Bisphosphonate-related osteonecrosis of the jaw

Drs Claudia Dib, Sara Salloum, Edgard Jabbour & Philippe Sleiman, Lebanon

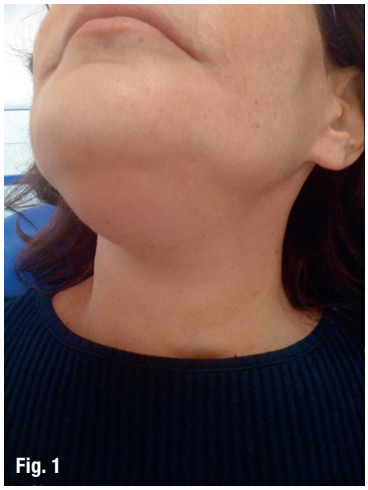


Fig. 1

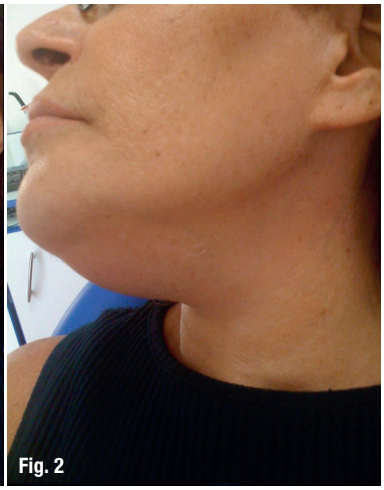


Fig. 2

Figs. 1 & 2: Swelling on the mandible.

Introduction

Bisphosphonates are a class of drugs that prevent the resorption of bone by osteoclasts.[1] These antiresorptive medications have become the principal mode of therapy for osteoporosis, Paget's disease of the bone, bone metastasis, breast cancer and other conditions that display bone fragility disease.[2–4] Their usage has continued to grow despite the concerns expressed recently regarding potential side effects, such as bisphosphonate-related osteonecrosis of the jaw (BRONJ).[5]

Apparently, a number of medical studies[6–8] have been recently published that document patients who developed osteonecrosis of the jaw after receiving bisphosphonate therapy.[9] At the moment, it is unpredictable whether this interconnection can be traced back to a coincidence or to the existence of a true causal relationship.[10] However, Marx et al. claimed in 2003 that bisphosphonates would lead to disrupted bone homeostasis by suppression of osteoclast function.[11] An accumulation of non-vital osteocytes and microfractures would be the effect of the disturbance of the normal bone remodelling.

However, it should be declared that BRONJ might be a persistent condition. As a matter of fact, withdrawal of bisphosphonate treatment would not decrease the risk rate of BRONJ, since the drugs may persist in the skeletal tissue for years. Several studies have highlighted that, if bisphosphonates were prescribed temporarily or interrupted for a specific reason (e.g. completed or discontinued the course or taking a drug break), the patient would have to be considered at risk. To clarify, BRONJ symptoms such as delayed healing after a dental extraction or other oral surgery, pain and soft-tissue infection may appear after dental treatment. Accordingly, any necessary dental treatment should be done under strict safety conditions.[12, 13]

Setting aside the spinous questions of the aetiological mechanisms of BRONJ and the extent of bisphosphonates' contribution to this process, it seems purposeful to reflect on recent clinical studies to seek the most effective treatment for BRONJ.

Case presentation

An oral oedema is considered to be the most common of symptoms caused by oral disease, and its cor-

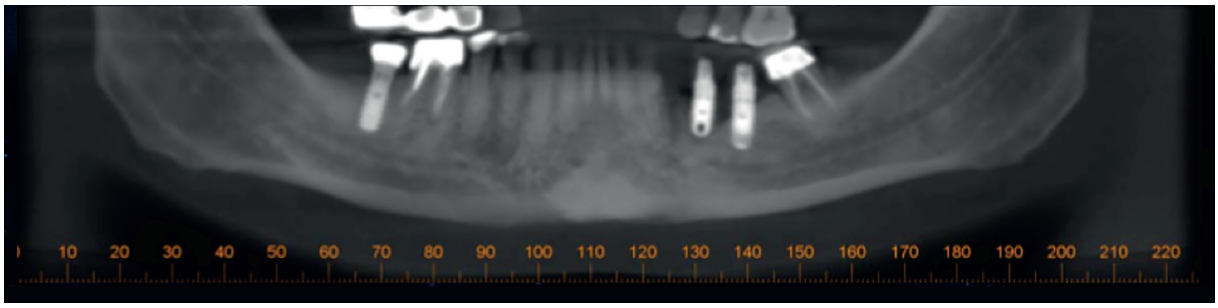


Fig. 3: Panoramic radiograph showing bone loss around the first implant.

