



Benefits and harmfulness of the use of bisphosphonate in the osseointegration process for dental implants in patients with osteoporosis: a concise systematic review

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Abstract

Introduction: In the scenario of implantology and osteoporosis, it is highlighted that the high need and use of treatments related to dental implants result from the combined effect of several factors, highlighting aging and bone fragility. In this context, osteoporosis is a global bone disease prevalent in human aging. Bisphosphonates (BPs) are commonly used as therapy because they influence hard and soft tissue calcium metabolism. **Objective:** It was to present the main considerations and scientific evidence of the use of bisphosphonate in the osseointegration process for dental implants in patients with osteoporosis, as well as to emphasize the harm caused by the occurrence of osteonecrosis. **Methods:** The rules of the Systematic Review-PRISMA Platform were followed. The research was carried out from February 2022 to May 2022 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 110 articles were found. In total, 58 articles were fully evaluated and 28 were included and evaluated in this study. Of the initial total of articles, 26 articles were excluded because they did not meet the GRADE classification, and 4 were excluded because they presented a risk of bias. It was concluded that osteoporosis is a metabolic condition that affects alveolar bone density, which may compromise the dental implant process. Therefore, the careful use of bisphosphonates is necessary for the osseointegration process, however, dental surgeons are encouraged to know the diagnosis so that they can

make a careful assessment, observing the quality of the bone through routine imaging exams, to prevent osteonecrosis. In addition, alendronate sodium is used to decrease bone resorption, being an adjuvant therapeutic agent for the treatment of osteoporosis.

Keywords: Dental implants. Osteoporosis. Bisphosphonate. Osseointegration. Osteonecrosis.

Introduction

In the scenario of implantology and osteoporosis, it is highlighted that the high need and use of treatments related to dental implants result from the combined effect of several factors, highlighting aging and bone fragility [1-3]. In this sense, one of the main causes of osteopenia in women over 60 is an estrogen deficiency. This deficiency associated with aging causes an osteoporotic picture. Hormone replacement is necessary for adequate treatment of menopausal symptoms and to prevent possible osteoporosis [1-5]. In this context, osteoporosis is a global bone disease prevalent in human aging. Bisphosphonates (BPs) are commonly used as therapy because they influence hard and soft tissue calcium metabolism [1].

In this sense, some drugs help in the treatment of postmenopausal osteoporosis, they are calcitonin, BPs, and selective estrogen receptor modulators [5]. Thus, BPs have been an important 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, hypercalcemia, and even severe osteoporosis [5].

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 [Duarte, Nociti, (2004)]. In 2003, a side effect associated with the use of oral BPs called Osteonecrosis Associated with BPs was described for the first time [6].

In this regard, ulceration of mucosa and dermis with exposure to underlying bone results from incomplete epithelial recovery due to reduced formation of desmosomes due to lack of available calcium [7,8]. However, pathological situations, such as osteonecrosis of the jaw related to BPs, have been described [9]. This hypothesis states that other situations that require intact functional desmosomes, such as skin healing over chronic pressure points leading to pressure ulcers, and hemidesmosomes, such as epithelial seals in contact with titanium surfaces, will have a higher prevalence of collapse among patients treated with PBs. This can be proven by the decreased modulation of calcium ions due to BPs and its effect on the formation of the intercellular junction [4, 10-14].

As one more example of literary support, one article reported a type of localized osteonecrosis that can occur in patients who have had osseointegrated implants successfully for many years and then started antiresorptive therapy. Eleven female patients who successfully implanted but were placed on antiresorptive therapy (BPs or denosumab) several years later and developed osteonecrosis around the implants were identified. In each case, osteonecrosis occurred only around the implants and not around the patient's remaining teeth. Implants from eight patients were removed with bone sequestration firmly attached to the implant. This is different from the normal pattern of implant failure. Implant failure can occur when patients with successfully integrated implants are later placed on antiresorptive therapy, and osteonecrosis takes a particular form where a sequestration forms that remain adherent to the implant. Why the remaining adjacent teeth are not affected is unclear [4].

Therefore, the present study aimed to present the main considerations and scientific evidence of the use of bisphosphonate in the osseointegration process for dental implants in patients with osteoporosis, as well as to emphasize the harmful effects of osteonecrosis.

Methods

Study Design

The rules of the Systematic Review-PRISMA Platform (Transparent reporting of systematic reviews and meta-analysis-[HTTP://www.prisma-statement.org/](http://www.prisma-statement.org/)) were followed.

