MedNEXT
Journal of Medical an Health Sciences

REVIEW ARTICLE

DOI: 10.54448/mdnt23S14

Major aspects of the use of bisphosphonates for dental implants in patients with or without osteoporosis: a systematic review of clinical studies

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DOI: https://doi.org/10.54448/mdnt23S14
Received: 10-14-2022; Revised: 10-27-2022; Accepted: 01-15-2023; Published: 01-20-2023; MedNEXT-id: e23S14

Abstract

Introduction: In the setting of Medication-Related Osteonecrosis of the Jaw (MRONJ) it was first reported in association with the use of bisphosphonates (BP) by maxillofacial surgeons. The potency and route of administration of BPs are identified as important risk factors. **Objective:** It was to evaluate the use of bisphosphonates and their side effects in patients with or without osteoporosis, with emphasis on osteonecrosis of the jaws, for dental implants. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from October to December 2022 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases, using articles from 2005 to 2022. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed accordingly. according to the Cochrane instrument. **Results and Conclusion:** A total of 120 articles were found, and 55 articles were evaluated in full and 34 were included and developed in this systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 15 studies with a high risk of bias and 32 studies that did not meet GRADE. For patients with established osteoporosis, there are drugs that, in general, act directly on the bone remodeling process, seeking to reduce bone resorption, including BP, which are drugs of proven efficacy that act in the prevention and treatment of several bone diseases. Osteoporosis is a factor that delays the regeneration of the maxillary bone in patients submitted to implant surgery, prolonging the normal recovery time of the maxillary bone, which can vary from three to six months. Alendronate sodium is used to decrease bone resorption, the drug should be considered an adjuvant therapeutic agent for the treatment of osteoporosis. However, studies have shown that there is a risk of osteonecrosis with the use of bisphosphonates.

Keywords: Bisphosphonates. Osteonecrosis. Osteoporosis. Dental implant. Complications.

Introduction

In the setting, Medication-Related Osteonecrosis of the Jaw (MRONJ) was first reported in association with the use of bisphosphonates (BP) by maxillofacial surgeons in 2003 and 2004 [1]. Later, this condition was also associated with other classes of drugs, including antiresorptive (AR) and anti-angiogenic drugs. In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) confirmed that other drugs (denosumab, sunitinib, sorafenib, bevacizumab, sirolimus, and others) are also associated with the development of MRONJ [2].

In this context, the potency and route of administration of BP are identified as important risk factors [2,3]. Thus, cancer patients receiving intravenous BP have a 2.7- to 4.2-fold increased risk of developing MRONJ. Among the intravenous medications, zoledronic acid, as it is a more potent drug, would represent a greater risk than the use of pamidronate [4]. Some authors also believe that the

duration of therapy is associated with increased risk. In cancer patients who used zoledronic acid or denosumab, the incidence of developing MRONJ was, respectively, 0.6% and 0.5% in the first year, 0.9% and 1.1% in the second year, and 1.3% and 1.1% in the third year [2]. According to Palaska et al., treatment time in patients who developed MRONJ was, on average, 1.8 years using zoledronic acid, 2.8 years using pamidronate, and 4.6 years using oral alendronate [5]. Also, a recent epidemiological study analyzed 13 studies on the occurrence of medication-related osteonecrosis of the jaw, showing that there is a large and growing group at risk of developing MRONJ [6].

Added to this, the etiology and pathogenesis of MRONJ have not yet been fully elucidated, however, the mechanisms of drug action may explain much of the development of this condition [7]. Bone physiology depends on the balance between resorption and tissue formation. As an example, denosumab is a human monoclonal antibody that blocks RANKL, a member of the tumor necrosis factor (TNF) superfamily that plays a key role in the regulation of uptake. RANKL is secreted by activated osteoblasts in response to circulating cytokines (interleukins) and hormones (glucocorticoids) and triggers an intracellular signaling cascade that results in osteoclast maturation and proliferation. Unlike BP, which tend to accumulate and persist in bone for several years after discontinuing therapy, denosumab may remain in the body for a limited period due to a lack of affinity for hydroxyapatite. In this sense, the irreversible deactivation of osteoclasts promoted by denosumab persists only until cell death. As new osteoclasts are formed daily if a new osteoclast is formed after one administration of the drug and before the next administration, this osteoclast will be fully functional. Thus, its effects are expected to dissipate after 6 months [7].

In this regard, MRONJ can have a major impact on the quality of life of patients due to episodes of pain, development of foci of infection, and, in more advanced cases, functional and/or aesthetic changes that can impair the social life of patients. These implications should encourage multidisciplinary teams to identify solutions to minimize the occurrence of this condition [8,9].

Therefore, a group from Spain showed that undergraduate students were more knowledgeable about MRONJ than dentists. This was confirmed in studies of physicians conducted by Al-Mahoya et al. [10] who showed that 75.6% and 91.1% of physicians did not have adequate knowledge about this adverse effect of antiresorptive drugs. These findings were also similar to other studies [11-13].