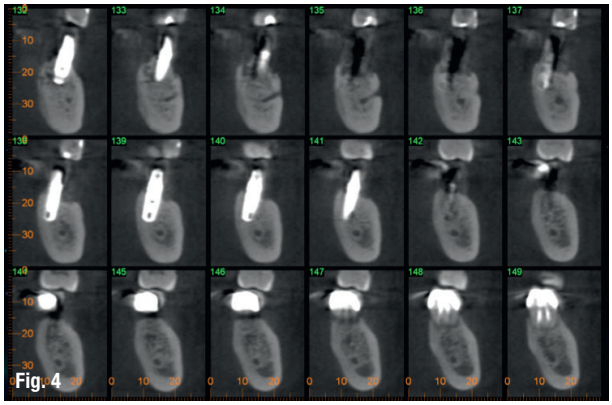


Fig. 4

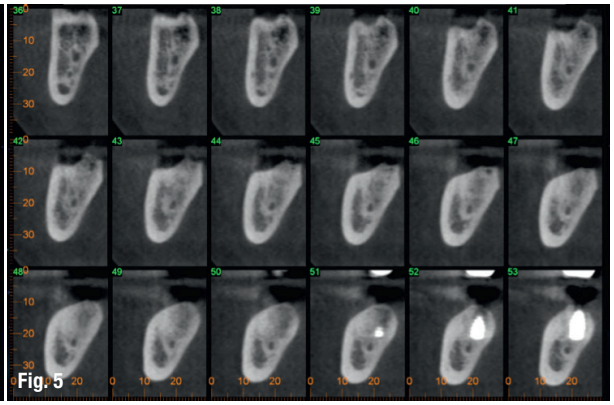


Fig. 5

Figs. 4 & 5: Damaged bone structure around the first implant was evident, but the bone surrounding the second implant seemed to be in good condition.

rect diagnosis and successful management is most challenging.[14]

A 55-year-old female patient presented to a dental clinic with no pre-existing oral disease for urgent care. An extra-oral examination showed one-sided facial swelling under the lower jaw that had followed implant placement (Figs. 1 & 2). The panoramic radiograph revealed an extensive osteolytic reaction surrounding the first implant on the left side (Fig. 3). Although the symptoms and the radiological signs from the examination could have indicated implant failure, a CT scan of the left part of the mandible was requested for better evaluation of the soft tissue and osseous involvement of the swelling. In addition, information gathered from the patient's medical history showed that she had been treated with bisphosphates. The cross sections of the scan exposed sclerotic lesions with cortical bone destruction. The necrosis of the bone with an open wound was determined from delineated focal lesions located at the first implant site (Figs. 4 & 5).[15] Therefore, BRONJ was diagnosed. A treatment plan detailed the therapeutic interventions.

The patient was put on antibiotic treatment, a combination of 1 g of amoxicillin and 500 mg of metronidazole twice daily for ten days with a chlorhexidine-based mouthwash. The symptoms cleared and the patient was kept under control without any additional dental work. During this time, a tiny piece of bone that was showing through the gingiva was delicately removed and sent to a pathology laboratory, and the results confirmed that it was bone necrosis. After three months, the patient showed the same signs of swelling and again she was prescribed the same antibiotics. During the AB cycle, the patient felt that the implant was becoming very loose, so removing the implant was the only solution, as it was floating and a scan was taken to check the progression. Several weeks later, a piece of bone where the implant had been become so loose that it could be removed with a pair of tweezers. At the same time, the patient was experiencing pain arising from the mandibular anterior teeth; two of them were confirmed necrotic, and root canal therapy was performed using TF Adaptive (Kerr Dental) and most importantly negative pressure (EndoVac, Kerr Dental) for chemical preparation, as any irritation to the apical area would have had poor consequences. Two months later, a fistula discharging green pus was found under the mandibular anterior teeth. Correspondingly, the patient was prescribed another cycle of antibiotics (clindamycin) for ten days, as well as instructed to use a chlorhexidine-based mouthwash for several weeks. The antibiotic treatment decision was taken in consultation with her physician. That was the last episode of swelling that the patient had. Two years later, when no more symptoms occurred, the patient requested some aesthetic work to be done, only if it was safe for her (Figs. 9–13).

