



Clinical findings and main considerations of the use of bisphosphonate in dental implants: a concise systematic review

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Abstract

Introduction: In the scenario of dental implant and osseointegration, it is highlighted that the scope of modern dentistry is to restore the patient's normal comfort, function, esthetics, speech, and health. More than one million dental implants are performed each year in the USA. Bisphosphonates (BP) 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, hypercalcemia, and even severe osteoporosis. **Objective:** Aimed to carry out a concise systematic review of the main considerations regarding the use of bisphosphonate in osseointegration for dental implants. **Methods:** The present study followed by a systematic review model, following the rules of systematic review - PRISMA. The search strategy was performed in the PubMed, Scielo, Cochrane Library, Web of Science and Scopus, and Google Scholar databases. The Cochrane Instrument was used to assess the risk of bias of the included studies. **Results:** Bisphosphonate coating of dental implants is a promising tool for surface modification, aiming to improve the osseointegration process and clinical outcome. The biological effects of bisphosphonates are thought to be primarily associated with inhibition of osteoclasts, whereas their effects on osteoblast function are unclear. Thus, surfaces coated with bisphosphonates to stimulate osteoblast differentiation have been investigated by several in vitro studies with contradictory results. **Conclusion:** Based on results, osteoporosis is a metabolic condition that affects alveolar bone density, but it does not present problems for the installation of osseointegrated implants, as long as there is sufficient bone mass in the region where the tooth will be implanted. Locally

administered bisphosphonates induce bone regeneration in periodontal defects and decrease the rate of marginal bone loss after dental implant therapy.

Keywords: Dental implant. Bisphosphonate. Osseointegration. Osteonecrosis. Complications.

Introduction

In the scenario of dental implant and osseointegration, it is highlighted that the scope of modern dentistry is to restore the patient's normal comfort, function, esthetics, speech, and health. What makes implant dentistry unique is the ability to achieve this goal. However, the more teeth a patient loses, the more challenging the task becomes [1-3]. It is estimated that the number of dental implants used in the United States increased more than 10 times between 1983 and 2002 and more than five times between 2000 and 2005 [4]. More than one million dental implants are performed each year [5]. The high need and use of implant-related treatments result from the combined effect of several factors, the most important being the aging of the population with longer life expectancy and age-related tooth loss.

In this sense, one of the main causes of osteopenia in women over 60 years of age is an estrogen deficiency. This deficiency associated with aging causes an osteoporotic condition. Hormone replacement is necessary for an adequate treatment of menopausal symptoms and to prevent possible osteoporosis [6]. Some drugs help in the treatment of postmenopausal osteoporosis: they are calcitonin, bisphosphonates (BP), and selective estrogen receptor modulators. Thus, BP has 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, hypercalcemia, and even severe osteoporosis [7].

These drugs are used worldwide in cancer patients and are given intravenously as zoledronic acid (Zometa®). They can also be given orally as alendronate (Fosamax®) and risedronate (Actonel®) for the treatment of postmenopausal osteoporosis [8]. However, in 2003, a side effect associated with the use of BP with oral manifestation was described for the first time, called BP-Associated Osteonecrosis [9].

Furthermore, osteoporosis is a global bone disease prevalent in human aging [2]. BPs are commonly used as therapy because they influence calcium metabolism in hard and soft tissues. Mucosal and dermis ulceration with underlying bone exposure results from incomplete epithelial recovery due to reduced desmosome formation due to lack of available calcium. However, pathological situations, such as blood pressure-related osteonecrosis of the jaw, have been described [10].

This hypothesis states that other situations that require intact functional desmosomes, such as healing of the skin over chronic pressure points that lead 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 BP. This can be demonstrated by the decreased modulation of calcium ions due to blood pressure and its effect on the formation of the intercellular communicating junction [1].

Also, one article reported a type of localized osteonecrosis that can occur in patients who have had a successful osseointegrated implant for many years and then started anti-resorptive therapy. Eleven female patients who successfully implanted but underwent antiresorptive therapy (BP or denosumab) several years later developed osteonecrosis around the implants. In each case, osteonecrosis only occurred around the implants and not around the patient's remaining teeth. The 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 subsequently placed on anti-resorptive therapy, and osteonecrosis takes a specific form in which a sequestration form remains adherent to the implant. Why the remaining adjacent teeth are unaffected is unclear [2].