In this way, questionnaires, both self-administered and those conducted through interviews [1], can be used to identify gaps in the knowledge of physicians and dentists and thereby develop didactic action plans and learning strategies and more assertive interventions [14]. Currently available scientific evidence obtained from physicians and dentists from different parts of the world shows that most of these professionals have insufficient knowledge about MRONJ as an adverse effect of these drugs [15-17].

Faced with this potential lack of training and knowledge of healthcare staff involved in treating patients affected by MRONJ, it is imperative to increase the number of epidemiological studies to apply questionnaires to assess knowledge related to MRONJ among healthcare professionals [1]. The results of these assessments can be used to develop teaching and professional training strategies. The literature clearly shows the knowledge gaps related to MRONJ among health professionals, both physicians, and dentists [14].

Therefore, the present study aimed to evaluate the use of bisphosphonates and their side effects in patients with or without osteoporosis, with emphasis on osteonecrosis of the jaws, for dental implants.

Methods

Study Design

This was followed by a systematic literature review model on the main clinical findings of mandible fractures, according to the PRISMA rules (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/).

Data sources and research strategy

The literary search process was carried out from October to December 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2005 to 2022, using the descriptors (MeSH Terms): “Bisphosphonates. Osteonecrosis. Osteoporosis. Dental implant. Complications", and using the Booleans "and" between the descriptors (MeSH Terms) and "or" between the historical findings.

Study quality and risk of bias

The quality of the studies was based on the GRADE instrument, with randomized controlled clinical studies, prospective controlled clinical studies, and studies of systematic review and meta-analysis listed as the studies with the greatest scientific evidence. The risk of bias was analyzed according to the Cochrane instrument.

Results and Discussion

Summary of Literary Findings

A total of 120 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 include the theme of this article, resulting in 102 articles. A total of 55 articles were evaluated in full and 34 were included and developed in this systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 15 studies with a high risk of bias and 32 studies that did not meet GRADE.

Figure 1. Selection of studies.

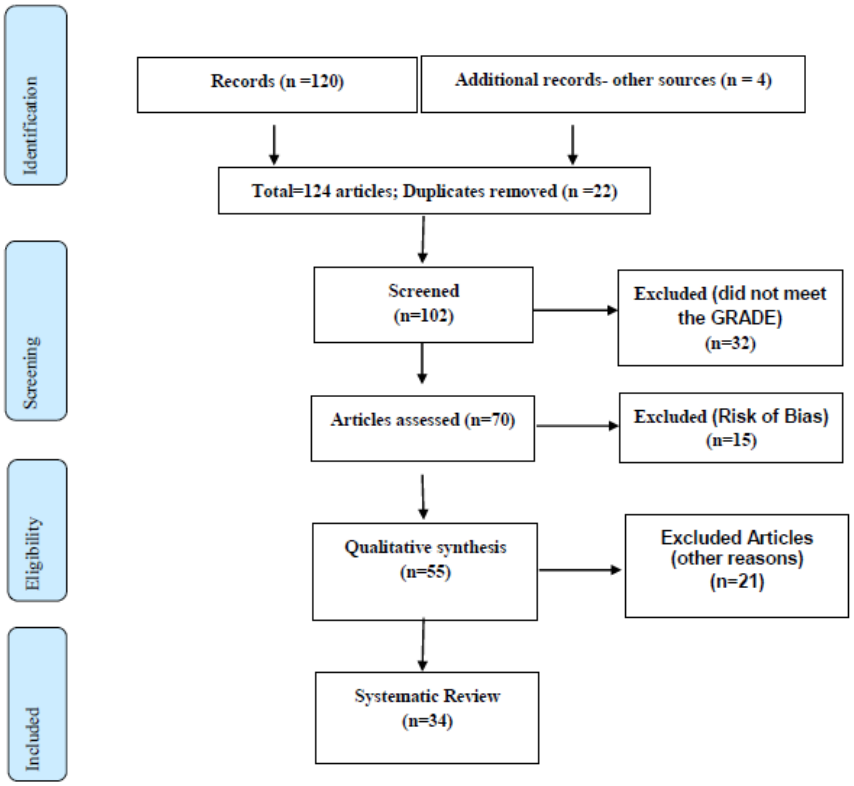

Figure 2 presents the results of the risk of bias in the studies using the Funnel Plot, through the calculation of the Effect Size (Cohen's Test). The sample size was determined indirectly by the inverse of the standard error. The number of clinical studies evaluated was n=. The graph showed symmetric behavior, not suggesting a significant risk of bias in studies with small sample sizes, which are shown at the bottom of the graph.

