Original Article

DENTAL IMPLANTS BEFORE DURING AND AFTER BISPHOSPHONATE THERAPY - A SYSTEMATIC REVIEW

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Abstract

Aim: To review articles that compared diphosphonate therapy patients who received dental implants before, during, or after bisphosphonate (BP) treatment to healthy patients, looking at the increase in implant failure and loss, as well as the incidence of bisphosphonate-related osteonecrosis of the jaw (BRONJ).

Methodology: After performing the extensive search on electronic databases PUBMED searched articles until Jan 2022 using MeSH terms and the systematic review in done according to prisma guidelines.

Results: There were 375 articles found after the search. After being chosen based on the qualifying criteria, 15 papers were included (eight retrospective, one prospective, and six case series), totaling 1339 patients, 3748 implants implanted, 152 implant losses, and 78 BRONJ instances.

Conclusion: Because there are few randomized clinical trials on this topic, more research with longer follow-up is needed to answer the remaining concerns. Because of the risk of developing BRONJ and implant failure in patients receiving bisphosphonate medication, it is prudent to exercise caution when considering dental implant surgery in these individuals. Furthermore, when such treatments are conducted, the patient's entire systemic state must be taken into account.

Introduction

Bisphosphonates (BPs) are pyrophosphate analogues that have a strong affinity for hydroxyapatite in the bone. They play a key role in skeletal diseases with increased or unbalanced bone remodeling rates due to their pharmacological actions on the bone (1). They are considered useful medications in the treatment of diseases that impact bone metabolism and are characterized by increased resorption, such as osteoporosis, Paget's disease, malignancy-induced hypercalcemia, multiple myeloma, and prostate, lung, and breast cancer bone metastasis (2,3).

These drugs are classified as first-generation non-nitrogen-containing (clodronate, etidronate, and tiludronate) and second and third-generation nitrogen-containing (alendronate, risedronate, ibandronate, and zoledronate), with the latter differing from the others in that it binds more tightly to the hydroxyapatite mineral in bone (1). The method

of administration has an impact on the medication's skeletal uptake. Oral bisphosphonates are poorly absorbed and have less than 1% bioavailability, but intravenous bisphosphonates have 100% bioavailability (1). Alendronate, risedronate, etidronate, and tiludronate are examples of oral bisphosphonates. Pamidronate and zoledronate are exclusively given intravenously, but ibandronate and clodronate are given both ways (4).

Bisphosphonate Related Osteonecrosis of the Jaws is one of the most devastating side effects of BP treatment (BRONJ). The American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed a nomenclature change from BRONJ to Medication Related Osteonecrosis of the Jaw (MRONJ) in 2014 due to an increase in the number of cases of osteonecrosis in the jaws associated with other antiresorptive and antiangiogenic therapies (5).

Bisphosphonate-induced osteonecrosis is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks in patients who have received current or previous antiresorptive or antiangiogenic agents and no history of radiation therapy to the jaws or metastatic disease to the jaws (5). The mandible and maxilla are bones that are exposed to the outside world through the teeth. The first occurrences of BRONJ were most likely linked to recent tooth extraction surgery or another disease that raises bone turnover requirement (6). As a result, there is debate about whether placing implants in individuals taking bisphosphonates for bone problems is safe.

The goal of this study was to look at studies that looked at patients who were on bisphosphonate medication and had dental implants before, during, or after the BP treatment. The outcomes identified were probable implant failures and loss, as well as the incidence of Bisphosphonate Related Osteonecrosis of the Jaws, when compared to healthy individuals who were not on BP medication.

Materials and methods

Search Engine Optimization

Articles published up until 2022, were electronically searched in the PubMed-Medline database of the United States National Library of Medicine, National Institutes of Health, Bethesda, Maryland. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline (7). In our study, the clinical question was written in the "PICO" style (P = patient issue / population, I = intervention, C = comparison, and O = outcome):

Do dental implants placed in bisphosphonate-treated patients increase the risk of implant failure and loss, or of bisphosphonate-related osteonecrosis of the jaw, as compared to healthy individuals?