In this sense, the present study aimed to carry out a concise systematic review of the main considerations regarding the use of bisphosphonate in osseointegration for dental implants.

Methods

Study Design

The present study followed a systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and meta-analysis, access available in: <http://www.prisma-statement.org/>).

Data Sources

The search strategy was performed in the PubMed, Scielo, Cochrane Library, Web of Science and Scopus, and Google Scholar databases, using scientific articles from 2002 to 2021.

Descriptors (MeSH Terms) And Bias

The main MeSH Terms used were "*Dental implant. Bisphosphonate. Osseointegration. Osteonecrosis. Complications*". For greater specification, the description "dental treatment phobia" for refinement was added during the searches, following the rules of the word PICOS (Patient; Intervention; Control; Outcomes; Study Design). The **Cochrane Instrument** was used to assess the risk of bias of the included studies.

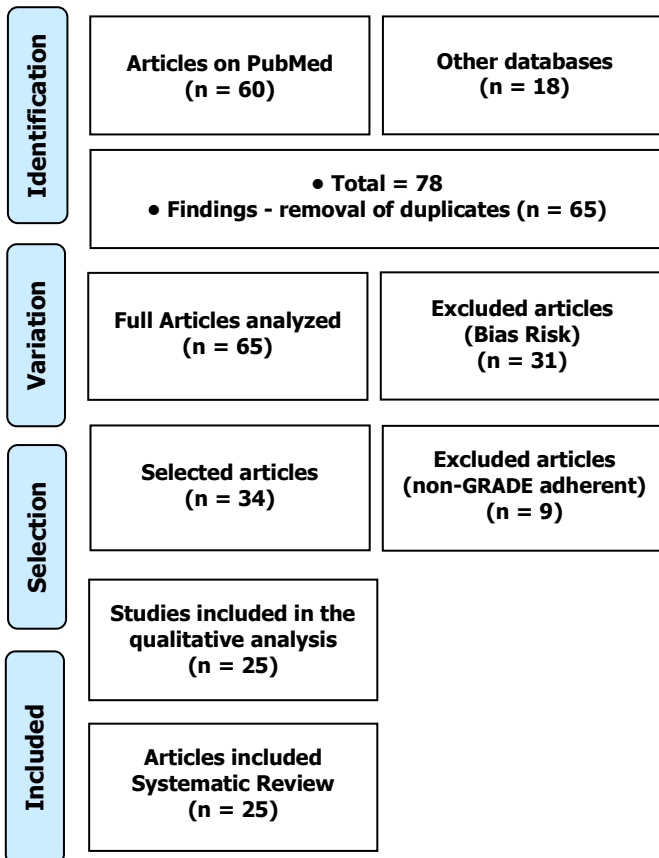
Results and Discussion

A total of 78 articles were found involving dental implant and bisphosphonate. Initially, the duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, based on the elimination of articles with biases that could compromise the reliability of the results, according to the rules of the Cochrane instrument, as well as articles that presented low quality in their methodologies, according to the GRADE classification. A total of 34 articles were fully evaluated and 25 were included in this study (Figure 1).

As a result of the main findings, there is a recent meta-analysis study that evaluated the effect of locally applied bisphosphonates on alveolar bone defects caused by periodontitis at the marginal bone level after the placement of dental implants. As a result, it was observed that bisphosphonates showed a significantly greater reduction in intraosseous defect depth than placebo/control in vertical bone defects treated with non-surgical approach or surgical approach and class II furcation defects treated with non-surgical approach or surgical approach. Clinical attachment loss increased by 1.39 mm and 1 mm in vertical bone defects after non-surgical and surgical treatments, respectively, and by 1.95 mm and 0.84 mm after non-surgical and surgical treatment in class II furcation defects, respectively. Less

marginal bone loss during the pre-loading and 1-year post-loading periods was observed when using bisphosphonate-coated dental implants [11].

Figure 1. Flowchart showing the article selection process.