Data sources and research strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "*Dental implants. Osteoporosis. Bisphosphonate. Osseointegration. Osteonecrosis*". The research was carried out in February 2022 to May 2022 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar. Also, a combination of the keywords with the booleans "OR", "AND", and the operator "NOT" were used to target the scientific articles of interest.

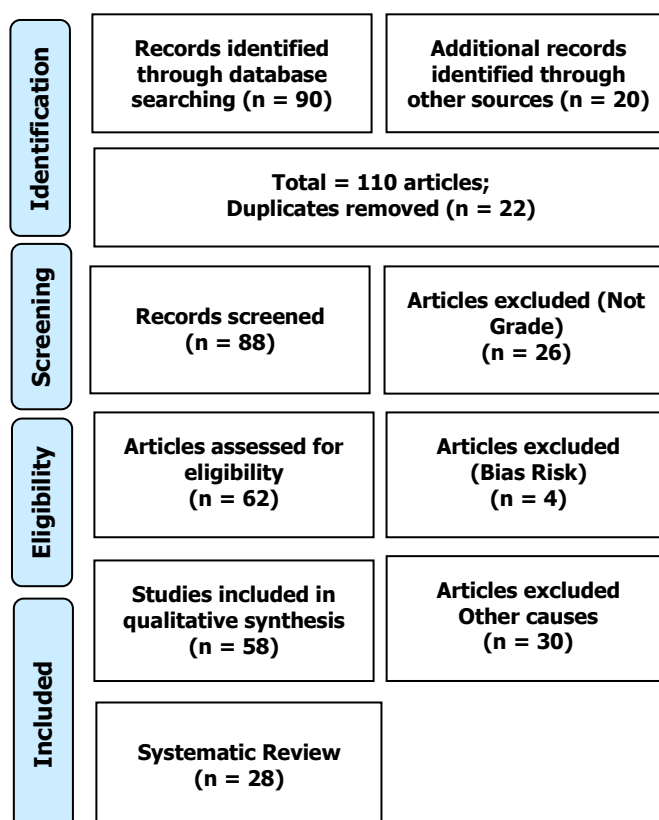
Study Quality and Bias Risk

The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

A total of 110 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not address the theme of this article. In total, 58 articles were fully evaluated and 28 were included and evaluated in this study (**Figure 1**). Of the initial total of articles, 26 articles were excluded because they did not meet the GRADE classification, and 4 were excluded because they presented a risk of bias that could compromise the credibility of the studies (**Figure 1**).

Figure 1. Study Eligibility (Systematic Review).



Osseointegration Process for Dental Implants in Patients with Osteonecrosis

Osteoporosis is defined as a systemic skeletal disorder, associated with aging, characterized by loss of bone mass, which makes the bone more fragile and more prone to fractures [15-18]. The World Health Organization defined osteoporosis as a level of bone mineral density greater than 2.5 standard deviations below the average of normal young women [19-22]. After 60 years of age, a third of the population has this disorder, it occurs twice more in women than in men and its diagnosis is made with greater prevalence from the third decade of life.

Among the systemic alterations, osteoporosis is one of the dysfunctions commonly found by implant dentists [19]. Osteoporosis acts by modifying the metabolism of the bone tissues, disorganizing the trabecular architecture of the cortical and alveolar bone, which are responsible for tooth support. It is estimated that 1.3 million of all fractures and 133,000 hip fractures occur each year as a result of osteoporosis [22].

Osteoporosis can be classified as type I and type II. Type I (postmenopausal) occurs when there is a loss of trabecular bone mass, resulting in fractures of the vertebrae and wrists, which may be more evident in the mandible and the alveolar bone, is associated with the aging and plasma decrease of estrogen in the menopause, affecting mainly women; And Type II (senile), occurs when there is loss of trabecular bone mass that can affect both cortical and spongy bone, resulting in hip fractures, which can affect both sexes and in ages over 70 years [14-19].

There is a higher prevalence of the development of osteoporosis in women, and there are some risk factors that may explain this difference, such as early menopause, artificial menopause, nulliparous, and estrogen replacement [23-26]. For men, reduced testicular function (male hypogonadism) can be cited as a risk factor. Several other risk factors may predispose to both sexes: heredity, tobacco, alcohol, caffeine, obesity, absence of physical activity, ethnicity, changes in calcium levels, malnutrition, decreased levels of vitamin D, elevated Levels of parathyroid hormone and other hormones, all these factors may manifest in both men and women with osteoporosis [15,19].