The MeSH (Medical Subjects Headings) terms "Diphosphonates", "Dental Implants", "Guided Tissue Regeneration", "Guided Tissue Regeneration, Periodontal", "Alveolar Bone Grafting", "Subgingival Curettage", "Gingivectomy", "Bisphosphonate-Associated Osteonecrosis of the Jaw", "Bisphosphonate-Associated Osteonecrosis of the Jaw", "B In addition, each of the researchers conducted a manual search.

Exclusion and inclusion criteria were defined prior to the commencement of the study:

EXCLUSION CRITERIA:

a)- Articles published in a language other than English or Portuguese;

b) experimental laboratory research;

c) animal studies;

d) studies in which the major theme was not the relationship between dental implants and systemic bisphosphonate treatment

(e) full text publications were not accessible on the database searched;

(f) systematic reviews;

(g) topical administration route of bisphosphonates;

(h) full text articles were not available on the database searched;

(i) individual case reports; I duplicated articles;

(j) letters to the editor;

(k) commentary

INCLUSION CRITERIA:

(a) Patients receiving bisphosphonate medication (oral and intravenous) and having a dental implant operation;

(b) case series;

(c) retrospective studies;

(d) prospective studies.

Results

A total of 375 items were found after the initial search. Following that, titles were examined, and only 152 abstracts were selected based on exclusion criteria. Following the evaluation of the available abstracts, 27 papers were read, two of which were omitted because they did not meet the inclusion criteria outlined below, and eight systematic reviews were utilized only as a research source. In the end, 17 pieces were selected.data extraction was assessed Three studies were eliminated after the final review because they did not focus on the association between dental implants and bisphosphonate therapy, or their sample recruited far more patients who were not on bisphosphonate medication than patients who were on bisphosphonate therapy. After a manual search, one additional item was found. Finally, this systematic review was constructed using data from 15 papers that met the inclusion criteria (Fig. 1).

Tables 1–2 show the following data: Author and year; patient group; patient age (years); risk factors; number of patients in the trial; number of implants implanted; number of implants lost; follow-up time (months); indication, kind of bisphosphonate used, and administration method; duration of BP therapyWith 3748 implants implanted (1330 in BP users and 2418 in control patients) and 152 implant losses (528 individuals with a history of BP use and 811 patients without a history of BP) (113 in BP users and 39 in control patients). The patients ranged in age from 17 to 91 years old, with the majority being female. The lesions were seen in the mandible (53 instances), maxilla (23 cases), and both jaws (2 cases). The bulk of lesions were found at the back of the body (63 cases). The duration of follow-up varied from one to 132 months.

Ten of the trials (alendronate, risedronate, ibandronate) were given orally (17,3,18,8-10,12-14,20), four were given both (alendronate, risedronate, pamidronate, zoledronate, and ibandronate) (11,19,15,21), and one was given intravenously (zoledronate) (16). Only two investigations (18,20) linked occurrences of osteonecrosis to the oral route of bisphosphonate treatment. On the other hand, incidences of osteonecrosis were found in one-hundred percent of investigations (11,19,15,21) involving the combination use of oral and intravenous BP. The length of BP treatment ranged from 3 to 192 months. The most prevalent reasons for BP usage were osteoporosis and malignant diseases.