In this aspect, bisphosphonate coating of dental implants is a promising tool for surface modification, aiming to improve the osseointegration process and clinical outcome. The biological effects of bisphosphonates are thought to be primarily associated with inhibition of osteoclasts, whereas their effects on osteoblast function are unclear. Thus, surfaces coated with bisphosphonates to stimulate osteoblast differentiation have been investigated by several in vitro studies with contradictory results. Therefore, a systematic review and meta-analysis study evaluated the effect of bisphosphonate-coated implant surfaces on the alkaline phosphatase activity in osteoblasts. Eleven studies met the inclusion criteria. Meta-analysis showed that coating titanium surfaces with bisphosphonates increase alkaline phosphatase activity in osteoblasts after 3 days (n=1), 7 (n=7), 14 (n=6), and 21 (n=3) days. The meta-analysis suggests that bisphosphonate coatings on titanium implant surfaces may have beneficial effects on the osteogenic behavior of osteoblasts cultured on titanium surfaces in vitro. More studies are needed to assess to what extent the coating

of bisphosphonates can improve osseointegration in clinical situations [12].

Also, BP is a group of drugs widely used for various bone disorders and has been approved by the US Food and Drug Administration for the treatment of osteoporosis, metastatic bone cancer, and Paget's disease [13]. They were first used for industrial purposes in the 19th century to prevent corrosion in the textile, fertilizer, and petroleum industries. In 1968, the first article describing the use of BP in medicine was published, but in 2002 serious side effects of these drugs were reported after dental surgery procedures. These include osteonecrosis, avascular necrosis, osteomyelitis, osteoradionecrosis, and maxillary Biss-Phossey.

There are currently two main types of BP, those that contain nitrogen (oral: alendronate and risedronate, intravenous: pamidronate and zoledronate) and those that do not (etidronate, clodronate, and tiludronate). BP works by suppressing and reducing bone resorption by osteoclasts, directly preventing osteoclast recruitment and function and indirectly stimulating osteoblasts to produce inhibitors of osteoclast formation [14].

Besides, BP is a drug derived from inorganic pyrophosphate, present in the body and physiologically regulating calcification and bone resorption. Pyrophosphate also provides greater resistance to chemical and enzymatic hydrolysis [15]. Camargo, Minosso, Lopes, (2007) [12] report that treatment should always combine an anti-resorptive agent with a non-pharmacological measure, such as physical exercise and calcium and vitamin D consumption in the diet. Anti-resorptive agents are described by Ishii (2009) [16] as estrogen replacement therapy, selective modulators of estrogen, BP, and calcitonin receptors, and also describe agents that stimulate bone formation, such as a parathyroid hormone.

Also, other authors [17] 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, races, hormonal pattern, decreased vitamin D synthesis, inhibition of calcium absorption, increased parathyroid hormone, nicotine, fragile physical structure, kidney deficiency, menopause, alcohol, and low Calcium consumption can compromise the success of an implant.

Besides, authors [18] stated that BP can contain bone loss, increase bone density and reduce the risk of fractures resulting from progressive loss of bone mass. In the BP group, alendronate is the most potent because

it has an affinity for bone tissue. Another indication for preventing osteoporosis is calcitonin, a peptide derived from parafollicular thyroid cells, helping bone strength. Alendronate, for patients with osteoporosis, can be administered orally at 10.0 mg/day or 70.0 mg/week, and cannot be exceeded because it causes gastrointestinal changes, such as erosive esophagitis. It is necessary to use this medication on an empty stomach, as it is poorly absorbed in the intestine and wait 40 to 60 minutes for food. It is a drug that deposits about 40-60% quickly in the bone and the rest is released in the urine. The plasma half-life of BP is very short, ranging from thirty minutes to two hours; therefore, after absorption of these drugs by bone tissue, they may persist for more than 10 years in skeletal tissues [19].

In addition, a meta-analysis study included clinical studies in humans, randomized or not. A total of 18 publications were included in the review. Regarding implant failure, the meta-analysis found a hazard ratio of 1.73 ($p=0.003$) for patients with BP when compared to patients who did not take the drug. The probability of implant failure in patients receiving BP was estimated to be 1.5%. It cannot be suggested that BP affects marginal bone loss from dental implants due to a limited number of studies reporting this result. Due to lack of sufficient information, the meta-analysis for the outcome "postoperative infection" was not performed. The results of the present study cannot suggest that the insertion of dental implants in patients undergoing BP 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 BP on the osseointegration and survival of dental implants is not well established [7].

Bisphosphonates – Complications

Ishii et al. [16] stated that patients using BP may have impaired healing of the damaged dental implant, as they impede bone remodeling and can lead to a condition called osteonecrosis, considered a side effect of this drug. Although there are much data on the beneficial effects of BP in the treatment of advanced bone diseases, several reports have documented the ability of these drugs to cause local lesions of bone osteonecrosis, mainly in the mandible [20].

