



Spontaneous Bisphosphonate-related Osteonecrosis Associated with a Tooth that Had a Necrotic Pulp: A Case Report

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ABSTRACT

This study reports the endodontic treatment performed in a patient who presented with spontaneous bone exposure in the mandible while using intravenous bisphosphonate medication (Zometa[®], Novartis Pharmaceuticals Co., Basel, Switzerland). A 63-year-old female patient was referred to a private dental clinic at Fortaleza, Brazil. The patient reported that one year before, she had undergone chemotherapy for the treatment of lung cancer and associated bone metastasis. Among the medications administered was the zoledronic acid, with dosage of 4 mg every 21 days. In the oral exam, the presence of extensive bone exposure was observed in the lingual region near tooth 37. The patient reported severe pain on palpation in the region; in the pulpal sensitivity test with cold stimulus, there was an absence of pain, characteristic of pulp necrosis. Radiographically, no periapical lesion was observed. Thus, endodontic treatment was performed, and instrumentation with Reciproc R25 files in the mesial root canals and R40 in the distal canal was done, alongside with abundant 2.5% sodium hypochlorite irrigation. Interappointment medication with calcium hydroxide was maintained for 15 days. In the second session, there was the spontaneous detachment of the exposed cortical bone fragment. The root canals were filled with gutta-percha and Endosequence BC Sealer cement. After two years, complete tissue repair was observed, and the patient presented with normal periapical tissues and the tooth in masticatory function. It may be concluded that a possible relationship between pulp and periapical infections and osteonecrosis exists in patients who use bisphosphonates.

Keywords: Bisphosphonates; Bisphosphonate-related Osteonecrosis of the Jaw; Endodontic Treatment; Pulp Necrosis

Introduction

Bisphosphonates (BP) are widely used in various therapies related to metabolic bone diseases, such as osteoporosis, Paget's disease and bone metastasis. With the aging of the population, due to the increase in the survival rate, the number of patients diagnosed with cancer is also increasing and many of these diagnosed patients will be elderly with some bone disease, that is, the number of people who will use this type of medication during their lifetime will increase [1].

The BP act has an affinity for bone minerals and a bond with the hydroxyapatite resulting in a high concentration in areas of intense bone remodeling. They act in the osteoclastic differentiation reducing its activity and promoting its apoptosis [2, 3].

However, the BP present some adverse effects, being the main and most severe osteonecrosis in the jaw, usually named as bisphosphonate-related osteonecrosis of the jaw (BRONJ). BRONJ usually presents as an area of bone exposure associated with soft tissue edema, purulent exudate and dental mobility, in addition to severe pain [3].