Figure. 1. Prisma flow digram of the search process and results

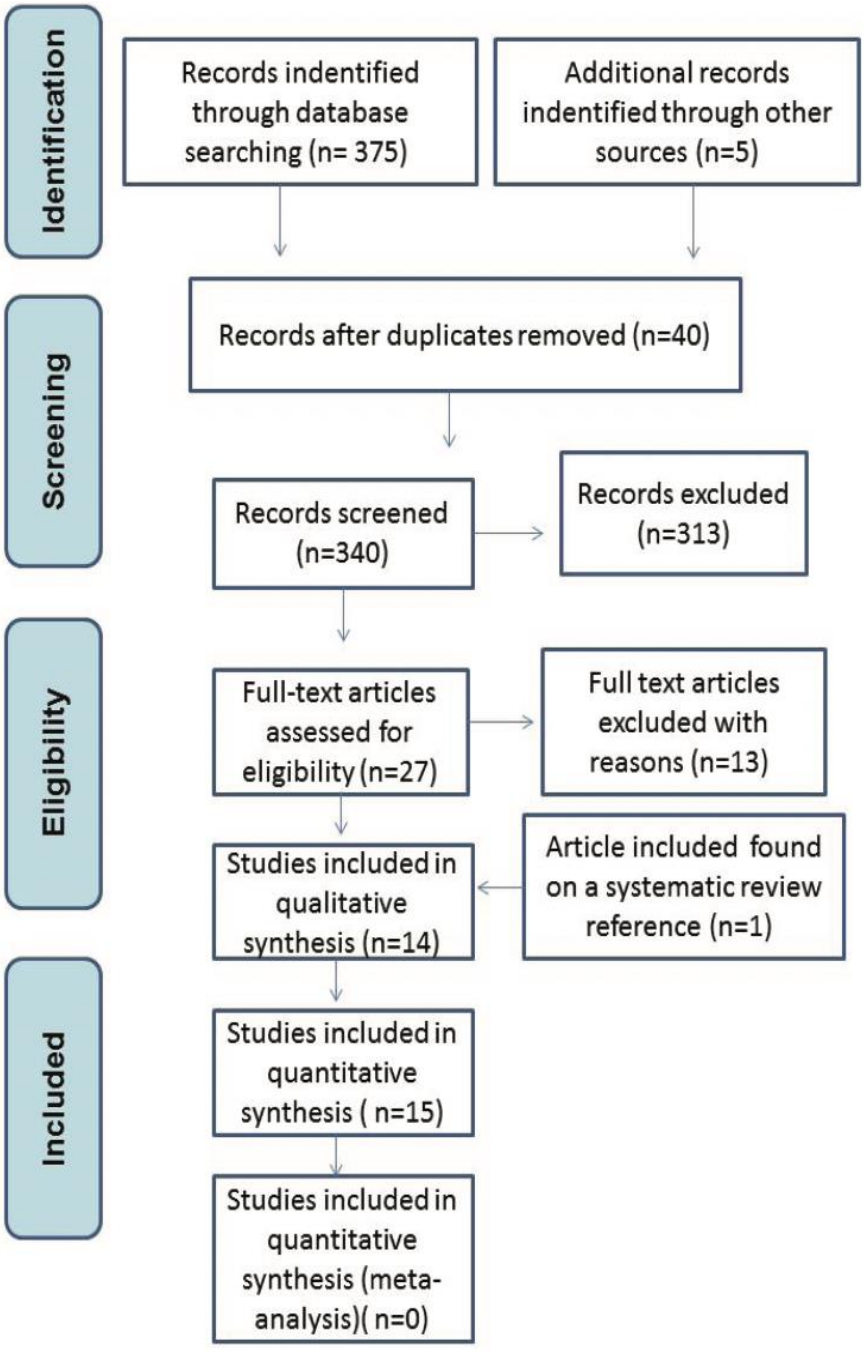

Table 1. Summary of the studies meeting the eligibility criteria

Author, year	Gender	Aver-age age or range (years)	Number of cases/ controls	Number of implants in BP users/ controls	Number of loss of implants	Risk factors	Follow-up (months)
Tam *et al.,* 2014	Female	71,8	6	19	10	Hyperten-sion, chemo-therapy	26 (mean)
Kwon *et al.,* 2014	17 Female 2 Male	42-85	19	NA	23	Hyperten-sion and diabetes	24
López-Cedrún *et al.,* 2013	8 Female 1 Male	66	9	57	12	Smoking, hypertension and steroids	3-36
Siebert *et al.,* 2013	Female	54	12/12	60/60	None	None	12
Jacobsen *et al.,* 2013	11 Female 3 Male	NA	12	23	12	NA	NA
Memon *et al.,* 2012	Female	46-91	100/100	153/132	10/6	Diabetes and smoking	NA
Zahid *et al.,* 2011	Female and Male	17-87	26/274	51/610	3/16	Smoking	26 (mean)
Koka *et al.,* 2010	Female	> 50	55/82	121/166	1/3	Steroids, diabetes and smoking	18
Lazarovici *et al.,* 2010	20 Female 7 male	70	27	NA	NA	Smoking, diabetes and steroids	3-43
Martin *et al.,* 2010	Female	70.2	16	44	26	Smoking and steroids	1-132
Shabestari *et al.,* 2010	Female	53	21	46	None	None	50 (mean)
Goss *et al.,* 2010	5 Female 2 Male	65.7	7	19	9	Diabetes and steroids	NA
Grant *et al.,* 2008	Female	67,4	115/343	468/1450	2/14	Diabetes and steroids	48
Bell e Bell, 2008	95% Fe-male	NA	42	100	5	Smoking	37 (mean)
Fugazzotto *et al.,* 2007	Female	51-83	61	169	None	NA	12-24

Discussion

Given the widespread use of bisphosphonates for a variety of conditions, the widespread use of dental implants for the treatment of partial or complete edentulism, and the rising number of cases of bisphosphonate-related osteonecrosis of the jaw, it is critical to assess the relationship between these topics in order to determine the risks for osseointegration and BRONJ appearance. The development of osteonecrosis in association with dental implants, according to Holzinger et al. (23), might be a side effect of therapy with oral or intravenous BPs. The occurrence