Oral Rehabilitation With Dental Implants and the Importance of a Preventive Evaluation for Osteonecrosis of the Jaws Associated With Medications

Gustavo Zanna Ferreira, DDS, MS[1*]
Amanda Bolognesi Bachesk, DDS[2]
Andressa Bolognesi Bachesk, DDS[3]
Gustavo Jacobucci Farah, DDS, PhD[3]
Liogi Iwaki Filho, DDS, PhD[3]
Rafael dos Santos Silva, DDS, PhD[4]
Rodrigo Lorenzi Poluha, DDS, MS[5]
Carolina Ferrairo Danieletto-Zanna, DDS, MS[1]
Eduardo Sanches Gonçales, DDS, PhD[6]

Osteonecrosis of the jaw is a possible oral complication resulting from antiresorptive therapies, such as bisphosphonates (Bfs). Although the etiology is not entirely clear, it has been shown to be dependent on several factors, with the traumatic stimulation caused by the placement of teeth implants indicated as one of the predisposing factors to this pathology. The indications and preventive methods for performing these procedures have been questioned, making it essential to determine the proper protocols. Thus, the present study aims to discuss the risks of the development of osteonecrosis in patients undergoing dental implant surgery who use Bfs as well as to discuss related local and systemic factors and possible methods for preventing this side effect. The study also aims to present a clinical case of an osteopenic patient who used Bfs and underwent rehabilitation through implants according to specific protocols, which resulted in successful treatment.

Key Words: bisphosphonates, implants, osteonecrosis, bone diseases

INTRODUCTION

Bisphosphonates (Bfs) are a group of drugs that are capable of modulating bone remodeling.[1] These are nonmetabolizable synthetic analogues of inorganic pyrophosphate, an endogenous substance that regulates bone mineralization.[2] These drugs can be administered orally or intravenously (IV). Enteral Bfs are indicated for the treatment of osteoporosis and osteopenia, in addition to less common conditions such as Paget disease and osteogenesis imperfecta. IV Bfs are primarily used to treat conditions related to cancer, including malignant hypercalcemia and osteolytic bone metastases, which are more common in breast, prostate, and lung cancer.[3,4] The most recent nitrogenated Bfs, called aminobisphosphonates, have great potency and better selectivity, with the most generally used orally being alendronate, risedronate, and ibandronate, whereas via IV, pamidronate and zoledronate are most common.[4] In the bloodstream, these medications rapidly distribute to the bone, exhibiting high affinity to hydroxyapatite crystals, and the plasma half-life may exceed 10 years.[1]

The mechanism of action of Bfs is not completely elucidated, but studies have indicated that it is mainly due to antiosteoclast activity,[1,2] altering the mechanisms of the bone tissue at the molecular, cellular, and tissue levels. At the tissue level, they act by reducing bone turnover and resorption.[2] At the cellular level, they disrupt the function of osteoclasts and inhibit their recruitment and activity. In addition, in molecular terms, they bind to surface receptors or intracellular enzymes, and because they are not metabolized, high concentrations are maintained in the bone for a long time, generally inhibiting bone resorption.[5] In addition, studies suggest that Bfs can have an anti-angiogenic effect.[1,5]

Bfs-induced osteonecrosis of the jaw was first described in 2003 by Marx.[3,6,7] The pathology was conceptualized by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2007, characterized by exposure of necrotic bone

[1] Oral and Maxilofacial Surgery of Bauru School of Dentistry – FOB/USP and Oral Surgery, UniCesumar, Maringá Paraná, Brazil.
[2] Private practice, Campo Mourão, Paraná, Brazil.
[3] Oral and Maxillofacial Surgery, Department of Dentistry, State University of Maringá, Brazil.
[4] Oral Rehabilitation, Department of Dentistry, State University of Maringá, Brazil
[5] Oral Rehabilitation of Bauru School of Dentistry, Maringá Paraná, Brazil.
[6] Oral and Maxillofacial Surgery of Bauru School of Dentistry – FOB/USP, Bauru São Paulo, Brazil.
* *Corresponding author*, e-mail: gustavozanna@hotmail.com
https://doi.org/10.1563/aaid-joi-D-19-00275

tissue in the maxilla or mandible for more than 8 weeks in patients who received bisphosphonate therapy and were not submitted to irradiation of the head and neck.[7,8] However, in 2014, the AAOMS special committee recommended a change in the nomenclature of osteonecrosis of the jaw related to Bfs, because of the increasing number of reports of cases of the disease involving other antiresorptive therapies, such as desonumab and other antiangiogenic medications.[4]