It was explained to the patient that, owing to her stable condition and since aesthetic work would not require any surgery or procedure involving trauma to the bone, it could be performed with a very mild anaesthetic without vaso-constrictors as a safety precaution. Mouthwash was prescribed for several days prior to any dental work and after it. The patient was very happy to have her smile back finally (Fig. 14).

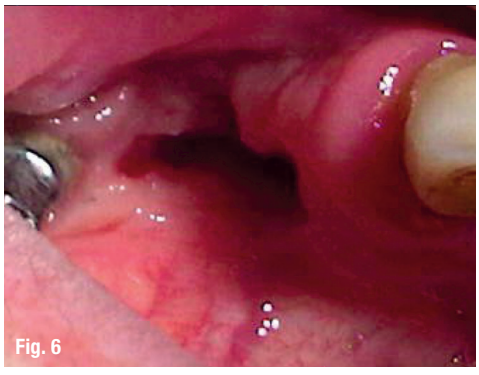


Fig. 6

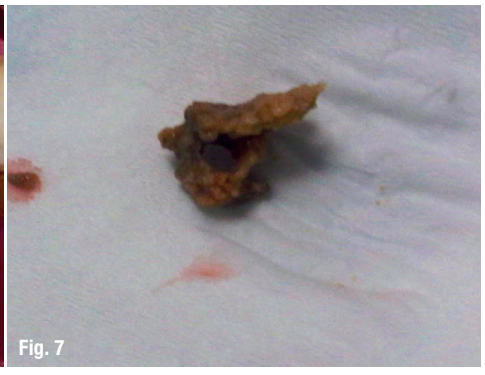


Fig. 7

Fig. 6: Clinical situation after the piece of bone come out. **Fig. 7:** The piece of bone sent for histopathologic examination.

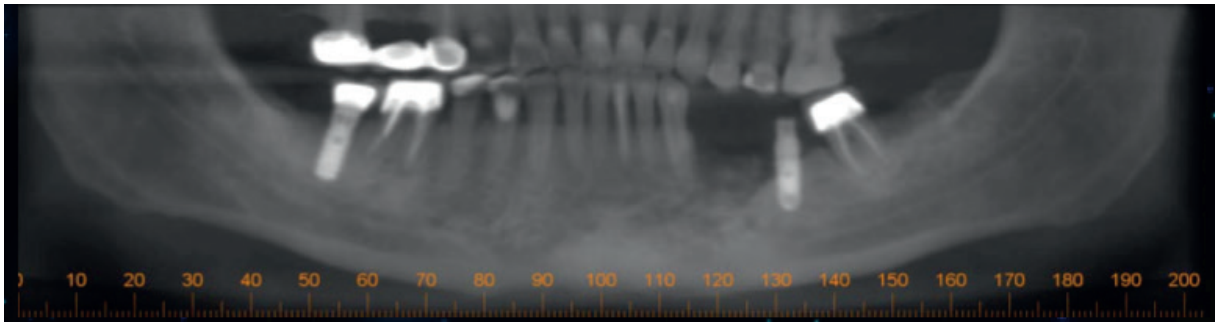
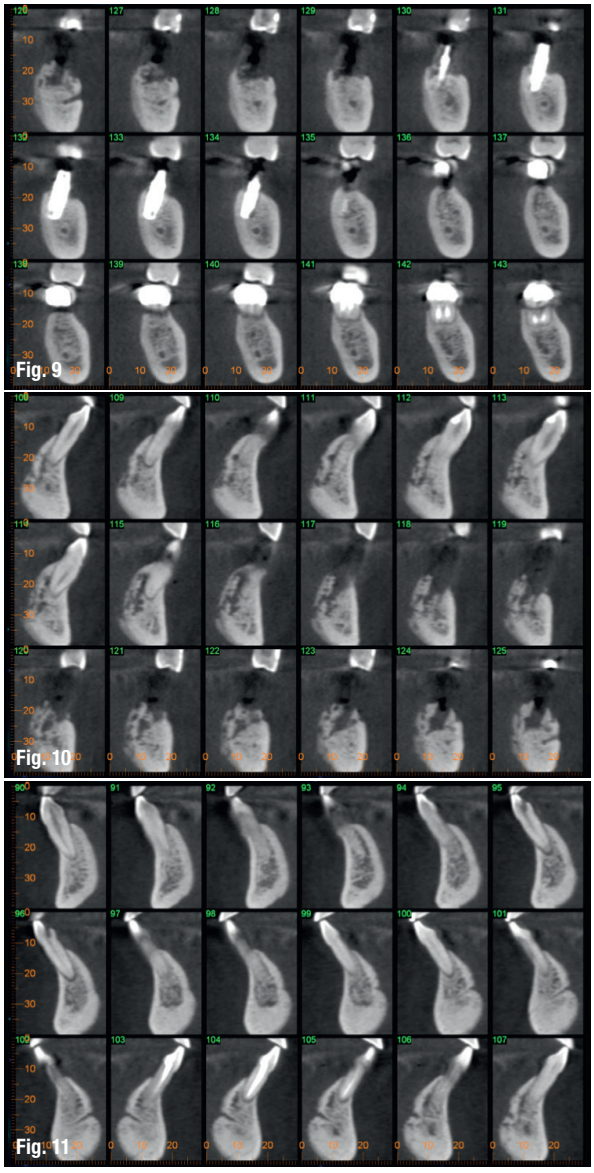