of BRONJ is increased after or throughout the course of BP medication. BPs may have a potentiating influence on peri-implantitis and implant loss, according to their findings. Javed and Almas (24) demonstrated this.In patients using oral and intravenous bisphosphonates, the rate of implant failure was low, and the researchers concluded that dental implants can osseointegrate and stay functionally stable in these individuals. On the other hand, Mnguez-Serra et al. (25) recommended that patients who have been receiving intravenous BPs avoid dental implant treatments. This is in line with the findings of the current study, which found that 100% of studies (11,19,15,21) involving the combined use of oral and intravenous BP showed instances of osteonecrosis. In the event of oral administration, extreme caution is essential, with certain methods being avoided or only mentioned when absolutely necessary. Bell and Bell (13) reported a 95% success rate in 100 dental implants placed in 42 patients who were taking oral bisphos- phonates and showed no symptoms of jaw osteonecrosis. As a result, they came to the conclusion that there is no link between oral BPs and implant failure. Bisphosphonates exposure and implant placement, according to other authors (3,8,9,10,14), have no effect on implant success and do not cause

osteonecrosis. Their follow-up, on the other hand, was brief. These findings are consistent with those seen in previous publications (24,26).

Yip et al. (27) found that women with implant failure were more likely than those without to disclose a history of oral bisphosphonate usage. These findings show that dental professionals should be aware of the increased risk of implant failure linked with the use of oral bisphosphonates in some patient groups. Their findings support the suggestion to discontinue oral bisphosphonate medication for 4-6 months before to implant installation and for many months thereafter in long-term oral bisphosphonate users in order to allow for bone remodeling recovery (28).