The etiopathogenesis of osteonecrosis has been reported as multifactorial and has not been fully elucidated. Studies indicate that the inhibitory effect of bone resorption and bone turnover, associated with the singularities of the maxillary bones, which are separated from the oral cavity by a thin mucosa and susceptible to frequent infections and traumas, are factors that imply the development of the disease.[1–4] Therefore, when an accumulation of Bfs capable of decreasing bone metabolism occurs, tissue repair following a trauma (induced or physiological) does not occur properly, leading to decreased blood flow, cellular necrosis, apoptosis, and, consequently, necrotic bone to the buccal area.[1,7] In addition, studies point to the role of bacterial infections in the development of the disease, having detected colonies of *Actinomyces*, *Staphylococcus aureus*, *Streptococcus sp*, and normal bacteria from the oral cavity flora in these lesions.[3,4]

Some predisposing factors to the development of osteonecrosis mentioned in the literature as the following: route, type of administration, and time of use of Bfs; concomitant use of other drugs, such as corticosteroids, chemotherapeutics, and antiangiogenic agents[3,4,6]; and underlying diseases such as diabetes, renal dysfunction,[7] and inflammatory rheumatic diseases.[9] Dental extraction is considered a local risk factor that most often precedes the development of osteonecrosis,[4,7,10,11] and the AAOMS committee considers that any procedure involving bone exposure and manipulation, including the installation of dental implants, has a risk comparable to that of a tooth extraction.[4] In this context, the present study aims to discuss the risks of the development of osteonecrosis in patients who use Bfs who are undergoing dental implant surgery as well as to describe a clinical case of an osteopenic patient: a Bfs user who was rehabilitated by means of implants, resulting in successful treatment.

Case Study

A 53-year-old female patient with leucoderma sought dental service for the installation of implants in edentulous areas (Figure 1). During anamnesis, she reported mild mitral valve stenosis and minimal aortic valve insufficiency and used atenolol 25 mg to treat this condition. In addition, she reported taking Rivotril 2.5 mg/m, 5 drops per night; vitamin D 7000 IU, 1 tablet per week; and a calcium supplement (Oscal D), 1 tablet daily.

When questioned about calcium supplementation, the patient reported having osteopenia and having used the medication for more than 3 years. While furthering the anamnesis, it was verified that the patient also used Bfs. She reported using Osteoblock (sodium risedronate) at a dosage of 1 tablet 35 mg, once a week for about 2 years, and currently used Osteotec (sodium ibandronate) at a dosage of 1 tablet 150 mg once a month. The patient was advised of the risks from osteonecrosis of the jaw using Bfs and agreed to undergo surgery by signing a free and informed consent form.

The orthopedic surgeon was informed of the case, and according to the drug holiday protocol, the use of Bfs was interrupted for a period of 3 months before and after the surgery, for a total 6-month break in medication use. Carboxyterminal telopeptide measurement of collagen type I (plasma CTX) was also required, with a result of 304 pg/mL. Medication prescription consisted of 1 tablet of Decadron 4 mg preoperatively and clindamycin 600 mg 1 hour before the procedure as well as a 7-day cycle of clindamycin 300 mg postoperatively. In addition, dipyrone sodium 500 mg was used for as analgesia.

The rehabilitation plan for the maxilla consisted of the installation of 2 implants in the region of elements 11 and 21 (Figure 2) and the confection of multiple prostheses, including the 4 incisors whereas for the mandible, the installation of 1 implant in the region of teeth 36 and 46 and the confection of a unitary prosthesis under them. The type of implants chosen were of the bone level tapered (BLT) type with SLActive surface Straumann. All had a diameter of 3.3 mm, and the length was 8 mm in region 46 and 10 mm in the other regions.

The prosthetic phase started 60 days after surgery. First, a provisional prosthesis was constructed, consisting of a multiple prosthesis encompassing elements 12 to 22 in the maxilla (Figure 3) and unitary prostheses corresponding to teeth 36 and 46 in the mandible. After 3 months, the definitive metaloceramic prostheses were made (Figure 4). The patient is currently in a 2-year follow-up, having presented peri-implant health and absence of necrosis on clinical and radiographic examinations (Figure 5), which demonstrates evidence of the success of the treatment (Figure 6).

