Bisphosphonates and Their Influence on the Implant Failure

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The use of bisphosphonate (BP) may impair the osseointegration. It is a class of drugs that are frequently selected when there is an alteration in the bone metabolism, which are utilized to prevent bone loss. It can be administered orally (e.g., daily, weekly, or monthly) for treatment of osteoporosis and Paget's disease, or intravenously (every 3 months or annually) to treat malignant skeletal oncological diseases.

Keywords: bisphosphonates ; dental implants ; osseointegration

1. BP Use and Dental Implants

BPs are prescribed in several pathologies, whether they affect the bone (osteoporosis, OI, Paget's disease) or in malignant pathologies (malignant hypercalcemia, bone metastases, lung and breast cancer, and MM), because they prevent bone resorption. Of the studies included in this systematic review, 44 patients had osteoporosis, 8 had MM, 10 had breast cancer, 2 had lung cancer, 1 had prostate cancer, 1 had Langerhans cell histiocytosis, and 1 had OI. The administration of BPs is more prevalent in patients with osteoporosis, since, as reported in the literature, this is one of the most common bone pathologies in developed countries and one which has the most indication for the prescription of these drugs due to the risk of occurrence of bone fractures [1].

Of all the studies included, the presence of patients undergoing therapy with second generation (Alendronate, Pamidronate) [2][3][4][5][6][7][8][9] and third generation BPs (Risedronate, Zoledronate and Ibandronate) [2][4][5][7][9][10][11][12][13] were greater than the use of first generation (Clodronate) [14]. The first generation seems to show a decreasing trend in use nowadays. On the other hand, the failure rate for osseointegration proved to be lower in patients who used therapy with second generation of BPs (about 37%) compared to patients who had therapy with first and third generations. Second generation BPs have been shown to be a well-tolerated drug, with low side effects. This fact has been shown through their growing use in recent years [15].

The interruption of therapy with BPs was a parameter with varied results in this systematic review, from patients who did not discontinue to patients who discontinued for 2, 3, or 6 months before surgery, with respective resumption for 1, 3, or 8 months after surgery. Tripodakis et al. [4] reported the case of two female patients, both in their seventh decade of life, who requested rehabilitation with implant placement. The patients were medicated with second and third generation BPs (Alendronate and Risedronate). After consultation with the attending physician, the patients discontinued BPs 3 months before and resumed 3 months after implant placement. They received antibiotic therapy after surgical interventions, and the treatment plan was completed uneventfully and without complications during a 2-year follow up. In another study, Flieger [3] reported the case of a female patient (56 years old), who intended to carry out the prosthetic reconstruction of the crown of two molars lost in the maxilla with the placement of two implants. She was medicated with Alendronate (a second-generation BP) for osteoporosis. There was no bone loss around both implants, and it was observed that the peri-implant soft tissue did not show any signs of inflammation. Bayani et al. [10] reported that the placement of dental implants in patients with MM undergoing therapy with third generation BPs (Zoledronate) can be performed. Therefore, a meticulous selection of cases, an adequate medical consultation, and a minimally invasive surgery should be considered.

Flieger [3], Yajima et al. [6], and Storelli et al. [8] recommended that patients (n = 13) not interrupt their therapy with BPs during implant placement surgery. Fliger [3] and Yajima et al. [6] obtained a low failure rate in the implant placement procedure of 0% and 12% respectively. On the contrary, Storelli et al. [8] had a complete failure rate (100%). Similarly, in the study carried out by Kwon et al. [5], a complete failure of implant placement was observed in patients who started therapy with BPs before implant placement surgery.

Otherwise, Bayani et al. [10] reported the discontinuation of BP therapy for6 months before surgery that was resumed therapy 8 months after surgery. The failure rate was 0%, and no complications were observed. The same happened with Tripodakis et al. [4] who interrupted therapy 3 months before the surgery and resumed it for 3 months after. After 17 implants were placed, none of them failed. Caicedo-Rubio et al. [12] discontinued the therapy 2 months before the surgery and resumed it 1 month later, and they also obtained 0% for implant failure rate. This fact suggests an association between discontinuing BP therapy with a low rate of dental implant failure (around 45%) than for non-interruption therapy (around 55%). These data may still be different depending on the involvement of risk factors. Moreover, the cumulative dose and duration of drug exposure, medical comorbidities (corticosteroids, diabetes, immunosuppressive conditions), and dental comorbidities (extractions, implant placement, invasive procedures, periodontal disease, trauma, infection) must be verified. In this way, all the most invasive dental procedures constitute a risk when we are facing patients who use BPs.