Lazarovici et al. (19) studied 27 individuals who developed BRONJ after receiving dental implants and found that it is a side effect of BPs therapy that manifests as a late consequence. They recommended that patients receiving dental implants who are on bisphosphonate therapy be followed for a long time, and that those who develop BRONJ as a result of their dental implants be treated with doxycycline 100 to 200 mg/d for a long time, with their dental implants being removed only if the antibiotic therapy fails to alleviate the signs and symptoms of BRONJ. The length of bisphosphonate therapy in trials with BRONJ patients ranged from 3 months to 120 months (with the longest being more than four years), therefore As a result, all of them have demonstrated long-term therapy. This information might be connected to the fact that, as Lazarovici et al. (19) have demonstrated, osteonecrosis is a late consequence, necessitating a longer follow-up time to detect late signs and symptoms.

According to the research examined, individuals who take oral bisphosphonates can undergo dental implant surgery as long as the risks are carefully recognised. Type of agent, dose, and duration of BP treatment (determinant); female gender, age greater than 65 years, comorbidities such as diabetes or obesity, tobacco abuse, concomitant treatment such as cortico-therapy, chemotherapy, immunosuppressive therapy, mandibular localization, posterior area, bone diseases such as exostosis, or tori, harboring a poorly fitted prosthesis (potentially aggravating); and perforated prosthesis (potentially aggrava (29).

The most prevalent risk factors observed among the individuals participating in the research were diabetes, chemotherapy, steroid usage, hypertension, and smoking behaviors. In comparison to traditional prosthetic appliances, implant supported dentures are excellent resources for rehabilitating edentulous areas; however, bone condition (quantity and quality) and healing capacity are factors that must be addressed because they can affect the success rate of dental implant procedures.

The majority of studies (18,11,19,15,21) with cases of osteonecrosis enrolled patients with underlying diseases such as malignant diseases, osteoarthritis, and polymyalgia rheumatica as an indication, whereas the majority (7,3,10,12,16) of studies without cases of osteonecrosis enrolled patients with only osteoporosis as an indication for BP therapy. This evidence implies that the patients' overall health may have played a role in the development of BRONJ.Some publications propose using the Telopeptide C ter- minal CTX Test to determine the risk of developing osteonecrosis of the jaws in bisphosphonate-treated patients by assessing a particular type I collagen crosslink peptide in bone (30,28). It is crucial to highlight, however, that contemporary recommendations do not consider such a procedure to be validated or recommended, and its usage is not recommended (29,5)

Individuals who have been taking oral BP for less than four years and have no risk factors, according to the AAOMS (5), do not require any changes to the surgical schedule. If dental implant surgery is being considered, informed consent should be given, outlining the possibility of long-term implant failure as well as the low chance of developing jaw osteonecrosis. Patients with this condition should have frequent dental checkups. Patients who have been using oral BP for less than four years and are simultaneously on corticosteroids or antiangiogenic medicines, as well as those who have been taking oral BP for more than four years with or without any concomitant medical therapy, may consider taking a drug holiday.

Dentoalveolar surgery is regarded as a high-risk factor for Medication-Related Jaw Osteonecrosis (MRONJ). It has been shown that tooth extraction is the triggering event in 52 to 61 percent of MRONJ patients (5). Above all, being aware of the significant destructive potential of osteonecrosis of the jaws is critical. Patients' faces can be severely deformed as a result of these lesions. Because the BRONJ generally entails debridement and excision of the afflicted region, it can cause substantial functional and cosmetic problems.

This research looked at 528 people who had previously used BP and had 1330 implants inserted in them. In BP users, there were 113 implant failures (8.49%) and 78 occurrences of osteonecrosis (14.77 percent). These findings demonstrate a significant rate of implant loss and, more importantly, a high rate of osteonecrosis. Given these findings, it is acceptable to use caution when planning implant surgery for individuals on bisphosphonates. Furthermore, perhaps health professionals should begin to recommend dental procedures such as dental prophylaxis, restorations, gingival curettage, root scaling, endodontic treatments, and extractions before patients begin bisphosphonate therapy in order to avoid invasive dental procedures during the BP treatment, similar to how it is done with patients who are taking statins.