Discussion

It is estimated that more than 190 million prescriptions for Bfs were made worldwide since 2011, with osteoporosis treatment being the most common indication. In this same period, approximately 95% of the reported cases of osteonecrosis were related to the use of high doses of IV Bfs and the other 5% in osteoporosis patients who received oral therapy.[4,11] For osteopenia and osteoporosis, oral Bfs are more commonly prescribed; however, an annual infusion of zolendronate and a parenteral formulation of Ibandronate administered every 3 months are also approved for this type of treatment.[4] Some studies have described that approximately 6-monthly doses of intravenous Bfs of zoledronic acid for the control of bone metastases are required for the patient to be at risk of developing osteonecrosis, whereas for oral Bfs such as alendronate, at least 3 years of use would be required.[7]

The incidence of osteonecrosis varies from 0.1% to 0.4% for patients receiving oral Bfs[4] and from 0.7% to 12% for IV administration,[7] whereas in cancer patients treated with IV Bfs, the authors pointed to a variation of 0.7% to 6.7%.[4] Therefore, it is evident that patients with IV use have a higher risk of developing the disease compared with oral drug users.[1,4,10,11]

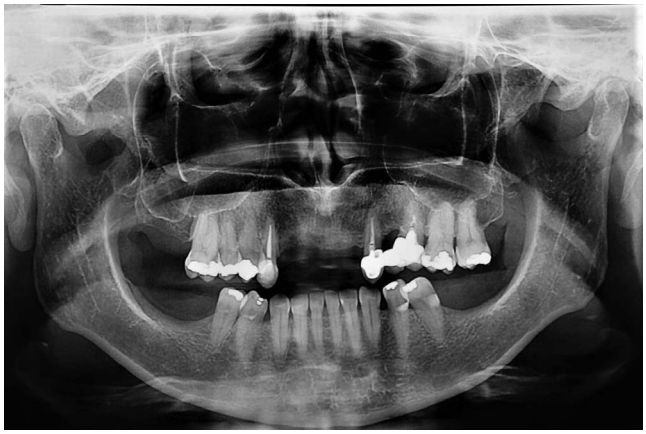


Figure 1. Initial panoramic radiograph of the patient.

The duration of therapy is also a factor that increases the risk of developing the disease,[9] increasing its prevalence over time, which becomes more evident after exceeding 4 years of medication use.[4] In addition, it is consistent that the concomitant use of other drugs, such as corticosteroids, potentiate this risk, as does the patient's age and his or her systemic condition.[1,6] Regarding local factors, dental extraction is exposed as the most common event preceding the development of osteonecrosis and is reported by up to 60% of patients. In addition, the mandible is described as the most affected region, comprising about 73% of the cases,[4] primarily in posterior regions.[6]

The oral rehabilitation of patients with unitary or multiple dental losses with implants is associated with high success rates. However, osteonecrosis of the jaw is a serious complication that can affect the survival of these implants.[12] Because of the generalized use of Bfs for various conditions and the high usage of dental implants for the treatment of partial or total edentulism, as well as the increase in the number of cases of drug-related osteonecrosis, it is important to evaluate the relationship between these topics to discover the risks for the osseointegration process and the appearance of osteonecrosis.[13]

The success of implant osseointegration includes 3 phases. The first phase involves the recruitment and migration of osteogenic cells on the surface of the implant. The second phase involves new bone formation at the junction of the preexisting bone and the implant. The third phase includes the phase of bone remodeling, which involves turnover itself. With the use of Bfs, there may be problems in the integration of the first phase or turnover of the third phase, increasing the potential for loss of osseointegration. In addition to this, there is a combination of the inhibition of endothelial keratinocytes, which results in a reduction in the healing capacity of the peri-implant tissues. Implantation failure is a multifactorial process, and repetitive failures have also been associated with individual susceptibility, suggesting associated genetic risk factors.[14]

In studies of large samples, research aimed at the analysis of implants installed in patients using oral Bfs, presented similar failure rates as in patients who did not use medication.[11] In one survey, 370 postmenopausal female patients >50 years of age were identified who underwent dental implant surgery, totaling 818 implants. The patients were divided into 2 groups: patients using Bfs for osteoporosis or osteopenia and non-Bfs users, resulting in 69 patients in the first group (with 148 implants) and 301 in the second group (610 implants). In both groups, the survival rate of the implants exceeded 98%.[15] Already, in a series of 119 cases of maxillary osteonecrosis, only 2.5% used Bfs for osteoporosis, and only 3.4% of the total cases were related to the installation of dental implants.[16]

