming more powerful (LAVOR, 2018).

Recently, there has been an intense debate in the scientific literature related to the use of BFs and the appearance of osteonecrosis after surgeries such as tooth extraction and those in which jaw and mandible bone tissue are involved, and even in cases where the patient was not subjected to such procedures. Based on studies carried out by the alendronate sodium manufacturer, the occurrence of BF-associated osteonecrosis is 1 in 143,000 people in dental treatment a year. (LAVOR, 2018).

The laboratory in charge of the insertion of pamidronate sodium and zoledronate sodium in the market warned health professionals about the risks related to the development of

osteonecrosis of the jaw only in 2004, and in the following year extended this alert to all BFs, including oral forms as possible triggers of osteonecrosis processes (CARVALHO et al., 2008).

BFs are prescribed to cancer patients to stop bone loss resulting from metastatic skeletal lesions or osteoporosis. The professional's choice regarding the route of administration depends on the illness to be treated (SCARPA et al, 2010).

Osteonecrosis associated to BFs is usually related to this drug intravenous administration for a period longer than three years in monthly doses. However, great part of the patients taking it orally for a long period of time to treat osteoporosis might also develop the lesion, since in addition to the route, time is also a risk factor (MOURÃO et al., 2013).

Osteonecrosis associated to BFs taken orally differs from that of the intravenous route. Patients in the oral route require a long therapy period and less frequently show bone exposure, presenting milder symptoms. There is also a possibility of improvement and even healing of the exposed bone when the drug treatment is interrupted. The intravenous route tends to affect the bone more severely, presenting greater risk of developing osteonecrosis, and increasing the risk according to the time of use of this medication (SCARPA et al., 2010).

BFs present several adverse reactions, most of them related to the digestive system, in addition to bone, muscle and articulation pain, and allergic reactions. Moreover, a new complication of great interest to dental professionals is the Osteonecrosis of the jaw or Biphosphonate-associated Osteonecrosis (OAB), which refers to a severe adverse reaction that affects jaw bones through unknown mechanisms and results in extensive tissue destruction (FERREIRA JR et al., 2007).

Regardless of its cause, OAB is nothing more than nonviable jawbone, which might be exposed in the oral cavity. According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), OAB is only diagnosed when the patient is being treated with BFs or has already used it, and presents necrotic bone areas exposed in the jaws that remain for over eight weeks (VIEIRA, 2014).

Jaw and mandible bones present greater propensity to osteonecrosis for receiving greater blood supply when compared to other bones, in addition to a faster remodeling rate in relation to the teeth, which is the main reason of the BFs concentration in their structure. When invasive and rehabilitating procedures are used in these areas of bone exposure, they end up favoring bacterial contamination. Mandible is considered the most affected region due to the fact that it is less vascularized than the jaw. Poor tooth hygiene might lead to contamination and cause periodontal or endodontic infections hampering the treatment due to the use of BFs (CHIANESI and MONTEIRO, 2018).

Biphosphonate-associated osteonecrosis presents three phases: asymptomatic bone exposure and necrosis (Figure 2), bone exposure and necrosis with pain and infection (Figure 3), and bone exposure and necrosis with pain, infection and pathological fracture, extraoral fistula, and massive osteolysis (Figure 4). In all cases, the use of chlorhexidine 0.12% is recommended (LUCIANO and DOMINGUETE, 2018).

Figure 2: Exposure to bone necrosis without symptoms.



Source: Brozoski et al., 2012.

Figure 3: Exposure to bone necrosis with symptoms.



Source: Brozoski et al., 2012.

Figura 4: Bone exposure in the mandibular region reaching the lower edge of the mandible in the lingual region.



Source: Brozoski et al., 2012.

The OAB progression is usually slow, and the necrotic bone exposure in the jaw or mandible region occurs after invasive dental treatment is carried out. Therefore, all preventive measures should be taken in an attempt to reduce osteonecrosis risks in patients treated with BFs. When patients are diagnosed with biphosphonate-associated osteonecrosis the main objectives are to stop pain, control the infection and mitigate bone necrosis occurrence and progression (LUCIANO and DOMINGUETE, 2018).