The lack of a randomized clinical trial relating to the issue is the study's principal weakness, which reduces the degree of proof of the information acquired. Furthermore, due to the heterogeneity of the studies and their given data, a meta-analysis was not possible.

Table 2. Summary of the studies presenting data about bisphosphonate related osteonecrosis of the jaws (BRONJ)

Author, year	Number of cases/controls	Indication of Bisphosphonate use	Route of administration	Type of Bisphosphonate	Treatment duration (months)	Incidence of BRONJ (number of cases)	Location of BRONJ
Tam *et al.*, 2014	6	Osteoporosis, breast cancer and multiple myeloma	Oral, intravenous and both	Alendronate, zoledronate and ibandronate	18-72	6	Posterior mandible (3), anterior mandible (1) and posterior maxilla (2)
Kwon *et al.*, 2014	19	Osteoporosis and multiple myeloma	Oral and intravenous	Alendronate, risedronate, zoledronate, ibandronate, and pamidronate	60,5 (mean)	19	Posterior mandible (8), anterior mandible (1), posterior maxilla (8) and both posterior jaws (2)
López Cedrún *et al.*, 2013	9	Osteoporosis, osteoarthritis and polymyalgia rheumatica	Oral	Alendronate, risedronate and ibandronate	6-120	9	Posterior mandible (7) anterior mandible (1), and posterior maxilla (1)
Siebert *et al.*, 2013	12/12	Osteoporosis	Intravenous	Zoledronate	24-36	None	–
Jacobsen *et al.*, 2013	12	Osteoporosis, multiple myeloma, breast cancer, prostate cancer and lung cancer	Oral and intravenous	Alendronate, zoledronate, ibandronate, and pamidronate	38-50	12	Posterior mandible (5), anterior mandible (3) and posterior maxilla (4)
Memon *et al.*, 2012	100/100	Osteoporosis	Oral	Alendronate, risedronate and ibandronate	12-36	NA	NA
Zahid *et al.*, 2011	26/274	Osteoporosis	Oral	Alendronate	6-192	None	–
Koka *et al.*, 2010	55/82	Osteoporosis and osteopenia	Oral	Alendronate	36-60	None	–
Lazarovici *et al.*, 2010	27	Osteoporosis, multiple myeloma, breast cancer and prostate cancer	Oral and intravenous	Alendronate, zoledronate, and pamidronate	16,4-68	27	Posterior mandible (15), anterior mandible (5), posterior maxila (4) and anterior maxila (3)
Martin *et al.*, 2010	16	Osteoporosis	Oral	Alendronate	38 (mean)	None	–
Shabestari *et al.*, 2010	21	Osteoporosis	Oral	Alendronate	20,5 (mean)	None	–
Goss *et al.*, 2010	7	Osteoporosis	Oral	Alendronate and risedronate	3-120	5	Posterior mandible (3), anterior mandible (1), and posterior maxilla (1)
Grant *et al.*, 2008	115/343	NA	Oral	Alendronate, risedronate, and ibandronate	38 (mean)	None	–
Bell e Bell, 2008	42	NA	Oral	Alendronate, risedronate, and ibandronate	6-132	None	–
Fugazzotto *et al.*, 2007	61	Osteoporosis	Oral	Alendronate and risedronate	40	None	–

Conclusion

Given the limitations of this study, it's prudent to proceed with caution when considering dental implant surgery in bisphosphonate-treated patients.There is a chance of developing BRONJ, as well as implant failure or loss, and this risk is higher in individuals receiving intravenous bisphosphonate medication. The patient's whole medical history must be reviewed, and in the case of bisphosphonate therapy, the duration of treatment, as well as the method of administration, must be taken into account. Then, if possible, halt therapy in accordance with the AAOMS recommendation. Finally, more randomized clinical trials with a longer follow-up time are required because it is still unclear at what doses these drugs are hazardous to implant therapy.

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