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Review Article

Dental implants in breast cancer patients receiving bisphosphonate therapy

Mai Ashraf Talaat [1]*

[1] *Faculty of Dentistry, October University for Modern Sciences and Arts, 6th of October City, Cairo, Egypt*

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ABSTRACT

This review article aims to assess the success of dental implants in breast cancer patients receiving bisphosphonate therapy, and to evaluate the risk of developing bisphosphonate related osteonecrosis of the jaw following dental implant surgery.

Breast cancer patients undergoing bisphosphonate therapy may receive dental implants. However, the risk of developing BRONJ and implant failure is quite high. Risk factors such as the type of BP received, the route of administration, and the length of treatment prior to surgery should be considered.

1. Introduction

Breast cancer is the most prevalent cancer in the world and the commonest cause of cancer death among women. By the end of 2020, there were about 7.8 million women who got diagnosed with breast cancer in the past 5 years, according to the World Health Organization (WHO).

The American Cancer Society estimated that in the year 2022; about 287,850 new cases of invasive breast cancer will be diagnosed in the United States, and about 43,250 women will die from breast cancer. It is estimated that approximately 12.9% of women will be diagnosed with breast cancer at some point during their lifetime.[1] This type of cancer can also develop in males, however, it is relatively very rare as it accounts for less than 1% of all breast cancer.[2]

Breast cancer is a metastatic cancer which can commonly spread from its site of origin to distant organs such as the lung, liver, and brain, which mainly accounts for its morbidity and mortality.[3] The commonest site of metastasis for breast cancer is the bone, which leads to complications such as pain, spinal cord compression, pathologic fractures, and hypercalcemia of malignancy.[4] Unfortunately, cancer that has metastasized to the bones is incurable; nevertheless, treatment can slow its growth and reduce the pain to improve the quality of life.[5]

Aromatase, also known as estrogen synthase, is the enzyme responsible for estrogen biosynthesis. It is found in breast tissue, and intratumoral aromatase is the main source of local estrogen production in breast cancer tissues.[6] Aromatase inhibitors are a class of drugs developed to potently inhibit aromatase activity and also lower estrogen levels in plasma and tissue.[7] As a hormone therapy, aromatase Inhibitors (AIs) are effective in patients with Estrogen Receptor positive (ER+) breast cancer.[8] Even though, this endocrinal therapy improves survival in breast cancer, it has adverse effects on bone. Aromatase inhibitors are associated with accelerated bone loss and an elevated risk of osteoporotic fracture.[9,10]

For the previous mentioned reasons, Bisphosphonates, which inhibit osteoclast-mediated bone resorption, are drugs commonly used in patients suffering from breast cancer primarily to hinder skeletal-related events, reduce bone loss (osteoporosis), improve pain control, and enhance the quality of life.[11–13] Bisphosphonates were also linked to

* *Corresponding author*.
E-mail address: mai.ashraf71999@gmail.com (M. A. Talaat).

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a reduction in the risk of breast cancer events and improved breast cancer survival in women with early stage breast cancer, studies showed that they may directly inhibit breast cancer cell proliferation and metastasis.[11,14]

Breast cancer patients should have the right to a better quality of life, and one way of achieving this is through the insertion of successfully osseointegrated dental implant to rehabilitate and replace missing teeth.

2. Materials and Methods

A thorough search was conducted, with no time or language restriction, using: PubMed, PubMed Central, Web of Science and ResearchGate electronic databases. Medical Subject Headings (MeSH) terms such as "bisphosphonate", "dental implant", "bisphosphonate-related osteonecrosis of the jaw (BRONJ)", "osteonecrosis", "breast cancer, MRONJ", and their related entry terms were used.

Eligibility criteria included studies and clinical trials that evaluated the impact of bisphosphonates on dental implants.