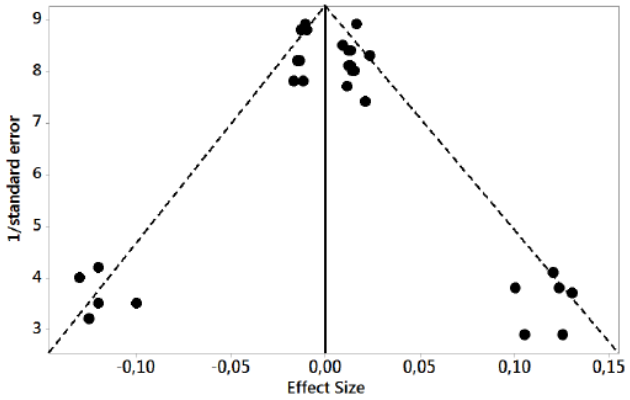

Figure 2. The symmetric funnel plot does not suggest a risk of bias between the small sample size studies that are shown at the bottom of the graph (N = 34 studies).

Source: own authorship

Osteoporosis, Bisphosphonate and Dental Implants – Major Approaches

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 [18-21]. 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 [22-25]. 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 [22]. 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 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 [18-22].

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 [25-29]. 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 [18,22].

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 [30,31]. 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, is BP, which are drugs of proven efficacy that act in the prevention and treatment of several Bone diseases [31].

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 [17]. 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) [18].

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 remaining immobile without mechanical trauma during the period of bone repair, end up full of compact bone without the interference of other tissues [17-20].

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 [30]. Therefore, it is necessary that people affected by this disease 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 [31].

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 [29]. 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 [29].

For the success of osseointegrate 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, evaluating it as a whole, from his complaint, including his expectation regarding the treatment, mainly comprising his pre-operative systemic and local conditions [30,31]. 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 [31].

Also, authors Ourique, Ito, and Suarez. [22] 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, 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 [1,2].

In this sense, BP is a widely used drug group for various bone disorders and has been approved by the U.S. Food and Drug Administration for the treatment of osteoporosis, metastatic bone cancer, and Paget's disease [29]. 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 BP 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, osteochimionecrosis, and maxillary BissPhossy [29].

At the moment there are two main types of BP those containing nitrogen (oral: alendronate and risedronate, intravenous: pamidronate and zoledronate) and those that do not contain (etidronate, clodronate, and tiludronate). BP 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 [30].

In this sense, BP is a drug derived from inorganic pyrophosphate, which is present in the body and physiologically regulates calcification and bone resorption. Pyrophosphate also provides greater resistance to chemical and enzymatic hydrolysis [20]. 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 [17]. Antireabsorption agents are estrogen replacement therapy, selective estrogen receptor modulators, BP, and calcitonin, and also describe bone formation stimulating agents such as parathyroid hormone [2-4].

Also, BP is an anti-resorptive agent derived from pyrophosphoric acid that invalidates bone resorption [5]. 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 to prevent osteoporosis is calcitonin, which is a peptide derived from parafollicular thyroid cells, aiding bone resistance [6,7].

Further, 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 BP 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 [22].

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 metaanalysis found a risk ratio of 1.73 (95% confidence interval [CI] 1.21-2.48, p = 0.003) for BP patients when compared to patients who did not take the medicine. The probability of an implant failure in patients receiving BP was estimated at 1.5% (0.015, 95% CI 0.006-0.023, standard error [SE] 0.004, p<0.001). BP 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

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 osseointegration and survival of dental implants is not yet well established [32].

Thus, patients who use BP 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 BP 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 [30].

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 [31]. In the dental office, the most common BP that the implant is exposed to is 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 [29].

In this context, another study using the BP analyzed the factors related to obtaining effective mechanical and immunological adhesion, viability, epidermal collagen growth factor, and immunoglobulin synthesis were evaluated. The presence of BP culminated in lower cell adhesion to titanium discs, particularly for sodium alendronate (SA) at 5 μM (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 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. BPs negatively affected the adhesion and metabolism of oral mucosal cells, and this effect was related to BP 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 [33].

Besides, a review study aimed to study the purpose of dental implant placement in patients who have been treated or are undergoing treatment with BP 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 BP medication for implant placement, three studies looked at intravenous BP 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 BP 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 BP 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 [34].

Conclusion

For patients with established osteoporosis, there are drugs that, in general, act directly on the bone remodeling process, seeking to reduce bone resorption, including BP, which are drugs of proven efficacy that act in the prevention and treatment of several bone diseases. Osteoporosis is a factor that delays the regeneration of the maxillary bone in patients submitted to implant surgery, prolonging the normal recovery time of the maxillary bone, which can vary from three to six months. Alendronate sodium is used to decrease bone resorption, the drug should be considered an adjuvant therapeutic agent for the treatment of osteoporosis. However, studies have shown that there is a risk of osteonecrosis with the use of bisphosphonates.

Acknowledgement
Not applicable.

Funding
Not applicable.

Ethics approval
Not applicable.

Informed consent
Not applicable.

Data sharing statement
No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

Similarity check
It was applied by Ithenticate@.

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