In a systematic review, 1339 patients were analyzed, of which 528 had a history of Bfs use and 811 did not use the drug. With 3748 implants placed (1330 in Bfs users and 2418 in control patients), there were 152 implant losses (113 in Bfs patients and 39 in control patients) and 78 cases of osteonecrosis. However, among the cases of osteonecrosis, only 2 were related to oral use of Bfs. All other cases had associated or exclusive IV use, and many of these patients were undergoing treatment for malignant diseases.[13] Thus, the prevalence of osteonecrosis in osteoporotic patients who have taken oral Bfs is very low.[17] Therefore, the historic use of Bfs is not an absolute contraindication for the installation of dental implants.[18,19] However, the authors affirmed that it is essential to carry out an individual risk assessment by observing the patient's general health status.[13,17,18]

With regard to the duration of Bfs use, the authors of a systematic review concluded that the placements of implants can be considered safe in patients who have been taking Bfs for up to 5 years and that the intake of Bfs did not influence the survival rate of implants in the short term (1–4 years).[20] Our patient used the medication for approximately 3 years, which favored the decision to conduct the surgery. Many authors have reported discontinuation of Bfs treatment for surgical procedures as a preventive measure aimed at reducing the risk of osteonecrosis development.[2] However, this issue remains controversial, since there is no evidence that discontinuation of therapy alters the risk of developing the disease.[4]

In 2011, the American Dental Association's Council on Scientific Affairs reviewed its recommendations and suggested that patients taking Bfs for less than 2 years do not need to cease the medication. For patients with major cumulative exposure to the drug (ie, greater than 4 years), it is recommended, if systemic conditions allow, to interrupt therapy with Bfs from 2 months prior to surgery up to 3 months after the procedure.[4] Our patient had used the medication for more than 3 years, and therefore, we chose to orient suspension of the medication 3 months before and 3 months after surgery. Damm and Jones[21] defend the cessation of therapy based on bone physiology and pharmacokinetics of drugs. They observed that 50% of the drug undergoes renal excretion and accumulates mainly in the osteoclast, whose life span is 2 weeks. Thus, most of the free Bfs within the serum would be extremely low 2 months after the last dose of medication, reducing the risk of osteonecrosis.

Care must be taken when performing tooth extraction in patients receiving long-term oral Bfs therapy and in those with a high cumulative dosage despite a low daily dose. The results