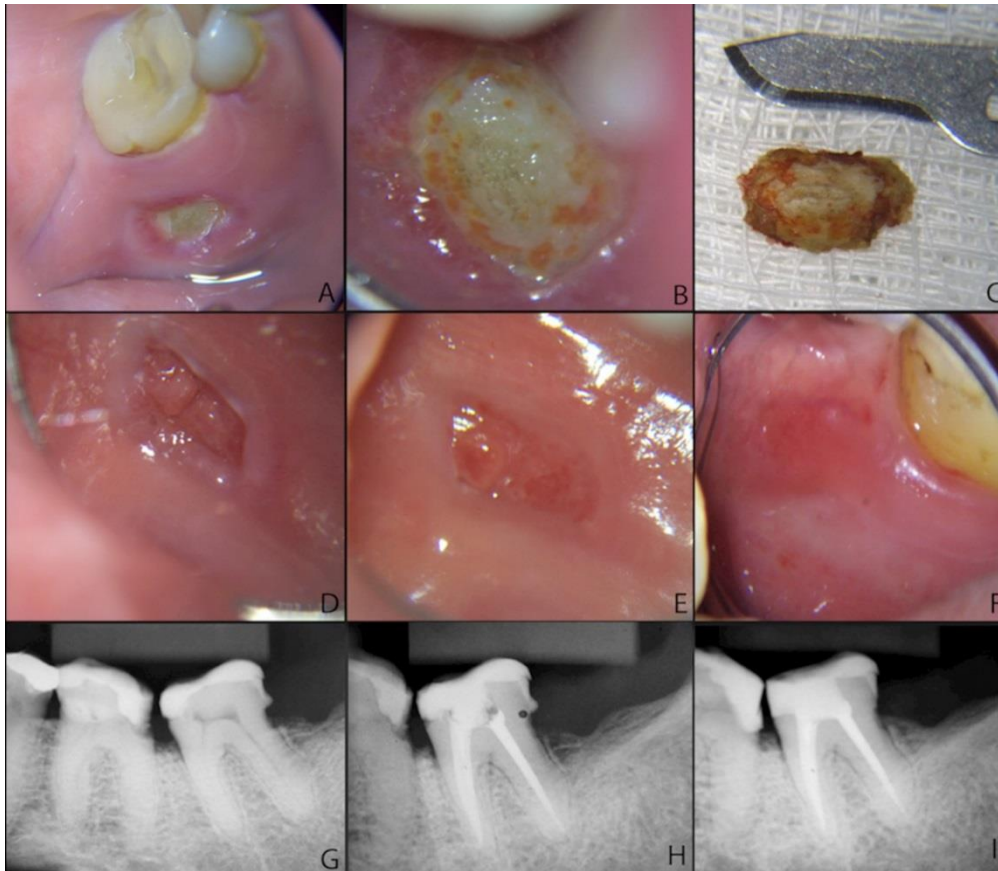


Figure 1. A) Clinical intra-oral examination, which evidences the presence of bone exposure in the lingual region adjacent to the tooth 37; B) Clinical appearance of exposed bone after 7 days of initiation of endodontic treatment and placement of intra-canal medication with calcium hydroxide, before bone removal is shown; C) Bone fragment removed; D, E and F) Clinical examination of the region after removal of the bone fragment, evidencing the repair process 14 days, 21 days, and 2-year of follow-up; G) Periapical radiograph before endodontic treatment; H) Immediately after endodontic treatment; I) After 2-year of follow-up showing normality of periapical tissues

Some dental procedures are considered risk factors for BRONJ, mainly surgical and invasive procedures; however, there have been cases that occurred spontaneously, and which have been reported [4, 5]. For widely deteriorated teeth, non-surgical endodontic treatment is still preferable to dental extraction, especially in patients reporting prolonged intravenous BP use [4, 5]. Ideally, all sites of infection should be treated prior to the BP therapy [5, 6].

Since apical periodontitis is a disease caused by pulpal necrosis, which is mainly related to bacterial colonization, endodontic treatment aims to control and prevent the spread of the infection to the periapical tissues. Some reports, however, show a possible relationship between non-surgical endodontic treatment and the development of BRONJ [5]. Currently, there is no scientific evidence on the correlation between pulp necrosis and BRONJ.

The purpose of the present study is to report a case of a patient who used BP and presented spontaneous bone exposure in the mandible and may be related to a pulp necrosis in tooth 37.

Case Description

A 63-year-old woman was referred to a private dental clinic at Fortaleza, Brazil, for evaluation and further endodontic treatment of the left mandibular second molar (tooth 37). In the medical history, the patient reported that began chemotherapy immediately after a lung cancer was diagnosed. After, the patient presented bone metastasis and a BP drug was added in chemotherapy. The medicines used at the moment of first appointment included disodium pemetrexed 500mg/m² (Atred 905mg) associated to 4 mg zoledronic acid (Zometa®, Novartis Pharmaceuticals Co., Basel, Switzerland) every 21 days, for 1-year. The last chemotherapy cycle was 6 months ago. The patient smoked no cigarettes nor consumed any alcohol.

In intraoral exam, it was observed a bone exposition in the lingual region next to tooth 37, measuring 3 cm approximately (Figure 1A). The patient reported that the bone exposition started 3 months ago and sensibility in tooth 37 was progressing

