



## Use of Bisphosphonates and their Relationship to Jaw Osteoporosis: Review of Main Considerations

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### Abstract

**Introduction:** The goal of Modern Dentistry is to restore normal comfort, function, aesthetics, phonation and health to the patient. It is estimated that the number of dental implants used in the United States has increased more than 10 times from 2002 to 2017. More than one million dental implants are performed each year in Brazil.

**Objective:** The objective of the present study was to describe the types of bisphosphonates and their relation with the incidence of Osteonecrosis, reviewing some important aspects of this pathology, reinforcing the therapeutic approach.

**Methods:** Experimental and clinical studies were included (case reports, retrospective, prospective and randomized trials) with qualitative and/or quantitative analysis. Mesh Terms: The words were included osteoporosis, bisphosphonates, efficacy and complications. For further specification, the "bisphosphonates" description for refinement was added during searches.

**Conclusion:** The use of bisphosphonate is an alternative for the reduction of loss and increase of bone density, including therapeutic and preventive measures, mainly in invasive practices such as dental implants.

**Keywords:** Osteoporosis; Bisphosphonates; Efficacy and Complications

### Introduction

The goal of Modern Dentistry is to restore normal comfort, function, aesthetics, phonation and health to the patient [1,2]. What makes Implantology unique is the ability to achieve this goal, however the more teeth a patient loses the more challenging this task becomes. It is estimated that the number of dental implants used in the United States has increased more than 10 times from 2002 to 2017. More than one million dental implants are performed each year in Brazil [2,3].

Bisphosphonates are analogues of natural organic pyrophosphates, whose main property is to inhibit the precipitation of calcium phosphate, having high adsorption to the molecules of hydroxyapatite [3]. Thus, two chemical characteristics distinguish the types of bisphosphonate: 1) its ability to interact, by chelation, with ions calcium 2) its antireabsorption ability [3,4].

Bisphosphonates, which have three generations, have a three-dimensional structure capable of fixing divalent cations, such as  $\text{Ca}^{2+}$ , with marked affinity for the bone, especially the bone surfaces in the process of remodeling and, therefore, osteoclast-mediated bone resorption [2-4].

Moreover, the bisphosphonates are classified into two groups: non-nitrogenated (etidronate, clodronate and tiludronate) and nitrogenated (ibandronate, neridronate, olpadronate pamidronate, risedronate, alendronate and zoledronate) [3-5]. These represent standard therapy for the control of hypercalcemia in patients with metastatic lesions associated with multiple myeloma, solid tumors including breast, prostate and lung cancer. And they are also used in Paget's disease, osteogenesis imperfecta and osteoporosis [6].

Bisphosphonate-induced osteonecrosis was first approached in the literature in 2003 in osteolytic lesion similar to osteomyelitis in maxillary bones, whose origin was attributed to the therapy with high doses of bisphosphonates. This lesion is defined as the presence of exposed necrotic bone in the maxillofacial region [5-8].

In relation to the pathogenesis of osteonecrosis associated with bisphosphonates, some hypotheses are still discussed, but the most accepted are: direct action on osteoclast leads to a significant decrease in bone remodeling and inhibit vascular endothelial growth factor [9].

### Objective of the Study

The objective of the present study was to describe the types of bisphosphonates and their relation with the incidence of Osteonecrosis, reviewing some important aspects of this pathology, reinforcing the therapeutic approach.

### Methods

Experimental and clinical studies were included (case reports, retrospective, prospective and randomized trials) with qualitative and/or quantitative analysis. Initially, the key words were determined by searching the DeCS tool (Descriptors in Health Sciences, BIREME base) and later verified and validated by MeSh system (Medical Subject Headings, the US National Library of Medicine) in order to achieve consistent search.

### Mesh Terms

The words were included Osteoporosis, Bisphosphonates, Efficacy and Complications. For further specification, the "Bisphosphonates" description for refinement was added during searches. The literature search was conducted through online databases: Pubmed, Periodicos.com and Google Scholar. It was stipulated deadline, and the related search covering all available literature on virtual libraries.