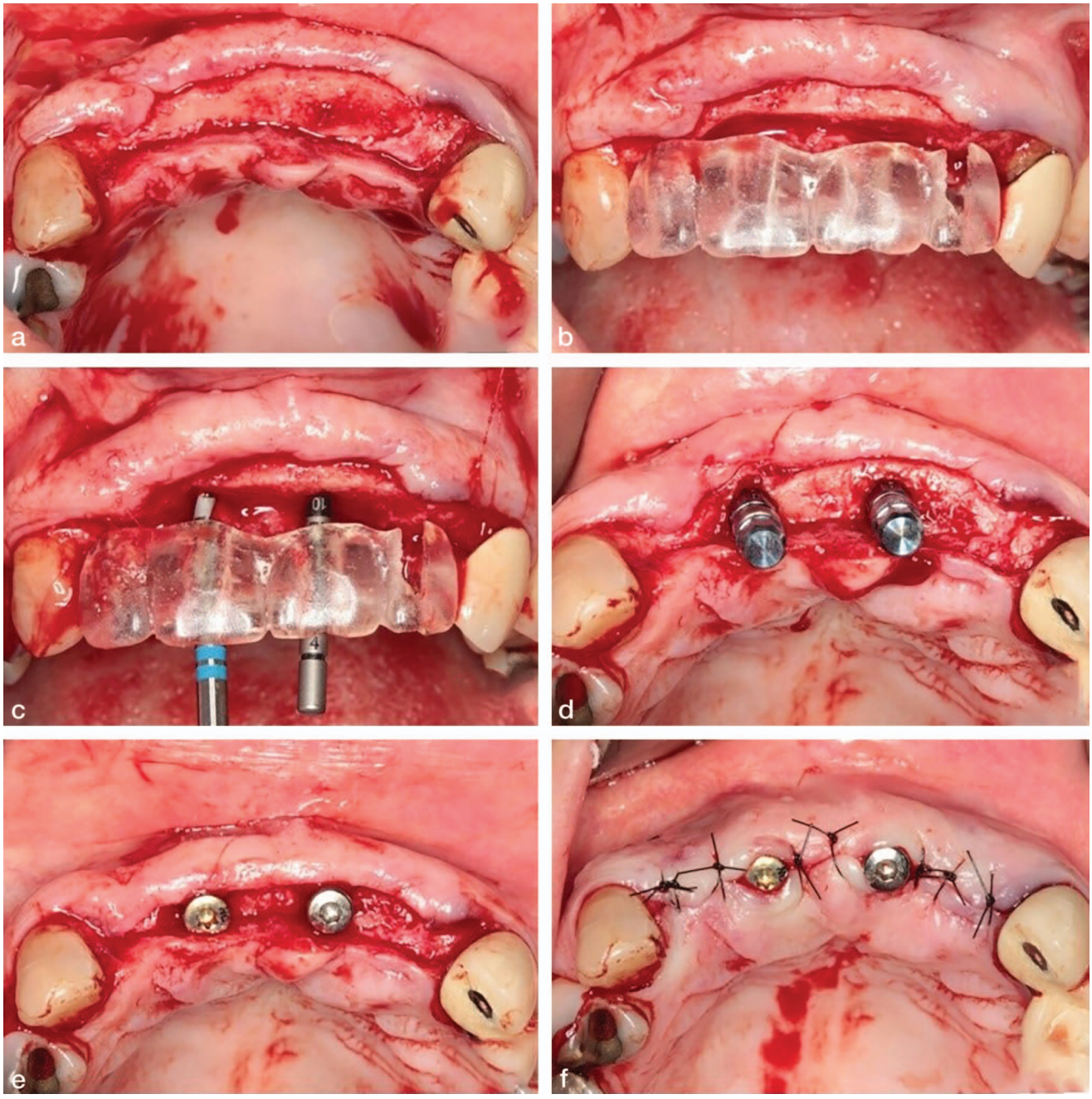
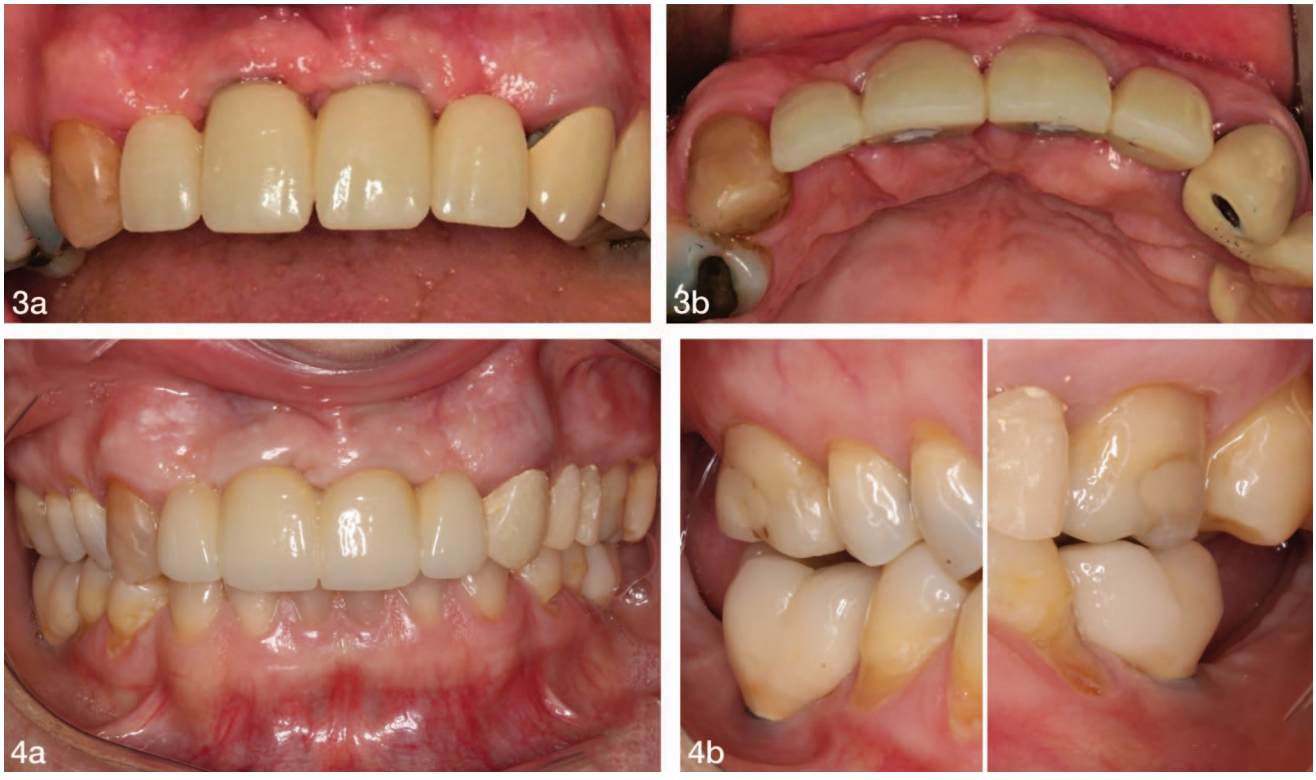