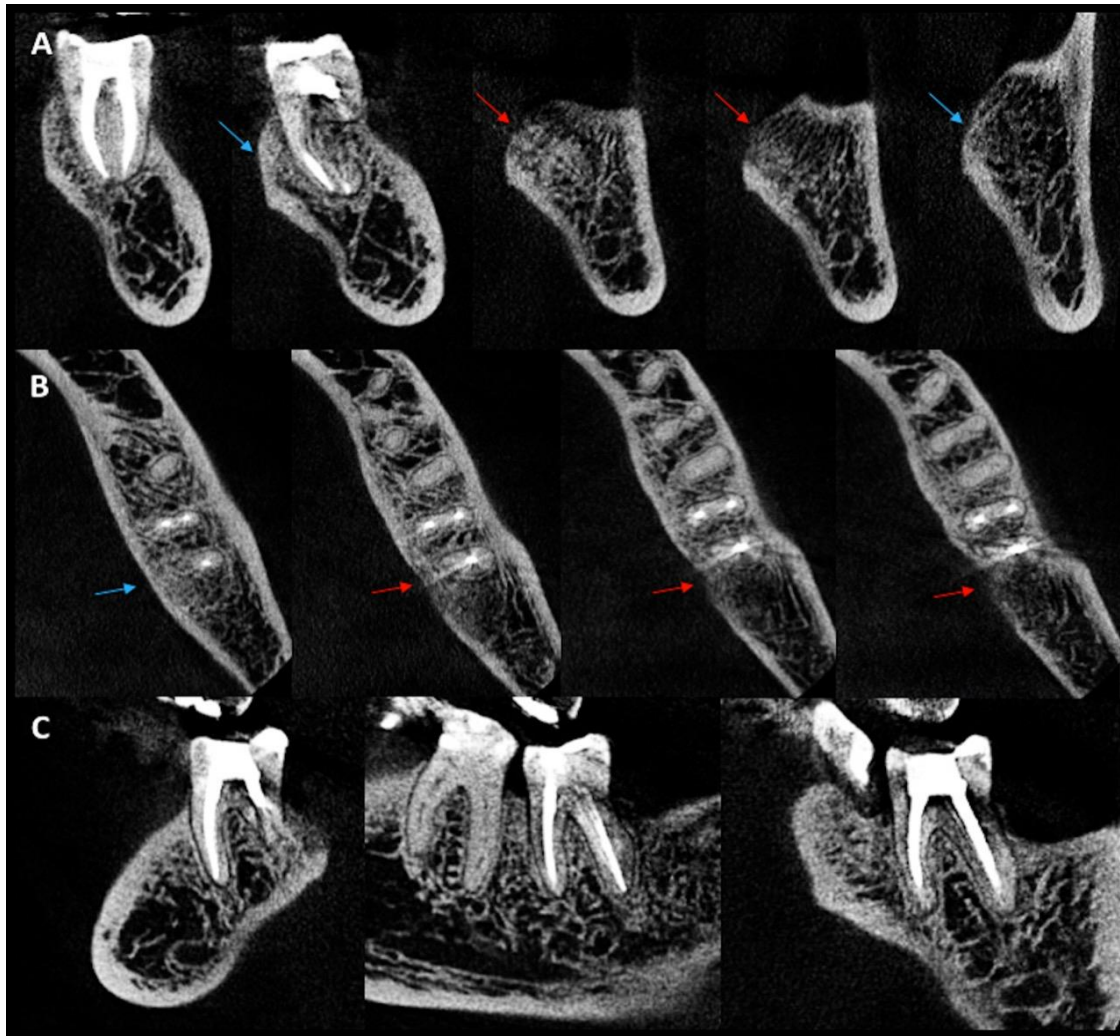


Figure 2. Cone beam computed tomography showing parasagittal (A) and axial (B) cross-sections exhibiting presence of cortical bone (blue arrows) and absence of cortical bone (red arrows). In sagittal cross-section (C), it may be observed the limits of working length, absence of overfilling and periapical tissues without evidences of resorption

slowly up to arising a strong pain. There was no intraoral or extra oral swelling, and tooth 37 reacted negatively pulp sensitivity when testing with cold. The patient reported apical sensibility during vertical, horizontal percussion and apical palpation. Periapical pocket was not observed around the tooth. A periapical radiograph showed a normal periapical condition, without evidence of apical periodontitis, resulting in an initial diagnosis of pulpal necrosis.

Firstly, the patient's physician was informed about the situation and recommended additional care during treatment, avoiding tooth extraction, if possible. An antibiotic prophylactic with 2 gr amoxicillin was also recommended 1-h before the appointments. The patient was consulted about the necessity of an endodontic treatment and she gave us informed consent with the proposed dental procedure to maintain the tooth.

The tooth was anesthetized with a local injection of 2% mepivacaine with epinephrine (1:100.000) and was isolated with rubber dam. Additional care was adopted to avoid damage to gingival tissue. The access cavity was prepared with a round diamond and 3083 burs (KG Sorensen, Cotia, Brazil). The canal was gently flushed with 20 mL of 2.5% sodium hypochlorite (NaOCl) solution. Using an electronic apex locator (Raypex 6; VDW, Munich, Germany), the working length was established 1 mm shorter than the apical foramen. The mesial root canals were instrumented with Reciproc R25 files (VDW, Munich, Germany) and the distal canal was prepared with Reciproc R40, associated to copious irrigating with 2.5% NaOCl. Special care was taken to avoid any instrumentation beyond the apical foramen. After complete root canal preparation, an intra-canal medication with calcium hydroxide was placed and kept for 15 days.