The OAB diagnosis is carried out based on the patient's medical and dental background that evidences signals and symptoms. The dental professional should seek to know the reason why the patient has been using BFs and whether this patient has some history of oral complications associated to the treatment, its toxicity and the type of drug and administration route, since this information should guide the professional's therapeutic conduct (LAVOR, 2018).

Radiographically, OAB appears as a diffuse bone sclerosis with the presence of bone sequestration and osteolytic lesions involving the cortical. Radiographic findings are nonspecific and usually require biopsy to determine the diagnosis. Histologically, they present necrotic trabecular bone surrounded by vascular tissue, unrestrained inflammatory infiltrate and the presence of *Actinomyces sp* (MOURÃO et al.,2013; SALES and CONCEIÇÃO, 2020).

Osteonecrosis associated with biphosphonates is a recently described disease and, thus, some measures must be better studied so that the treatment offered to these patients can become more efficient. Patients using BFs must be assisted by a multidisciplinary team including oncologists, dentists, endocrinologists, among others, for the identification of the risks each patient runs of presenting osteonecrosis and the possible interventions required (LUCIANO and DOMINGUETE, 2018).

The risk of OAB related to the installation of dental implants has not been clarified, thus, it is believed to appear when the bone exposure and manipulation are similar to those of a tooth extraction. Although implant installation and tooth extraction are surgical procedures, in implant surgery, the repair occurs by primary intention, while in tooth removal, it mostly occurs via secondary intention. Repair, in such case, is the tissue neoformation with the purpose of repairing accidental or surgical wounds produced on the body, and might occur in two ways, either primary or secondary intention. In primary intention healing, wound edges are held together and absence of infection is observed, while in the second intention healing, the wound edges cannot be put together, therefore the wound is exposed to bacteria, the healing is slower and most times followed by local infection (CHAVES et al., 2018).

The OAB treatment is extremely varied, questionable and challenging, and no effective treatment has been proposed to date. The treatments commonly used include antibiotics, mouth-washing with antimicrobial agents, bone sequestration surface debridement, platelet rich plasma (PRP), hyperbaric oxygen, low power laser, ozone therapy, and wound artificial closure.

These methods aim to reestablish the patient's life quality, by controlling pain and secondary infection, and preventing lesion increase and the appearance of new necrotic areas (MARTINS et al., 2009; CHAVES et al., 2018; MAUES et al., 2020).

4 DISCUSSION

According to Brozoski et al. (2012), BFs have been considered the most widely prescribed medication for the treatment of osteoporosis worldwide. These drugs present varied dosage and power which are proportional to the OAB risk (FERREIRA JR et al., 2007). Although it has been recently described, bisphosphonate-associated osteonecrosis already presents several cases reported in the literature. The disease presents a slow behavior that is difficult to control, and might lead to chronic bone exposure and persistent inflammatory conditions (MARTINS et al., 2009).

In cases where rehabilitating procedures are required by patients treated with BFs, there is no consensus regarding the installation of dental implants. However, the AAOMS recommends that this drug should be avoided in the treatment of oncologic patients and those being treated with this medication intravenous route (SALES and CONCEIÇÃO 2020).

In a study carried out by Grant et al. (2008) including 115 patients that had been using oral BFs and were also treated with dental implants, postoperative OAB incidence was investigated. However, the development of this disease was not observed, therefore, those authors concluded that the drug did not influence the treatment success.

According to Coléte et al. (2019), differences found in OAB incidence might be related to some factors such as the administration route (either oral or intravenous), the type of bisphosphonate, dose, and treatment duration. Since oral BFs are less powerful than those used intravenously, route seemed to be indicative of lower incidence in the oral group.