According to Holzinger et al. [2], the occurrence of complications seems to be delayed when dental implants are inserted before starting BP therapy. However, the incidence of complications seems to be higher when implants are placed after BP treatment or during its therapy. Thus, it is suggested as ideal to proceed with implant placement before initiating BPs therapy; once therapy is started, the risk becomes higher.

Specifically, for four studies without implant failure [3][4][10][12], all cases reported types of study that must be carefully interpreted, due to the low level of scientific weight, Bayani et al. [10] found excellent results after a 1-year follow up in a 54-year-old man patient with multiple myeloma (MM) who complained of difficulty in mastication and esthetical concern for his upper anterior teeth. He received a monthly infusion of 3.5 mg of the IV BP drug Zoledronate for a period of 22 months, which is considered a long period and a high-risk treatment. The other two studies, Flieger [3] and Tripodakis et al. [4], had 2-year follow up periods without complications and bone loss. Similar results were obtained by Caicedo-Rubio et al. [12], after 4-year follow up, which showed no evidence of pathology in the peri-implant tissues.

2. Dental Implants Characteristics

Flieger [3] performed a surgical procedure using two implants with widths of 3.45 mm and lengths of 10 mm at the tissue level. Bayani et al. [10] opted for the placement of a bone-level implant that was 3.6 mm in diameter and 10 mm in length. Tripodakis et al. [4] placed a total of 17 implants that were 13 mm long at the bone level. Caicedo-Rubio et al. [12] placed three implants of 3.75 × 10 mm and 3.75 × 11.5 mm at the subcrestal level; Junquera et al. [13] placed two subcrestal implants. All these implants showed a significantly acceptable success rate, except for the implants placed by Junquera et al. [13], which resulted in severe complications and implant failure due to the MRONJ. The literature showed in the Hammerle et al.'s study [16] that the placement of implants at the subcrestal level was not recommended for these types of patients, who can achieve greater marginal bone loss [17].

3. Implants Associated with Risk Factors

Implant placement can also be influenced by risk factors, local or systemic, which can lead to complications. This includes cases of smoker patients, patients with pathologies (diabetes), with poor oral hygiene, and with a history of recent stroke (first 6 months after the episode) [18]. According to several authors, the risk of implant failure is greater with the increase in the number of cigarettes smoked per day; therefore, this factor is considered a real risk factor for implant placement [2]. On the other hand, Caicedo-Rubio et al. [12] reported that smoker patients and those with poor oral hygiene had favorable results for the implants. These data must be carefully analyzed due to the reduced sample size present in the study. This fact has led researchers to exclude from their studies all smoker patients, patients with diabetes, those using steroids, or those with poor oral hygiene, precisely because of the higher implant failure risk [6].

In our study, we found a somewhat significant failure rate in the case of smoker patients (19%), patients who had diabetes (7%), hypertensive patients (8%), and those who had poor oral hygiene (2%). However, even though the patients did not present any risk factor, they had very similar failure rates to those with risk factors. In the case of diabetes mellitus, this was closely related to oral health. From the data available to date, it increases the susceptibility to infection and impairs the tissue healing. In addition, there is evidence that patients with diabetes are more likely to develop complications than patients without this pathology [5].

4. MRONJ and Route of Administration

Several studies have focused on the risk factors for MRONJ development with the treatment of IV BPs (nitrogenated) and performing tooth extractions (identified as important risk factors) [19]. There is scientific evidence showing that drugs

(Pamidronate and Zolendronate) whose route of administration is exclusively IV have been strongly associated with cases of MRONJ [7]. This can be explained because these drugs are more potent and have greater bioavailability due to the type of administration (IV).