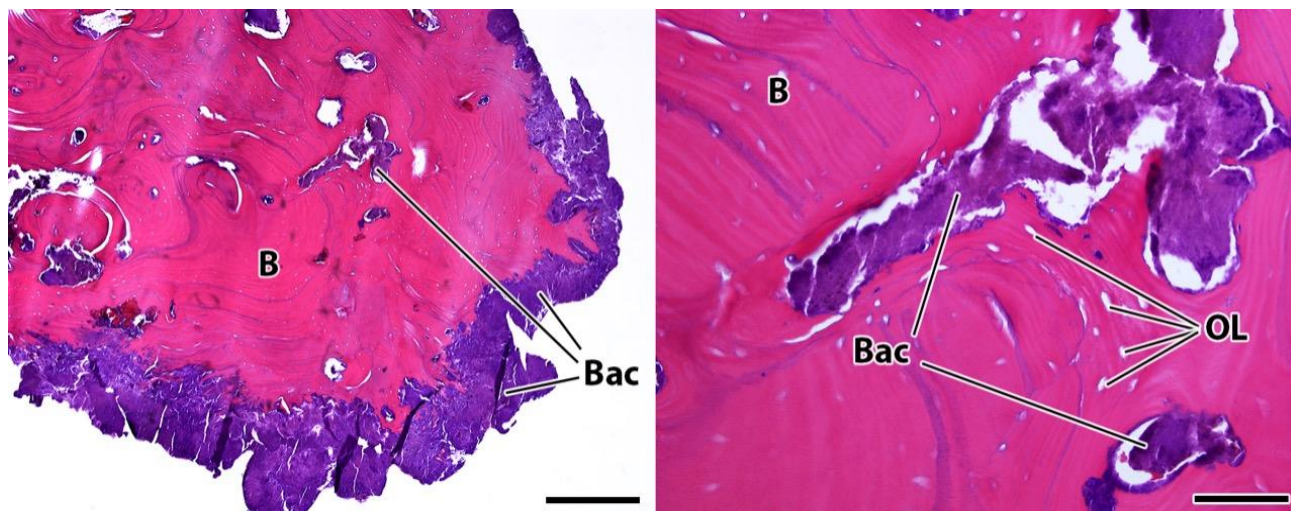


Figure 3. Histopathological analysis of necrotic bone fragment stained with hematoxylin and eosin (H & E). On the left, the bone matrix (B) is surrounded by a layer of amorphous material with apparent bacterial infection (Bac). Bar=500 μ m. On the right, a larger increase in the central portion of the necrotic bone shows empty osteocyte (OL) and infected amorphous (Bac) gaps inside a few bone cavities. Bar=100 μ m

In the second session, the intra-canal interappointment medication with calcium hydroxide was renewed to be kept for 15 days more. The patient reported improvement, but the region was much sensitive to palpation. It was observed that the exposed cortical bone presented spontaneous detachment (Figure 1B). The region was anesthetized with a local injection of 2% mepivacaine with epinephrine (1:100.000) and the bone fragment was carefully removed. The bone was inserted in 10% formalin to posterior laboratorial analysis (Figure 1C). The patient was informed about care with food and with local hygiene. After 15 days, the patient reported substantial decreasing of pain and the region presented a healing process (Figure 1D).

In the third session, the intra-canal interappointment medication with calcium hydroxide was removed with copious irrigation of saline and 17% ethylenediaminetetraacetic acid (EDTA), for 3 min saline was used to final rinse the root canals [7, 8]. The root canals were dried with sterilized paper points and obturation procedure was performed with gutta-percha cones adapted in working length associated to Endosequence BC Sealer (Brasseler USA, Savannah, USA) bioceramic endodontic sealer using the single cone obturation technique. The tooth was restored with nano-hybrid resin composite (Filtek Z550, Shade A1, 3M Espe, St. Paul, MN, USA) using two-step self-etching adhesive system (Clearfil SE Bond, Kuraray Inc, Tokyo, Japan) according to manufacturers' instructions. The evolution of soft tissue healing (14, 21 days and 2-year) is showed in Figures 1D-F. Figure 2 shows cross sections of a cone-beam computed tomography (CBCT) after endodontic treatment. It may be observed a losing of cortical bone after removal of necrotic bone fragment.