Fig. 8: Panoramic radiograph after the piece of bone come out and root canal therapy was performed on the mandibular lateral incisor.

Discussion

From a number of clinical studies, it is well substantiated that bisphosphonates cause drug-induced osteonecrosis.[16–19] Osteonecrosis is a condition that occurs when there is loss of blood to the bone. Bisphosphonates inhibit the resorption of bone by osteoclasts and may have an effect on osteoblasts.[20] By the same token, these two types of cells represent the origin of the bone remodelling cycle. Therefore, any cell dysfunction would influence the cycle, preventing bone formation and resulting in bone necrosis.[21–23]



Figs. 9–11: Complete healing of the bone structure.

In dentistry, the association of osteonecrosis with bisphosphonate therapy is a matter of recent knowledge. Nevertheless, Schuster et al. suggest that, when the risk factors of the disease change, the intensity changes accordingly.[24] The risk factors induced by bisphosphonates increase with the increase of the uptake and potency of this class of drugs. Science declares that the body is exposed to higher levels of drugs via intravenous administration than via the oral route.[25, 26] That is why it has been observed that osteonecrosis related to oral bisphosphonate therapy is less common than that related to intravenous administration.[27]

Wood et al. showed that bisphosphonates can be classified into two groups as nitrogen-containing and non-nitrogen-containing bisphosphonates. Nitrogen-containing bisphosphonates pose a higher risk regarding BRONJ development.[28]

Another factor that should be taken into consideration is the duration of therapy. According to a study, it was discussed earlier that oral bisphosphonates have lower bioavailability that intravenous ones, but the risks of BRONJ increase with the prolonged duration of administration.[29–31]

Equally important, ceasing the use of bisphosphonates would not be considered safe, since the BRONJ risk might remain. Some practitioners still prefer stopping the drugs for six months to one year before and after a traumatic procedure. Bisphosphonates could be preserved in bone for months, even years, after the drugs have been used. According to some research, unfavourable effects from these drugs would not appear until three years after treatment ends, and after that time, the possibility of developing BRONJ remains very low.[32, 33]