The recommended intake of calcium is 800 mg day⁻¹, in women who have already gone through menopause, 1.5 g may be required to maintain a positive calcium balance [27,28]. For patients with established osteoporosis, there are drugs that, in general, act directly in the process of bone remodeling, seeking to reduce bone resorption, among them, BP, which are drugs of proven efficacy that act in the prevention and treatment of several Bone diseases [28].

In this sense, dental implants are defined as supports or structures of titanium metal, which through surgeries are fixed in the maxillary bone replacing the dental roots, thus allowing the artificial teeth to fit the metal. Dentistry uses several rehabilitation techniques for masticatory functions, and osseointegrated implants are considered safe, provided they are implanted in areas of good quantity and bone quality [14]. However, some systemic conditions may interfere with implant stability, such as osteoporosis. Implantology has shown increasing success rates when it presents a harmonious bone/implant relationship (osseointegration) [14].

Also, the discovery of osseointegration occurred through studies of microcirculation in the bone marrow performed on the rabbit fibula, developed by Per-Ingvar Branemark. He verified in Branemark's studies that a titanium implant when inserted into the medullary space, under certain conditions, and remained immobile without mechanical trauma during the period of bone repair, ends up full of compact bone without the interference of other tissues [15-17].

In this context, osteoporosis is a factor that retards the regeneration of maxillary bone in patients who have undergone implant surgery, prolonging the normal recovery time of maxillary bone which can vary from three to six months [27]. 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 [28].

To obtain osseointegration of the implant, which is the direct and structural unit 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 [26]. Thus, it is necessary to control the traumatogenic 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. 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 per implant interface, without osseointegration [26].

For the success of osseointegrated implants, other factors must also be considered, not only related to the professional (surgical technique), but also the industry and the patient himself. In addition to performing the appropriate surgical technique, it is up to the professional to select the patient, and evaluate it as a whole, from his complaint, including his expectation regarding the treatment, mainly comprising his pre-operative systemic and local conditions [27,28]. At the moment of preparation of the receptor bone bed for the

subsequent 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 [28].

Several authors Ourique et al. [19] 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. All care is necessary for the success of this process since the immediate benefit of the rehabilitative treatment with implants is observed in the improvement of the capacity to crush the food, and in the physical and psychological well-being of the patient.

Besides, Ishii et al. [14] state that although osteoporosis is a significant factor that can interfere with bone volume and density, it cannot be considered 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 case.

Bisphosphonate - Major Benefits

BPs 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 [26]. They were first used for industrial purposes in the 19th century to prevent corrosion in the textile, fertilizer, and oil industries. In 1968, the first paper describing the use of BPs 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, osteochemionecrosis, and maxillary Biss-Phossy [26].

At the moment there are two main types of BPs: those containing nitrogen (oral: alendronate and risedronate, intravenous: pamidronate and zoledronate) and those that do not contain (etidronate, clodronate, and tiludronate). BPs act by suppressing and reducing bone resorption by osteoclasts, directly preventing the recruitment and function of osteoclasts, and indirectly stimulating osteoblasts to produce inhibitors of osteoclast formation [27].

Besides, BPs 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 [17].

Camargo, Minosso, and Lopes, (2007) [8] report that 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. Antireabsorption agents are described by Ishii (2009) [14] as estrogen replacement therapy, selective estrogen receptor modulators, BPs, and calcitonin and also describe bone formation stimulating agents such as a parathyroid hormone.

In this sense, Ourique et al. [19] have shown in their studies that calcium intake is associated with hormone replacement (estrogen), which leads to an increase in trabecular bone mass. 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, race, 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.

Also, BPs, according to Ishii et al. [14] Are anti-resorptive agents derived from pyrophosphoric acid that invalidates bone resorption. Ferreira Junior et al. [12] stated that BPs can contain bone loss, increase bone density, and reduce the risk of fractures resulting from progressive loss of bone mass. In the BPs group, alendronate is the most potent because it has an affinity for bone tissue. Another indication to prevent osteoporosis is calcitonin, which is a peptide derived from parafollicular thyroid cells, aiding bone resistance.

Besides, alendronate, for osteoporotic patients, can be administered orally at 10.0 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 medicine in fasting, for being little absorbed in the intestine, and to wait 40 to 60 minutes to feed. It is a drug that deposits about 40-60% rapidly into the bone and the rest is released through the urine. The plasma half-life of BPs is very short, ranging from thirty minutes to two hours, so after these medications are absorbed by the bone tissue, they may persist for more than 10 years in skeletal tissues [19].