Figure 2. Installation of the implants in region of elements 11 and 21. (a) Incision and syndesmotomy. (b) Surgical guide test. (c) Installed implants observing parallelism. (d) Occlusal view of installed implants. (e) Installation of the cicatrizadores. (f) Suture.

suggest that the effect of Bfs administration for more than 5 years should be considered; this is also the time at which reassessment of oral Bfs administration is recommended.[22] Although it is uncertain how effective a short-term Bfs drug holiday would be considering bone physiology and the pharmacokinetics of Bfs, it may be valuable to consider a drug holiday in high-risk patients, such as those who have taken oral Bfs for more than 5 years.[23]

Another controversial measure is the use of CTX mensuration in the risk assessment for osteonecrosis. CTX is a serum marker of bone resorption that assesses the elimination of specific fragments produced by the hydrolysis of type I collagen[11] and is used to monitor bone resorption levels.[2] High values for this marker indicate active bone turnover.[7] Marx was among the first authors to defend the use of this test as a parameter to evaluate the risk of osteonecrosis.[10,16] CTX values less than 100 pg/mL indicate high risk, and discontinuation of Bfs treatment is recommended, with the test repeated after 3 months.[11,16] Values between 100 and 150 pg/mL indicate medium risk, and values greater than 150 pg/mL assume low



Figures 3 and 4. Figure 3. Provisional multiple prosthesis installed. (a) Front view of the prosthesis comprising elements 12, 11, 21, and 22. (b) Occlusal view of the prosthesis. **Figure 4.** Metaloceramics installed. (a) Region of 12, 11, 21, and 22. (b) Region of 36 and 46.

risk.[11] In the present case, the patient underwent the CTX test and was ascertained to have a low risk indicative for the surgery. However, some researchers did not find this correlation between CTX values and risk of osteonecrosis, so this test should not be used as a definitive indication for the risk of the disease.[3,24]

Studies have also indicated the presence of bacterial colonization in osteonecrosis lesions, especially *Actinomyces* and *Staphylococcus*.[4] In a study in rats, osteonecrosis was induced by 1 infusion of zoledronic acid per week for 4 weeks. One week after the final injection, infusions of saline solution, Freund's immune complement, or bacterium *Aggregatibacter actinomycetemcomitans* were performed in different groups. After a period of 4 weeks, the rats were euthanized, and the areas of osteonecrosis were measured histologically. The group injected with the bacterium presented larger and more significant areas of necrosis in both jaws.[25] Therefore, another preventive measure considered and defended by some authors is the use of antibiotic therapy in these patients, to reduce the risk of infection and contamination of the surgical wound.[19] Thus, we opted for a cycle of clindamycin 7 days before and after the surgical procedure, because of the greater bone perfusion that this medicine has.

The Straumann BLT type implant was chosen, with an SLActive surface, which, according to some studies, presents a faster osseointegration process compared with other implants[26] and thus favors a faster healing of bone around the implants, minimizing the risk of problems arising from osseointegration and consequently osteonecrosis around these implants. Therefore, all measures proposed in the literature were performed to minimize the risks of osteonecrosis development, resulting in a successful treatment.