In this sense, osteonecrosis can remain asymptomatic for weeks and possibly months, and lesions usually develop around conical areas and anterior surgical sites, including extractions, retrograde apical tetanus, periodontal surgery, and dental implant

surgery [21]. Symptoms include pain, soft tissue swelling, infection, tooth loss, and drainage. Radiographically, osteolytic changes are observed and tissue biopsy shows the presence of actinomyces [22]. In the dental office, the most common BP exposed to the implant are oral ones that contain nitrogen, such as risedronate, ibandronate, and alendronate. Comprehensive history-taking is essential before starting any elective treatment, the risk versus benefits of dental treatment should be discussed in detail with the patient [23].

In this context, another study using the BP analyzed factors related to achieving effective mechanical and immunological adhesion, viability, epidermal collagen growth factor, and immunoglobulin synthesis. The presence of BP resulted in lower cell adhesion to titanium discs, especially for alendronate sodium (SA) at 5 μM (40%) and zoledronic acid (ZA) at all concentrations (30 to 50% according to the increase in concentrations). Reduced cell viability occurred after exposure of these cells to ZA (40%); however, only 5 μM 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. BP negatively affected the adhesion and metabolism of cells in the oral mucosa, and this effect was related to the type of BP, as well as the concentration and period of treatment. The negative effects of BP on the cells of the oral mucosa can prevent the formation of an effective biological seal in osseointegrated implants [8].

In addition, a review study aimed to study the purpose of placing dental implants in patients who were treated or are being treated with BP medication. Outcome measures included implant failure or implant-related mandibular osteonecrosis. In total, 32 sources in the literature were reviewed and 9 of the most relevant articles that met the criteria were selected. Heterogeneity between studies was found and no meta-analysis could be performed. Five studies looked at intraoral BP medication for implant placement, three studies looked at intravenous BP medication for implant placement, and one study looked at the two types of medication administered for implant placement. Patients with intraoral therapy appeared to have better implant survival (5 implants failed 423), rate 98.8% versus patients treated intravenously (6 implants failed 68) at 91%. The control group compared to the intraoral BP group appeared with a 97% success rate in the implant survival rate (27 implants failed out of 842), showing no significant difference in the success of implant placement. Patients treated with intravenous BP appear to have a greater chance of developing implant-related

mandibular osteonecrosis. The group of patients treated intraorally seemed to have more successful results. Implant placement in patients treated intraorally can be considered safe with precautions [9].

In this sense, BP is a synthetic drug analogous to inorganic pyrophosphate, being endogenous regulators of bone mineralization. Its chemical structure presents phosphate PO₃ linked to a central carbon and the union of chains called R1 and R2, chains of extreme importance for the effectiveness of these drugs. The R1 chain is short and is also responsible for having the pharmacokinetic and chemical properties of BP [24]. However, the R2 chain is long and determinant in relation to the mechanism of action and anti-resorptive power, presenting non-nitrogenous BP and nitrogenous structures, which are incorporated by osteoclasts in bone resorption, resulting in cell death by apoptosis. In the chemical structure of BP, which is non-nitrogenous, when metabolized by osteoclasts, they will be substrates for the synthesis of cytotoxic ATP analogs, where cell death will occur. However, nitrates after being reabsorbed by osteoclasts act by interrupting the mevalonate pathway, responsible for controlling cholesterol synthesis. This interruption will compromise intracellular vesicular transport, causing cell death, impairing bone resorption [24].

Finally, bone resorption is performed by osteoclasts, which consist of bone mineral dissolution, leading to the formation of cavities and the release of elements from the bone matrix; in bone deposition, the synthesis of the osteoblastic matrix occurs, leading to primary mineralization and an extensive sequence of secondary mineralization [25]. In addition to resorption, bone production is also limited by a decrease in the surface of the neoformation. This decrease in bone formation occurs secondarily to reduced resorption. Newly formed bones will have less chance of being neoformed, due to the reduced volume of remodeling, generating more time for complete mineralization [1,2].

Conclusion

Based on results, osteoporosis is a metabolic condition that affects alveolar bone density, but it does not present problems for the installation of osseointegrated implants, as long as there is sufficient bone mass in the region where the tooth will be implanted. Locally administered bisphosphonates induce bone regeneration in periodontal defects and decrease the rate of marginal bone loss after dental implant therapy.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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