Later on, the exposed bone was processed according to standards for hematoxylin-eosin (HE) analysis and observed under optical microscopy (Figure 3). A histopathological analysis of the necrotic bone fragment stained with HE evidenced the presence of bone matrix surrounded by a layer of amorphous material with apparent bacterial infection and empty osteocyte gaps.

After a two-year follow-up, the patient reported no pain or sensibility in region, and the masticatory function was reestablished. In the periapical radiography, it was observed normality of periapical tissues (Figure 1I).

Discussion

The present case report demonstrates the treatment of BRONJ in a tooth with pulp necrosis at the adjacent site as one of the possible triggering factors. Despite the numerous publications on BRONJ, the risk factors are still unclear [6, 9] and, to date, there are no reports in the literature regarding endodontic treatments and the mechanisms that trigger BRONJ lesions.

The BRONJ is based on the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks in an individual treated or exposed to BP without a history of radiotherapy in the craniofacial region [5, 10]. In most patients, the main finding is the associated severe pain, even though in some patients the condition is asymptomatic. Imaging findings, although not specific, are important tools in the diagnosis, treatment and monitoring of cases [11, 12]. The clinical examination, along with the detailed information of the anamnesis, is undoubtedly very important. In the present case, the patient had not undergone any treatment with radiotherapy,

however had undergone chemotherapy with 4 mg zoledronic acid (Zometa®, Novartis Pharmaceuticals Co., Basel, Switzerland) 6 months before presenting spontaneous pain on the tooth 37, but she did not report pain in the region of the exposed bone. Radiographically, it was not possible to verify any bone changes. In addition, the patient in this case is no longer immunosuppressed due to myelosuppression generated by 500 mg/m² disodium pemetrexed, because the last cycle of chemotherapy was six months before endodontic treatment. Myelosuppression generated by 500mg/m² disodium pemetrexed only happens during the chemotherapy cycle, between the fifth and eighth day decrease, after infusion of the drug [13]. In order to avoid some local and systemic undesirable consequence, prophylactic antibiotic therapy is recommended during non-surgical treatment for patients at risk for BRONJ and with compromised immunity [14, 15].

The lesion was detected in the mandible in the region corresponding to element 37, which was coincidentally diagnosed with pulp necrosis. The mandible is the arch most affected by BRONJ, being about twice more affected than the maxilla. This factor is associated with greater BP accumulation in this region, due to the high rates of bone turnover, associated with the inability to repair structural micro damages [10, 16, 17].

Some reports show a possible relationship between non-surgical endodontic treatment and the development of BRONJ [18]. Regarding endodontic procedures, it is recommended to avoid surgical endodontic treatments, once that bone manipulation may result in osteonecrosis [5, 17-19]. With the result of this study, it is clear that non-surgical endodontic treatments should be favored in relation to the dental extraction in patients with a higher risk of BRONJ whenever possible [10, 17]. Non-surgical endodontic treatment aims to control and prevent the spread of infection to the periapical tissues. However, there is still no reliable scientific evidence on the risk/safety relationship in patients using BP.

Some procedures during non-surgical endodontic treatment may be able to initiate the pathophysiological process of BRONJ. Placement of the clamp during rubber dam, as soft tissue damage can be a trigger for BRONJ. One should try to be as cautious and atraumatic as possible by putting a rubber clip and dock [5, 18, 20]. Nase and Suzuki [21] reported a case where gingival correction without bone involvement before non-surgical endodontic treatment led to BRONJ in a patient receiving oral BP for five years. Thus, it seems prudent to avoid any damage to the gingival tissue during rubber dam. In the present case report, the tooth was anesthetized with local anesthetics containing vasoconstrictor and no local alteration was observed after 2-year

of follow-up. BRONJ results from abnormal bone turnover and healing after treatment rather than loss of vascularity, therefore the use of vasoconstrictors in local anesthetic should not be a concern [22-24]. The use of vasoconstrictor is still a controversy, although previous researches indicate the use of local anesthetics without vasoconstrictor [15]. Further studies should be performed to clarify this point.