3. Discussion

Bisphosphonates (BPs) are a class of drugs with potent anti-resorptive actions, commonly used for the treatment and management of skeletal and oncological diseases such as bone metastases, osteoporosis, multiple myeloma, low bone density, osteogenesis imperfect, Paget's disease and several childhood inherited disorders.[15,16]

The importance of bisphosphonates to breast cancer patients is not only limited to the treatment of bone metastasis. According to multiple studies, it was evident that potent nitrogen-containing bisphosphonates, such as zoledronic acid, have anti-tumor effects on breast cancer cells as it can inhibit angiogenesis, dissemination, and adhesion of tumor cells.[17–19]

However, a serious complication related to bisphosphonate therapy is necrosis of the jaw, also known as Bisphosphonate-related osteonecrosis of the jaw (BRONJ). BRONJ is defined as exposed necrotic bone or bone that can be probed through a fistula in the maxillofacial region persisting for at least 8 weeks in a patient currently or previously treated with bisphosphonates with no history of radiotherapy to the jaws.[20] In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) renamed the condition "medication-related osteonecrosis of the jaw" (MRONJ) instead of "bisphosphonate-related osteonecrosis of the jaw" (BRONJ) due to increasing number of patients with osteonecrosis of the jaw related to anti-resorptive and anti-angiogenic medications other than bisphosphonates.[21,22] Another adverse effect of bisphosphonate is suppression of bone turnover which leads to impaired healing.[23]

Due to the major side effects of bisphosphonates there is controversy whether it is safe to place implants in breast cancer patients receiving bisphosphonates.

The aim of this review article is to evaluate the success of dental implants in breast cancer patients treated with bisphosphonates according to multiple studies and case reports.

A case report[24] of a 52-year old female patient with a history of breast cancer with no recurrence or metastasis, suffered from second degree mobility of all the maxillary incisors and severe alveolar bone loss. The patient was on prophylactic infusions of zoledronate (Zometa 4 mg IV) twice -yearly for 2 years. Treatment procedures included atraumatic extraction of the maxillary incisors which was followed by immediate placement of a removable partial prosthesis to replace the extracted teeth, after six weeks from the extraction, 4 implants were inserted to replace the missing teeth. Six months later, the final prosthesis was placed. At 3 Years follow up, x-ray showed satisfactory osteointegration of the implants, there was no signs of local infection or bone resorption, the patient had no complains and was satisfied with the results.

Another case[25] of a 66-year old female patient with a history of breast cancer and bone metastasis, who had been receiving 4 mg intravenous zoledronate/monthly for 33 months. The patient was suffering from intraoral necrotic bone exposure related to 4 dental implants placed on the right anterior mandible accompanied with pain, purulence, and paresthesia of the right inferior alveolar nerve. (CT) showed mandibular osteolytic lesions involving the area of implants placement and the inferior alveolar nerve, resulting in paresthesia. The dental implants had been inserted more than 6 months before the start of BPs therapy, and radiologically seemed properly osteointegrated at the beginning of BPs administration, therefore indicating a non-implant surgery-triggered peri-implant medication-related osteonecrosis of the jaw (PI-MRONJ).

A case[26] was reported by the Oral and Maxillofacial Surgery clinic at Virgen de las Nieves University Hospital (Granada, Spain), the patient was a 62-year-old female suffering from an intraoral lesion of several months' evolution. She had a history of breast cancer that was previously treated. However, she suffered a relapse of the cancer and was also diagnosed with bone metastasis in the right supra-acetabular iliac blade, she received adjuvant drug treatment with intravenous zoledronic acid (1 dose per month for 14 months). The patient had received dental implants 2 years before starting her treatment with zoledronic acid, the implants were placed as follows: one implant at 24 which was missing, and two implants to replace teeth 14 and 16. The patient had been receiving treatment for peri-implantitis in the region of the implant at 24, before the intraoral lesion appeared. She had signs of discomfort in the left maxillary premolar region, few months later extraction of 25 was performed, which had signs of pain on percussion and associated pathology,

while the implant at 24 remained in place. Antibiotic treatment was later prescribed to the patient as the onset of osteonecrosis of the jaw was suspected. The symptoms persisted but with no signs of infection focus or evident bone necrosis, the peri-implantitis treatment was carried on. In less than 2 years later implant mobility at 24 was observed along with associated infection and bone necrosis. (CT) showed that necrosis extended from 21 to 25, with bone exposure being only in the area of 24. The patient also presented with intraoral fistula and pus discharge. The case was diagnosed as stage 3 bisphosphonate-related ONJ, which was confirmed by orthopantomograph and facial CT, and was treated by sub-total maxillectomy.