### Series of Articles and Eligibility

A total of 53 articles were found involving temporomandibular dysfunction. Initially, it was held the exclusion existing title and duplications in accordance with the interest described this work. After this process, the summaries were evaluated and a new exclusion was held. A total of 25 articles were evaluated in full, and 15 were included and discussed in this study.

## Literature Review

### Osteoporosis and Dental Implants

Osteoporosis is a factor that retards the regeneration of maxillary bone in patients who underwent implant surgery, prolonging the normal recovery time of maxillary bone that can range from three to six months [1-3]. Therefore, it is necessary that people affected by this disease and who will receive dental implants need a longer time for bone repair. Due to the increase in life expectancy, rehabilitation with implants in people over 60 years old is the most common age group in which there is a higher probability of metabolic pathologies [3,4].

In order to obtain osseointegration of the implant, which is the direct and structural union of the bone tissue to the titanium and function, it is necessary to respect several principles, among them, those related to the surgical technique, respecting tissue physiology [1,2]. Thus, it is necessary to control the traumatic factors during surgery, such as intensity, frequency and duration of the milling (osteotomies), which can generate excessive trauma to the bone tissue, impairing the bone repair potential of the injured area [1,3]. Facing situations where the traumatic stimulus exceeds its physiological limit, the implant may be involved by fibrous connective tissues, leading to the formation of a bone or fibrous peri-implant interface, without osseointegration [4].

For the success of osseointegratable implants other factors must also be considered, not only related to the professional, but also the industry and the patient himself. In addition to performing the proper surgical technique, it is up to the professional to select the patient, evaluating him/herself as a whole, from his/her complaint, including his expectation regarding the treatment, mainly understanding his/her pre-operative systemic and local conditions 5. At the time of preparation of the receptor bone bed for the posterior installation of the osseointegrated implant, bone necrosis occurs, which will be replaced by new bone tissue. When there is osteoporosis, the process of bone remodeling can be compromised, preventing or delaying osseointegration [7].

Several authors have already reported on the importance of knowledge of systemic alterations, so that necessary measures are taken to minimize or prevent eventual damages caused by osteoporosis in the anatomical, physiological and functional integrity of the alveolar bone [8]. All care is necessary for the success of this process, because the immediate benefit of rehabilitative treatment with implants is observed in the improvement of the capacity to crush the food, in the physical and psychological well-being of the patient [8].

Although osteoporosis is a significant factor that can interfere with bone volume and density, it cannot be considered as an absolute contraindication for implant installation. It is essential that during the anamnesis, all patients are questioned about their state of health, reporting the use of medications and the type of medical treatment they are undertaking, so that a safe and effective treatment plan is drawn up for each individual case [9].

### Series of Articles and Eligibility

Bisphosphonates are a widely used drug group for various bone disorders and have been approved by the U.S. Food and Drug Administration for the treatment of osteoporosis, metastatic bone cancer and Paget's disease [10]. They were first used for industrial purposes in the 19th century to prevent corrosion in the textile, fertilizer and oil industries [11]. In 1968, the first article describing the use of bisphosphonates in medicine was published, however in 2002 serious side effects of these medications were reported following dental surgery procedures. This includes osteonecrosis, avascular necrosis, osteomyelitis, osteochemonecrosis and maxillary Biss-Phossy [12].

At present there are two main types of bisphosphonates: those containing nitrogen (oral: alendronate and risedronate, intravenous: pamidronate and zoledronate) and those that do not contain (etidronate, clodronate and tiludronate) [13,14].

Bisphosphonates act by suppressing and reducing bone resorption by osteoclasts, directly preventing the recruitment and function of osteoclasts, and indirectly stimulate osteoblasts to produce inhibitors of osteoclast formation [15]. Bisphosphonates are drugs derived from inorganic pyrophosphate, which are present in the body and physiologically regulate calcification and bone resorption. Pyrophosphate also provides greater resistance to chemical and enzymatic hydrolysis [14,15].

Some authors report that therapeutic treatment should always combine an anti-resorptive agent with a non-pharmacological measure such as physical exercise and consumption of calcium and vitamin D by diet [13]. Antireabsorption agents are described as estrogen replacement therapy, selective estrogen receptor modulators, bisphosphonates and calcitonin and also describes bone formation stimulating agents such as parathyroid hormone [15].