Moreover, regardless of the technique or instrument used during root canal preparation, it is known that the extrusion of dentinal debris and bacteria beyond the apical foramen is unavoidable [25-28]. Although AlRahabi and Ghabbani [15] have no recommended reciprocating files, due the possible greater apical extrusion of dentine than rotary files, several previous researches [25-28] disagree with that information and support the use of reciprocating systems, as used in the present case report. Moreover, Reciproc files present an excellent efficacy to remove root canal bacteria and endotoxins [29, 30]. Calcium hydroxide medication was used interappointment to complement the decreasing of the endotoxins levels that could promote apical bone resorption and several systemic consequences [31, 32]. A specific situation in the present case report was that the patient presented difficult to keep with open mouth for a long time, needing of some appointments to finish the endodontic treatment.

We also observed the importance of using the electronic apex locators, in order to minimize the chances of an instrumentation beyond the apical foramen when compared to radiographic methods to determine the working length. Also, the use of a sensor or radiographic film can cause more damage to the soft and hard tissue of the area. Thus, we consider it safer to keep the working length 1-mm short of the apical foramen and without foraminal patency [5, 15]. In this way, a possible aggression to the adjacent bone would be avoided, which could result in a periapical osteonecrosis. In the same way, we also found it prudent to avoid extravasation any intra-canal medication with calcium hydroxide and endodontic cement, which could generate some unwanted reaction in the bone tissue [18, 33]. To remove calcium hydroxide medication, 17% EDTA was used to rinse the root canal [34], before root canal obturation. 17% EDTA may still optimize the removal of smear layer and improve the disinfection inside dentinal tubules, once that increases the dentin permeability [35, 36]. Bioceramic endodontic sealer was used due its suitable physical-chemical and biological properties [37, 38]. The single cone obturation technique was used because promotes a proper fill of root canal without additional damages to periapical tissues [39].

A recent clinical study observed that there was strong evidence of a relationship between the duration of zoledronic acid medication (less than 1-year) and the success in endodontic treatment. In the present case report, the patient was being treated with bisphosphonate therapy 6 months ago. Maybe this fact has contributed to the success [40].

Once that the occurrence of BRONJ has been reported as consequence of an oral trauma, the present work presented the first case reported of a spontaneous BRONJ associated tooth with necrotic pulp tissue. Even though there is no clear evidence that infection is a primary or secondary event in the pathophysiology of BRONJ [5, 10], bacterial species have been identified in the adjacent bone [41]. In the present study, bacterial colonies were observed in the exposed bone, which shows that some microorganisms already migrated beyond the apical foramen. So, oral infections could present some influence to induce the BRONJ. However, further studies are still necessary to verify the possible clinical association between BRONJ and pulpal necrosis.

The cure of BRONJ is not yet possible, which is why dental extractions are recommended before the start of cancer therapy. However, patients may have dental problems in progress during or after the course of treatment with BP drugs, in these cases consultation with patient's physician to need for antibiotic prophylaxis, change of anesthesia drug and more is necessary the choice of non-surgical procedures can greatly reduce the incidence and recurrence of BRONJ [2, 41]. In the present case, extraction of tooth in question could exacerbate the BRONJ process and the patient was informed about the risks.

Since dental extraction should be avoided as much as possible, endodontic treatment is an important therapy to be performed in order to keep the teeth in the mouth [16, 19, 20, 40]. In some cases, it is recommended to perform endodontic treatment, followed by crown amputation, leaving only the remaining root, mainly because the BP does not interfere with the apical repair process [1, 4, 10, 19, 21]. Thus, the endodontist needs to know how to properly treat patients who use bisphosphonate medications and to work often in a multidisciplinary team in order to avoid the onset of BRONJ [2, 9, 21]. In regard to the subject, there is a need for further clinical and laboratory studies to help establish a safe protocol for endodontic treatment in patients under continuous medication with bisphosphonates.

In patients under therapy with bisphosphonate, the endodontic treatment is an important alternative approach to avoid tooth extraction. The endodontic treatment should be performed with additional care to avoid tissue damages. BRONJ may occur even after stopping the use of bisphosphonate, since its half-life is long and individual, from months to years and may difficult the diagnosis and the treatment, consequently [42].

Conclusion

It may be concluded that there is a likely relationship between pulp and periapical infections and resulting osteonecrosis in patients who use bisphosphonates.

Conflict of Interest: 'None declared'.

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