A case series[27] reported by the Department of Oral and Maxillofacial Surgery, College of Medicine at the University of Ulsan, Asan Medical Center in Seoul, Korea. Aimed to describe a series of cases of ONJ (osteonecrosis of the jaw) that may be related to dental implant placement in patients who had received nitrogen containing bisphosphonates taken orally or by injection, the case series included six female patients, one of which suffered from breast cancer (will be discussed in details). All of the patients selected had a history of bisphosphonate use. Overall results included: resection of necrotized bone, removal of dental implant, and primary closure were done to five patients, four patients showed uneventful healing. One patient suffered from recurrence at the maxilla and underwent further extraction and resection. One patient suffered from an exposure of the bone after implant insertion.

One of those patients was a 70-year-old female, with a history of breast cancer that was surgically resected, she also had spine metastases. The patient had received IV zolendronate (Zomecta) once a month for 1 year to prevent further bone metastasis. Due to lack of further cancer metastasis, three implants were placed for the patient. She came with signs of pain, bleeding, and swelling of the mandibular right quadrant after implants were placed. One month after insertion of the implants, one implant was removed due to swelling, pain, and mobility. Even after the implant was removed, the pain and bleeding did not resolve and the condition became worse. The treatment involved resection of the implant and the surrounding necrotic bone, sequestectomy and wide resection and application of Collagen and fibrin glue along with primary closure of the wound. No sign of recurrence was detected after a 36-month follow-up.

A review[28] of 25 cases was done by the Department of Oral and Maxillofacial Surgery, College of Medicine, University of Ulsan, Seoul, South Korea. The aim of the study was to report BRONJ in breast cancer patients with metastasis. The study included 25 female patients with an average age of 55.4 years, all of whom had received zolendronate as a treatment for bone metastasis. The patients were referred for jaw bone discomfort. When BRONJ was diagnosed, patients was suggested to stop administration of zolendronate, except for one patient who suffered from bone metastasis on mandible. The etiologies for BRONJ were stated as follows: tooth extraction in 19 patients (76%), dental implant in 2 (8%), endodontic treatment in 1 (4%), and spontaneously occurred in 3 patients (12%). The 2 cases of BRONJ that was triggered by dental implant had signs of pain, pus discharge, swelling and unhealing implantation site. The treatment of all 25 patients consisted of administration of antibiotics, chlorohexidine gargle, and analgesics at the time of initial visit, 21 (84%) patients received surgical treatment (with success in 18 patients), and the majority required sequestrectomy and saucerization. One of the two patients with dental implants underwent dental implant fixture removal. The study suggested that dental procedures should be avoided during BP therapy and bisphosphonate therapy should be delayed until all essential dental treatments are done, except in case of life-threatening hypercalcemia. According to this study dental extraction was the commonest cause for BRONJ initiation. In addition, BRONJ could also be triggered by other surgical procedures such as dental implant surgery and preprosthetic surgical treatment.

A study[29] was done at Tokyo Medical University, Japan to evaluate the status of dental implants in breast cancer patients receiving bisphosphonates. The study included 247 breast cancer patients given intravenous bisphosphonates. The BP treatment period was estimated to be 19.2 month on average. Risk evaluation was performed using the clinical data of 44 cases, and a case control study of the risk factors of the 44 patients was performed. The patients were divided into 2 categories: 6 patients with a dental implant and 38 without a dental implant. On the final evaluation 8 patients out of 247 patients received a diagnosis of BRONJ. Out of the 44 patients who received comprehensive oral examination, 6 had dental implants inserted. One out of these 6 patients developed BRONJ at the implant site, and in two patients it occurred at a distant site from the dental implants. It was concluded that dental implants which were inserted before the administration of bisphosphonates were not a risk factor for the development of osteonecrosis of the jaw in breast cancer patients.