For this purpose, Shirota et al. [9] described a case of a 54-year-old woman with gum ulceration, bone exposure, and intense spontaneous pain around implants. The patient in question had undergone IV therapy with BPs (Pamidronate and Zoledronate) for 2 years to treat bone metastases from breast cancer. The authors reported MRONJ related to BPs, with symptoms of necrotic bone for more than 8 weeks; the patient did not undergo radiotherapy in the maxillofacial area.

Drugs, such as Alendronate and Risedronate, are administered exclusively orally. It has been reported that these drugs are safer and have a lower risk of MRONJ [4]. This was observed in the Flieger's study [3] of a a 56-year-old woman who underwent rehabilitation of two missing molars in the maxilla. She was taking oral Alendronate and, during the time of osteoporosis treatment with Alendronate, there were no episodes of MRONJ.

Upon analyzing the studies included in this systematic review, it was not possible to be precise in presenting the failure rates for both routes of administration, due to the lack of data provided by the studies. Nevertheless, there was a consensus among authors that the IV route of administration results in a high number of failure cases. Thus, the oral route of administration still seems to be the safest route.

5. MRONJ and Implant Failure

MRONJ can be manifested through several signs and symptoms. Its development may present clinical manifestations such as the presence of pain, necrotic bone, bone exposure, the presence of purulent secretion, redness, abscess, swelling, paresthesia of the right inferior alveolar nerve, an ill-defined radiolucent area, bleeding upon probing, bone resorption around the implants, and the presence of mobility. These symptoms can persist for more than 8 weeks. It is a problem with a multifactorial origin; it is difficult to predict its occurrence.

Favia et al. [11] showed failure in four of the seven implants placed in the same patient that were related to the occurrence of MRONJ. In this case, the reported symptoms were essentially pain, the presence of purulent secretion, and paresthesia of the inferior alveolar nerve on the right side associated with an ill-defined radiolucent area that extended from the right posterior mandible to the opposite region of the premolar. These data were attributed to the patient's poor oral hygiene. As for the remaining implants that still showed acceptable osseointegration, it was not possible to conclude what would be the long-term prognosis, since the follow-up only occurred after 18 months.

Similar results happened with Junquera et al. [13]. The patient had two implants presenting features compatible with MRONJ (necrotic bone, left lower lip paresthesia, and purulent secretion in only one of the implants). Also, Shirota et al. [9] reported a case with three implants placed; two of them presented pain, bone exposure, redness, and swelling. On the other hand, we had cases, in this study, where there was complete failure of the implants, and all patients developed MRONJ. Kwon et al. [5] and Jacobsen et al. [7] obtained the same results from evaluating a total of 23 implants, which all failed with reports of necrotic bone exposure, purulent secretion, pain, abscess, paresthesia, fistula, and swelling for more than 8 weeks.

Storelli et al. [8] reported a case of MRONJ in a 77-year-old female patient. After receiving oral implant rehabilitation and an immediate-load fixed prosthesis in the maxilla, she began to report pain and purulent secretions, which were neglected by the responsible professional. She returned to see the same professional after another episode of acute pain. The fixed prosthesis was removed and exposure of necrotic bone around the implants was observed. In this case, all implants failed. The patient was submitted to surgery to remove necrotic bone blocks.

References

1. Serrano, A.J.; Begoña, L.; Anitua, E.; Cobos, R.; Orive, G. Systematic review and meta-analysis of the efficacy and safety of alendronate and zoledronate for the treatment of postmenopausal osteoporosis. Gynecol. Endocrinol. 2013, 29, 1005–1014.
2. Holzinger, D.; Seemann, R.; Matoni, N.; Ewers, R.; Millesi, W.; Wutzl, A. Effect of dental implants on bisphosphonate-related osteonecrosis of the jaws. J. Oral Maxillofac. Surg. 2014, 72, e1–e8.
3. Flieger, R. Bilateral bone ridge splitting in maxilla with immediate implant placement in a patient with osteoporosis: A clinical report with 2-year follow-up. Case Rep. Dent. 2019, 6, 1458571.