Conclusion

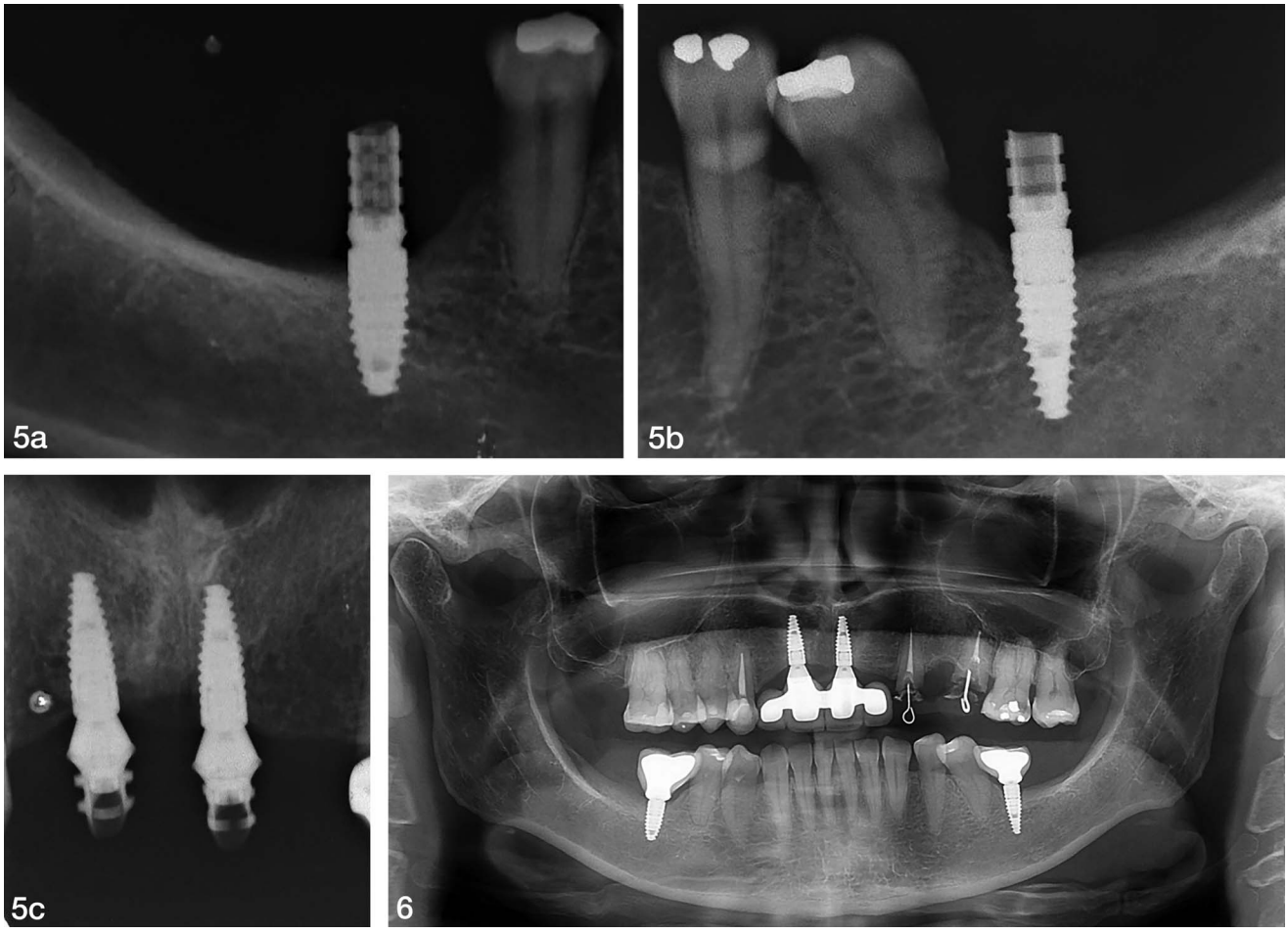
Bfs promote a clear risk of osteonecrosis development in the jaw. The duration of therapy and type and administration method of the Bfs are factors directly related to the onset of this pathology. Bone trauma through the installation of osseointegratable implants is a predisposing factor of the disease. Therefore, its indication must be carefully evaluated, and if this treatment is chosen, preventive measures should be taken, such as the interruption of the use of Bfs, antibiotic prophylaxis use prior to surgery, and adequate prosthetic rehabilitation.

Abbreviations

AAOMS: American Association of Oral and Maxillofacial Surgeons
Bfs: Bisphosphonates
BLT: bone level tapered implant
CTX: carboxyterminal telopeptide of collagen type I
IV: intravenously

Note

The authors declare no conflicts of interest.



Figures 5 and 6. Figure 5. Osseointegrated implants. (a) Region of 46. (b) Region of 36. (c) Region of 11 and 21. **Figure 6.** Panoramic radiograph of the patient in a 2-year follow-up.

References

1. Ruggiero SL, Woo S-B. Biophosphonate-related osteonecrosis of the jaws. *Dent Clin North Am*. 2008;52:111–128, ix.

2. George EL, Truesdell SL, Magyar AL, Saunders MM. The effects of mechanically loaded osteocytes and inflammation on bone remodeling in a bisphosphonate-induced environment. *Bone*. 2019;127:460–473.

3. Ata-Ali F, Ata-Ali J, Flichy-Fernandez AJ, Bagan JV. Osteonecrosis of the jaws in patients treated with bisphosphonates. *J Clin Exp Dent*. 2012;4: e60–e65.

4. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72: 1938–1956.

5. Son H-J, Kim J-W, Kim S-J. Pharmacoepidemiology and clinical characteristics of medication-related osteonecrosis of the jaw. *Maxillofac Plast Reconstr Surg*. 2019;41:26.