In this context, a review study with Meta-Analysis included clinical human studies, randomized or not. A total of 18 publications were included in the review. Regarding implant failure, the meta-analysis found a risk ratio of 1.73 (95% confidence interval [CI] 1.21-2.48, $p = 0.003$) for BPs patients when compared to patients who did not take the medicine. The probability of an implant failure in patients receiving BPs was estimated at 1.5% (0.015, 95% CI 0.006-0.023, standard error [SE] 0.004, $p < 0.001$). BPs cannot be suggested to affect marginal bone loss from dental implants due to a limited

number of studies reporting this result. Due to a lack of sufficient information, the meta-analysis for the outcome of "postoperative infection" was not performed. The results of the present study cannot suggest that dental implant insertion in patients taking BPs affects implant failure rates due to a limited number of published studies, all characterized by a low level of specificity, and most of them dealing with a limited number of cases without an adequate control group. Therefore, the real effect of BPs on osseointegration and survival of dental implants is not yet well established [5].

Bisphosphonates- Major Complications

The authors Ishii et al. [14] states that patients who use BPs may have impaired healing of the damaged dental implant as it impedes bone remodeling and may lead to a condition called osteonecrosis, which is considered a side effect of this drug. Although there are much data on the beneficial effects of BPs 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 [27].

Also, osteonecrosis may remain asymptomatic for weeks and possibly months, and lesions usually develop around tapered areas and prior surgical sites, including extractions, retrograde apical tetanus, periodontal surgery, and dental implant surgery. Symptoms include pain, soft-tissue edema, infection, tooth loss, and drainage. Radiographically, osteolytic changes are observed and tissue biopsy shows the presence of actinomyces [28].

In the dental office, the most common BPs that the implant is exposed to are the oral ones that contain nitrogen, such as risedronate, ibandronate, and alendronate. Comprehensive anamnesis is essential before the initiation of any elective treatment, the risk versus benefits of dental treatment should be discussed in detail with the patient [26].

In this context, another study using the BPs analyzed the factors related to obtaining effective mechanical and immunological adhesion, viability, epidermal collagen growth factor, and immunoglobulin synthesis were evaluated. The presence of BPs culminated in lower cell adhesion to titanium discs, particularly for sodium alendronate (SA) at 5 μ M (40%) and zoledronic acid (ZA) at all concentrations (30 to 50% according to increased concentrations). Reduced cell viability occurred after an exposure of these cells to ZA (40%); however, only 5 μ M of SA-treated cells had decreased viability (30%). Reduced synthesis of growth factors and collagen was observed when cells were treated with ZA (20 and 40%, respectively), while about

70% of IgG synthesis was increased. BPs negatively affected adhesion and metabolism of oral mucosal cells, and this effect was related to BPs type as well as concentration and treatment period. The negative effects of BPs on oral mucosa cells may hinder the formation of an effective biological seal in osseointegrated implants [6].

Also, a review study aimed to study the purpose of dental implant placement in patients who have been treated or are undergoing treatment with BPs medication. Outcome measures included implant failure or implant-related jaw osteonecrosis. In total, 32 literature sources were reviewed, and 9 of the most relevant articles that fit the criteria were selected. Heterogeneity between studies was found and no meta-analysis could be performed. Five studies looked at intra-oral BPs medication for implant placement, three studies looked at intravenous BPs medication for implant placement, and one study evaluated the two types of medication administered for implant placement. Patients with intraoral therapy appeared to have better implant survival (5 implants failed 423) rate of 98.8% versus intravenously treated patients (6 implants failed 68) by 91%; The control group compared with the intraoral BPs group appeared with 97% success in implant survival rate (27 implants failed in 842), showing no significant difference in implant placement success. Patients treated with intravenous BPs appear to have a greater chance of developing implant-related jaw osteonecrosis. The intraorally treated group of patients appeared to have more successful results. Implant placement in intraorally treated patients can be considered safe with precautions [7].

Conclusion

It was concluded that osteoporosis is a metabolic condition that affects alveolar bone density, which may compromise the dental implant process. Therefore, the careful use of bisphosphonates is necessary for the osseointegration process, however, dental surgeons are encouraged to know the diagnosis so that they can make a careful assessment, observing the quality of the bone through routine imaging exams, to prevent osteonecrosis. In addition, alendronate sodium is used to decrease bone resorption, being an adjuvant therapeutic agent for the treatment of osteoporosis.

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Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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