Intake of calcium if it is associated with hormone replacement (estrogen) reveals that it leads to an increase in trabecular bone

mass [13-15]. Calcium when ingested alone is not able to definitively prevent the onset of osteoporosis. The authors also report that in addition to osteoporosis, age, sex, races, hormonal pattern, decreased vitamin D synthesis, inhibition of calcium absorption, parathormone increase, nicotine, fragile physical structure, renal deficiency, menopause, alcohol and low consumption of calcium may jeopardize the success of an implant [12,13].

Bisphosphonates are anti-resorptive agents derived from pyrophosphoric acid that invalidate bone resorption [1,4]. Bisphosphonates can contain bone loss, increase bone density, and reduce the risk of fractures resulting from progressive loss of bone mass. In the bisphosphonate group, alendronate is the most potent because it has an affinity for bone tissue [2,5]. Another indication to prevent osteoporosis is calcitonin, which is a peptide derived from parafollicular cells of the thyroid assisting bone resistance [6].

Further, alendronate, for osteoporotic patients, can be administered orally at 10 mg/day or 70.0 mg/weekly, and cannot be exceeded because it causes gastrointestinal changes such as erosive esophagitis. It is necessary to use this medication fasting, because it is not absorbed in the intestine, and wait for 40 to 60 minutes to feed [8]. It is a drug that deposits about 40.0 to 60.0% rapidly into the bone and the rest is released through the urine. The plasma half-life of bisphosphonates is very short, ranging from thirty minutes to two hours, so after these medications are absorbed by the bone tissue, they can persist for more than 10 years in skeletal tissues [9].

Patients who use bisphosphonate may have a poor healing response to the impaired dental implant, since this medication prevents bone remodeling and may lead to a condition called osteonecrosis, which is considered a side effect of this drug [2-4].

Although there are many data on the beneficial effects of bisphosphonates in the treatment of advanced osseous diseases, numerous reports have documented the ability of these medications to cause local lesions of bone osteonecrosis mainly in the jaw. Osteonecrosis may remain asymptomatic for weeks and possibly months, and lesions usually develop around tapered areas and prior surgical sites, including extractions, retrograde apicectomies, periodontal surgery, and dental implant surgery [4,5]. Symptoms include pain, soft tissue edema, infection, tooth loss, and drainage. Radiographically, osteolytic changes are observed and tissue biopsy shows the presence of *Actinomyces* [6].

In the dental office, the most common bisphosphonates that are implanted in the dental office are the nitrogen-containing oral ones, such as risedronate, ibandronate and alendronate [10]. Comprehensive anamnesis is essential before the start of any elective treatment, the risk versus benefits of dental treatment should be discussed in detail with the patient.

## Discussion

The high need and use of treatments related to implants result from the combined effect of several factors and the most important are: (1) aging population with longer life expectancy; and (2) age-related dental loss [1].

One of the major causes of osteopenia in women over 60 years of age is estrogen deficiency (E2). This deficiency associated with aging causes an osteoporotic picture. It is necessary a hormonal replacement for an adequate treatment of the symptoms of the menopause and to prevent the possible osteoporosis [2].

There are some drugs that help in the treatment of postmenopausal osteoporosis, they are: calcitonin, bisphosphonates and the selective modulators of estrogen receptors. Bisphosphonates have been the best drug associated with a significant improvement in the quality of life of patients with bone diseases such as Paget's disease, bone metastases, osteogenesis imperfecta, malignant hypercalcemia and even severe osteoporosis [3].

These drugs are used worldwide in cancer patients and are given intravenously as zoledronic acid (Zometa®). They can also be administered orally, such as alendronate (Fosamax®) and risedronate (Actonel®) for the treatment of postmenopausal osteoporosis [4-6]. In 2003, a side effect associated with the use of bisphosphonates with oral manifestation denominated Osteonecrosis Associated with Bisphosphonates was described for the first time [7].

## Conclusion

The use of bisphosphonate is an alternative for the reduction of loss and increase in bone density, including therapeutic and preventive measures, mainly in invasive practices such as dental implants.

## Conflict of Interests

There is no conflict of interest between authors.

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