In the report put forward by Holzinger et al. (2014), patients that had implants installed during or after treatment with BFs tended to develop osteonecrosis earlier than patients that used the medication after implant installation. Conversely, Chadha et al. (2013), showed that the use of BFs was not an absolute impediment for the installation of dental implants, since they might present satisfactory osteointegration.

It seems relevant to emphasize that studies on dental implants refer to the oral administration of BFs, since according to the literature this use results in lower osteonecrosis incidence (CARVALHO et al., 2010).

Borges (2015) stated that the literature indicates that implant installation in patients that were or are in BF intravenous treatment should be an absolute contraindication, since the power of the biphosphonate used is higher.

OAB development is more commonly observed in cases where the rehabilitation with dental implants is carried out after the BF treatment has been used for some time. In such cases, osseointegration lower success rate is observed, since bone remodeling and turnover are suppressed. According to the AAOMS, patients that use oral BFs for over three years should suspend the use of this medication three months before and three months after the oral surgical procedure. This should reduce the chances of developing osteonecrosis, since the suspension of oral BFs tends to restore the osteoclastic function and bone turnover in three months (COLETÉ et al., 2019).

Although the literature still reports a low OAB incidence, these numbers might increase fast, since more and more people are taking this medication and the BF effects on the bone tissue are cumulative and persistent. BFs might remain in bones for 12 years after the interruption of the treatment. Thus, patients that used BFs in the past or still use them must be subjected to a thorough OAB prevention protocol (MARTINS et al., 2009).

The interaction between the dentist and the patient's medical doctor is important, so that they can carry out a careful and individualized analysis of each case, evaluating the medication used and the risks and benefits of the treatment suspension for the dental implant surgery. Each patient must be evaluated individually, since preventive measures have shown a three-fold reduction in the risk of osteonecrosis development (CHAVES et al., 2018).

For being a recently described complication, a truly efficient treatment for OAB has not been found yet (MIGLIORATI et al., 2006). Patients presenting asymptomatic bone exposure might be treated with chlorhexidine irrigation, use of systemic antibiotics such as penicillin or clindamycin, in addition to a strict clinical and radiographic control. In cases of symptomatic bone sequestration, removal of the necrotic bone tissue is indicated, which should be carried out in the most atraumatic manner possible for both the bone and the adjacent soft tissue. In severe cases, BF treatment interruption has been considered. However, it is also necessary to analyze whether the benefits reached are greater than the skeletal damage that might be caused by the drug use interruption.

Although there are few cases reported in the literature, some researchers obtained successful outcomes when using PRP in the OAB treatment. However, it was often associated with other therapies such as hyperbaric oxygen therapy and resorbable membranes, which might directly influence the treatment results (MOZZATI et al., 2012).

Ozone therapy has been used to prevent and treat OAB aiming to reestablish the bone normal physiology and prevent superinfection. Ozone can also be used as a mild analgesic, which does not damage tissues when prescribed in therapeutic doses (AGRILLO et al., 2007).

The use of hyperbaric oxygenation did not show positive results in the OAB initial treatment. For this reason, constant irrigation with chlorhexidine and the use of oral antibiotic therapy has been the current treatment prescribed (MARTINS et al., 2009).

Photodynamic therapy also seems to be a viable alternative for treatment, as it can help in alveolar repair, in addition, it does not promote microbial resistance and does not present contraindications, however, more clinical studies are still needed to prove the effectiveness of the treatment for osteonecrosis with photodynamic therapy (MENEZES et al., 2021).

5 CONCLUSION

The literature still does not present concrete data on the installation of dental implants in patients that were or are being treated with biphosphonates. Although this procedure is not an absolute contraindication, the dentist should be careful when treating such patients, becoming aware of their drug therapy and its limitations.

Continuous communication between the patient's medical doctor and the dentist and thorough anamnesis and physical examination are necessary in order to analyze the risks and benefits of submitting the patient to a surgical procedure. Such cautious behavior aims at OAB prevention and the patient's general health guarantee.

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