A retrospective analysis[30] was conducted on 112 patients who were receiving or had previously received bisphosphonates, a total of 140 dental implants were inserted. The overall dental implant success rate was slightly above 92%, only 10 cases of implant failure occurred, the failure was only 7.1% which was comparable to the results found in patients who were not receiving BP therapy in previous studies. Eight of the dental implants that failed were seen in females and two were seen in males. However, implant failure occurred within 3 weeks of implant surgery in patients who were on bisphosphonates therapy for the

last 3 years prior to this analysis. It was concluded that no significant difference in terms of implant failure is seen in patients on bisphosphonates therapy compared with other patient who did not receive the medication. However, it is still doubtable in patients receiving BP therapy for more than 3 years, and other treatment options should be considered.

A review[31] of 115 cases was conducted by the Department of Oral and Maxillofacial Surgery, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA. The aim of the review was to evaluate the extent to which BRONJ has occurred in their dental implant patients and to determine the effect of bisphosphonate therapy on the success of the implants. The 115 cases were female patients over the age of 40 who had a history of receiving oral bisphosphonate therapy. A total of 468 implants were inserted for the 115 cases, and there were no signs or symptoms of BRONJ in any of the patients. Out of the 468 implants, all, except for 2 implants, osseointegrated fully and met criteria for establishing implant success, and the success rates in patients who had a history of receiving oral bisphosphonates were comparable to those not receiving oral bisphosphonates. According to this review oral bisphosphonates did not appear to significantly affect implant success.

A case report,[32] published by the Department of Oral and Maxillofacial Surgery and Periodontology, School of Dentistry of Riberao Preto, University of Sao Paulo, Sao Paulo, Brazil, of a 76-year-old white female suffering from recurrent episodes of acute pain in the left side of the mandible and a bad taste in her mouth. She had a history of breast cancer that was surgically removed along with sessions of chemotherapy and radiotherapy, the patient received 4 mg of intravenous zoledronic acid once a month for 6 years to prevent the occurrence of bone metastasis. One year after the start of the BP therapy the patient received 3 dental implants which were placed in the right posterior region of the mandible, however, they had to be removed due to the extreme mobility presented 1.5 years after the prosthetic rehabilitation.

Five years after the start of the BP therapy the patient underwent surgical procedure for the placement of 3 dental implants on the left posterior region of the mandible, few months later the patient came suffering from pain and a small discharging fistula was located where the implants were lost, she had spontaneous pain that increased with manipulation on the left side and a small area of bone exposure located between the cuspid and the adjacent implant. The implants were stable and there were no signs of mobility, hence, prosthetic rehabilitation was performed.

The pain around the implants elevated after the rehabilitation, and the prosthesis was removed after 2 months. The patient returned with severe pain related to the implant adjacent to the lower left cuspid and the area of bone exposure slightly increased along with a slight mobility of the implant and pain on manipulation. Four months after the implant was removed, the bone exposure increased and involved the remaining adjacent implant and the patient experienced recurrent episodes of acute spontaneous pain. The patient developed BRONJ, and treatment involved removal of the implants and the necrotic crestal bone.

4. Conclusion

It is possible for breast cancer patients undergoing bisphosphonate therapy to receive dental implants. However, it is quite precarious and the dentist should be well aware of the increased risk of developing BRONJ and implant failure. Cautions should be taken before, during and after the surgery and the complete systemic condition of the patient must be thoroughly evaluated.

Patients must be informed about the possibility of suffering a necrosis of the jaw bone and the risk of possible loss of the dental implant, and give their informed consent before the surgery.

The type of BP received might play a role in developing osteonecrosis of the jaw, as in most studies zoledronic acid has been strongly associated with BRONJ, in addition, the route of drug administration is thought to have an impact, the risk is lower in patients receiving orally administrated bisphosphonates. Period of BP administration is also considered a possible risk factor, in patients with a history of bisphosphonate treatment exceeding 3 years, alternate treatment options should be considered. Randomized controlled trials with long-term follow-up are relatively lacking, further prospective cohort studies are needed to draw more evidence based conclusions.

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6. Conflict of Interest

The author declares no conflict of interest.

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Author biography

Mai Ashraf Talaat, Teaching Assistant at Faculty of Dentistry, MSA University https://orcid.org/0000-0002-5586-7379

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