4. Tripodakis, A.P.; Kamperos, G.; Nikitakis, N.; Sklavounou-Andrikopoulou, A. Implant therapy on patients treated with oral bisphosphonates. J. Osseointegration 2012, 4, 9–14.
5. Kwon, T.G.; Lee, C.O.; Park, J.W.; Choi, S.Y.; Rijal, G.; Shin, H.I. Osteonecrosis associated with dental implants in patients undergoing bisphosphonate treatment. Clin. Oral Implants Res. 2014, 25, 632–640.
6. Yajima, N.; Munakata, M.; Fuchigami, K.; Sanda, M.; Kasugai, S. Influence of bisphosphonates on implant failure rates and characteristics of postmenopausal woman mandibular jawbone. J. Oral Implantol. 2017, 43, 345–349.
7. Jacobsen, C.; Metzler, P.; Rössle, M.; Obwegeser, J.; Zemann, W.; Grätz, K.W. Osteopathology induced by bisphosphonates and dental implants: Clinical observations. Clin. Oral Investig. 2013, 17, 167–175.
8. Storelli, S.; Storelli, S.; Palandrani, G.; Dondi, C.; Tagliatesta, L.; Rossi, A. Severe case of Osteonecrosis following implant placement in a patient in therapy with bisphosphonates: A case report. J. Oral Implantol. 2019, 45, 139–144.
9. Shirota, T.; Nakamura, A.; Matsui, Y.; Hatori, M.; Nakamura, M.; Shintani, S. Bisphosphonate-related osteonecrosis of the jaw around dental implants in the maxilla: Report of a case: Case Report. Clin. Oral Implants Res. 2009, 20, 1402–1408.
10. Bayani, M.; Anooshirvani, A.A.; Keivan, M.; Mohammad-Rabei, E. Dental implant in a multiple myeloma patient undergoing bisphosphonate therapy: A case report. Clin. Case Rep. 2019, 7, 1043–1048.
11. Favia, G.; Tempesta, A.; Limongelli, L.; Crincoli, V.; Piattelli, A.; Maiorano, E. Metastatic breast cancer in medication-related osteonecrosis around mandibular implants. Am. J. Case Rep. 2015, 16, 621–626.
12. Caicedo-Rubio, M.; Ferrés-Amat, E.; Ferrés-Padró, E. Implant-supported fixed prostheses in a Patient with Osteogenesis Imperfecta: A 4-year follow-up. J. Clin. Exp. Dent. 2017, 9, e1482–e1486.
13. Junquera, L.; Gallego, L.; Pelaz, A. Multiple Myeloma and Bisphosphonate-Related Osteonecrosis of the Mandible Associated with Dental Implants. Case Rep. Dent. 2011, 2011, 568246.
14. Favia, G.; Piattelli, A.; Sportelli, P.; Capodiferro, S.; Iezzi, G. Osteonecrosis of the Posterior Mandible after Implant Insertion: A Clinical and Histological Case Report. Clin. Implant Dent. Relat. Res. 2011, 13, 58–63.
15. Aghaloo, T.; Pi-Anfruns, J.; Moshaverinia, A.; Sim, D.; Grogan, T.; Hadaya, D. The Effects of Systemic Diseases and Medications on Implant Osseointegration: A Systematic Review. Int. J. Oral Maxillofac. Implants 2019, 34, s35–s49.
16. Hämmerle, C.H.; Brägger, U.; Bürgin, W.; Lang, N.P. The effect of subcrestal placement of the polished surface of ITI implants on marginal soft and hard tissues. Clin. Oral Implants Res. 1996, 7, 11–119.
17. Pellicer-Chover, H.; Peñarrocha-Diago, M.; Peñarrocha-Oltra, D.; Gomar-Vercher, S.; Agustín-Panadero, R.; Peñarrocha-Diago, M. Impact of crestal and subcrestal implant placement in peri-implant bone: A prospective comparative study. Med. Oral Patol. Oral Cir. Bucal 2016, 21, e103–e110.
18. Hwang, D.; Wang, H.L. Medical contraindications to implant therapy: Part I: Absolute contraindications. Implant Dent. 2006, 15, 353–360.
19. Gelazius, R.; Poskevicius, L.; Sakavicius, D.; Grimuta, V.; Juodzbalys, G. Dental Implant Placement in Patients on Bisphosphonate Therapy: A Systematic Review. J. Oral Maxillofac. Res. 2018, 9, e2.