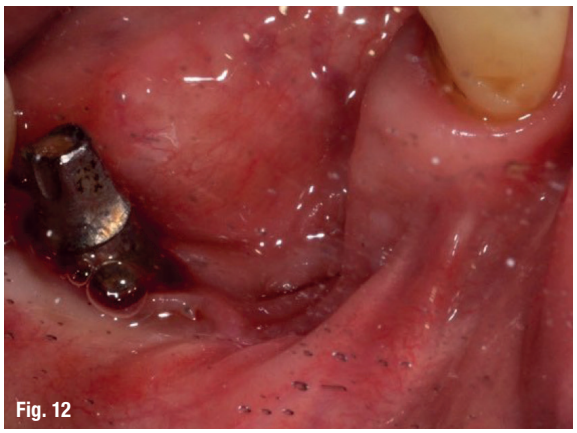


Fig. 12

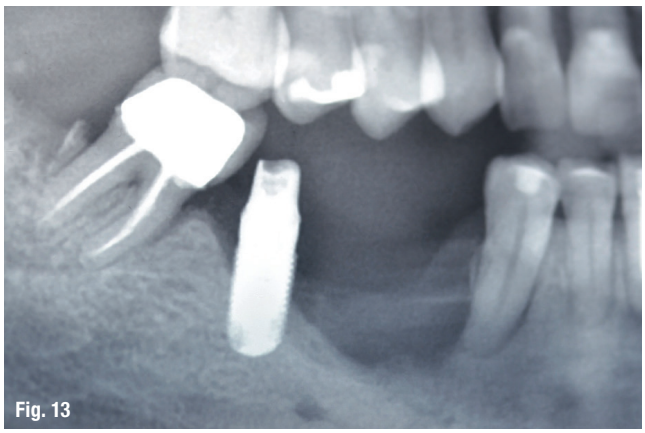


Fig. 13

Fig. 12: Complete closure of the wound with new epithelium (one year post-op). **Fig. 13:** One year post-op radiograph.

Furthermore, bisphosphonates have been shown to inhibit the proliferation of keratinocytes in the oral mucosa; thus, injury of the oral mucosa due to any dental procedure may increase the risk of BRONJ in bisphosphonate users. In most cases, dental procedures such as tooth extraction and surgeries were considered the initiator of the BRONJ. However, some papers have reported the spontaneous development of BRONJ without a prior invasive dental procedure.[34]

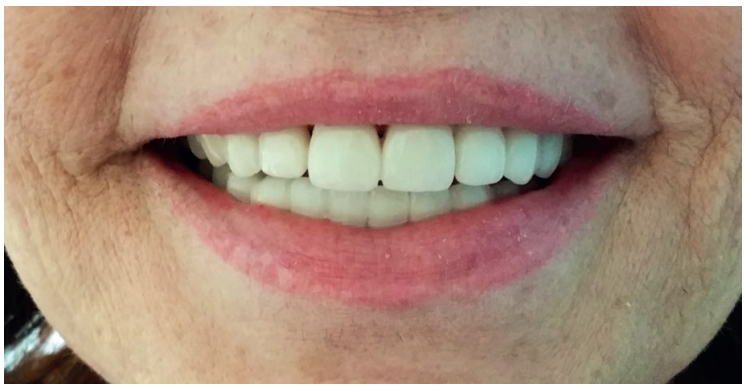


Fig. 14: The patient's healthy smile.

Unfortunately, BRONJ is irreversible, meaning the bone cannot regenerate. There are no controlled studies on the long-term management of BRONJ.

Under these circumstances, making a treatment plan decision must consider the stage, or progression, of the disease. Ruggiero et al. identified four stages of BRONJ.[31, 35, 36] Not so long ago, the stage of BRONJ was one of the most significant factors in choosing treatment options;[37] however, a new protocol has recently been proposed. It is noted that one should ensure the completion of a dental examination before the commencement of bisphosphonate treatment. Any dental procedure concerning the patient should be done with two weeks preceding the administration of the medication.

Accordingly, patients are grouped into high risk and low risk.[38] The factors in the high-risk category include intravenous administration of bisphosphonates, the intake of oral bisphosphonates with immunosuppressants and the existence of BRONJ in the medical history of the patient. The treating dentist should determine whether an extraction can be avoided. If so, root canal therapy and coronectomy can then be considered. However, if not, the dentist should discuss the case with an oral and maxillofacial surgeon.[37]

The factors in the low-risk category include the oral administration of bisphosphonates. If an extraction is indicated and the patient has risk factors such as smoking or poor oral hygiene, before proceeding with the plan, the dentist should work on reducing the risk factors. If there are no threatening risk factors, the patient should be prepared for the extraction with the provision of 0.2 % chlorhexidine. Either an atraumatic or surgical extraction can be applied. If the latter is chosen, periosteal flaps and bone exposure should be kept to the minimum and antibiotics should be prescribed postoperatively. The wound is given a period of four to eight weeks to heal, and if healing does not occur in the given time, the dentist should refer to an oral and maxillofacial surgeon. It should be noted that treatments are intended to control the condition and resolve certain symptoms of osteonecrosis of the jaw.[39]

Editorial note: A list of references is available from the publisher.

contact

Dr Philippe Sleiman is an assistant professor at the Faculty of Dentistry of the Lebanese University in Beirut in Lebanon. He can be contacted at profsleiman@gmail.com.