6. Granate-Marques A, Polis-Yanes C, Seminario-Amez M, Jane-Salas E, Lopez-Lopez J. Medication-related osteonecrosis of the jaw associated with implant and regenerative treatments: Systematic review. *Med Oral Patol Oral Cir Bucal*. 2019;24:e195–e203.

7. Gupta S, Gupta H, Mandhyan D, Srivastava S. Bisphophonates related osteonecrosis of the jaw. *Natl J Maxillofac Surg*. 2013;4:151–158.

8. Flichy-Fernandez AJ, Gonzalez-Lemonnier S, Balaguer-Martinez J, Penarrocha-Oltra D, Penarrocha-Diago MA, Bagan-Sebastian JV. Bone necrosis around dental implants: a patient treated with oral bisphosphonates, drug holiday and no risk according to serum CTX. *J Clin Exp Dent*. 2012;4:e82–e85.

9. Schwaneck EC, Streit A, Krone M, et al. Osteoporosis therapy in patients with inflammatory rheumatic diseases and osteonecrosis of the jaw. *Z Rheumatol*. 2020;79:03–209.

10. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003;61:1115–1117.

11. Paiva-Fonseca F, Santos-Silva A-R, Della-Coletta R, Vargas P-A, Lopes M-A. Alendronate-associated osteonecrosis of the jaws: a review of the main topics. *Med Oral Patol Oral Cir Bucal*. 2014;19:e106–e111.

12. Meira H, Rocha M, Noronha V, Aguiar E, Sousa A, Rodrigues Neto D. Mandibular osteonecrosis associated with bisphos-phonate use after implant placement: case report. *Dent Press Implantol*. 2013;7:107–114.

13. de-Freitas N-R, Lima L-B, de-Moura M-B, Veloso-Guedes C-C-F, Simamoto-Junior P-C, de-Magalhaes D. Bisphosphonate treatment and dental implants: a systematic review. *Med Oral Patol Oral Cir Bucal*. 2016;21: e644–e651.

14. Goss A, Bartold M, Sambrook P, Hawker P. The nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in dental implant patients: a South Australian case series. *J Oral Maxillofac Surg*. 2010; 68:337–343.

15. Koka S, Babu NMS, Norell A. Survival of dental implants in post-menopausal bisphosphonate users. *J Prosthodont Res*. 2010;54:108–111.

16. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg*. 2005;63:1567–1575.

17. Ata-Ali J, Ata-Ali F, Penarrocha-Oltra D, Galindo-Moreno P. What is the impact of bisphosphonate therapy upon dental implant survival? A systematic review and meta-analysis. *Clin Oral Implants Res*. 2016;27:e38–e46.

18. Chadha GK, Ahmadieh A, Kumar S, Sedghizadeh PP. Osseointegration of dental implants and osteonecrosis of the jaw in patients treated with bisphosphonate therapy: a systematic review. *J Oral Implantol*. 2013;39:510–520.

19. Walter C, Al-Nawas B, Wolff T, Schiegnitz E, Grotz KA. Dental implants in patients treated with antiresorptive medication: a systematic literature review. *Int J Implant Dent*. 2016;2:9.

20. Madrid C, Sanz M. What impact do systemically administrated bisphosphonates have on oral implant therapy? A systematic review. *Clin Oral Implants Res*. 2009;20(suppl 4):87–95.

21. Damm DD, Jones DM. Bisphosphonate-related osteonecrosis of the jaws: a potential alternative to drug holidays. *Gen Dent*. 2013;61:33–38.

22. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2016; 31:16–35.

23. Shudo A, Kishimoto H, Takaoka K, Noguchi K. Long-term oral bisphosphonates delay healing after tooth extraction: a single institutional prospective study. *Osteoporos Int*. 2018;29:2315–2321.

24. Dal Pra KJ, Lemos CAA, Okamoto R, Soubhia AMP, Pellizzer EP. Efficacy of the C-terminal telopeptide test in predicting the development of bisphosphonate-related osteonecrosis of the jaw: a systematic review. *Int J Oral Maxillofac Surg*. 2017;46:151–156.

25. Tsurushima H, Kokuryo S, Sakaguchi O, Tanaka J, Tominaga K. Bacterial promotion of bisphosphonate-induced osteonecrosis in Wistar rats. *Int J Oral Maxillofac Surg*. 2013;42:1481–1487.

26. Oates TW, Valderrama P, Bischof M, et al. Enhanced implant stability with a chemically modified SLA surface: a randomized pilot study. *Int J Oral Maxillofac Implants*. 2007;22:755–760.