

Bisphosphonates-induced osteochemonecrosis of the jaw: A clinical and radiological presentation of evolution and prognosis

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Abstract

Bisphosphonates induced osteochemonecrosis of the jaw (ONJ) is a rare, but serious and, most often, irreversible condition correlated to bisphosphonates treatment. Bisphosphonates are defined as agents used for the treatment of many skeletal-related problems, and have been shown to alleviate many devastating consequences associated with cortico- induced osteoporosis, steroid-induced bone loss, Paget's disease, osteoporosis and cancer-induced bone disease. Yet they remain the main cause of osteochemonecrosis of the jaw. Today the prognosis and evolution of ONJ are still unclear - many cases may heal totally, while others may evolve into fractures of the jaw bone and fistula with other devastating complications.

The purpose of this article is a comparative analysis of the factors influencing the prognosis and evolution of this disease by describing three clinical cases, emphasising the importance of meticulous control and follow up of patients undergoing bisphosphonates treatment, with the aim of achieving total healing and prevention of any complication that can exacerbate the pre-existing situation.

Key words: Bisphosphonates, osteochemonecrosis, jaw bone, prognosis, evolution, follow-up, fracture, fistula, healing.

Bisphosphonates-induced osteochemonecrosis of the jaw was defined by Ruggiero as a condition characterized by the exposure of bone in the mandible or maxilla persisting for more than 8 weeks in a patient with no history of radiation therapy in the jaws, who has taken or currently is taking a bisphosphonate.¹

Marx, in 2003, described the first case of osteonecrosis of the jaw (ONJ) as being associated with bisphosphonate therapy. Since then, the number of cases reported is increasing and the complication has become a "growing epidemic."²

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Bisphosphonates are powerful inhibitors of osteoclastic activity. They are analogues of inorganic pyrophosphates and have a high affinity for hydroxyapatite crystals.^{3,4}

The fundamental action of bisphosphonates is to inhibit bone resorption and reduce bone turnover, which reduces serum calcium levels as well. The reason for this antiresorption effect is the irreversible death of the osteoclast. The action differs whether it is an amino- or non amino-bisphosphonates.

Patients who are receiving intravenous, nitrogen-containing bisphosphonates are at the greatest risk for osteochemonecrosis of the jaw.

Clinically, ONJ is usually presented as a yellow-brown exposure of bone, sometimes with a purulent discharge. Radiographically, the condition manifests either with a normal appearance or one identical to either bacterial osteomyelitis or osteoradionecrosis. ONJ is classified in 3 main stages (Table I).

Risk assessment and determination of prognosis begins with the medical history in order to depict the evolution pathway. This assessment is done by meticulous questions asked on the duration period of bisphosphonates, comorbidity factors, dental and medical history.

Table I: Staging of ONJ

Stage 1:	Asymptomatic exposed necrotic bone with no evidence of infection
Stage 2:	Symptomatic exposed necrotic bone with pain and infection
Stage 3:	Symptomatic exposed necrotic bone with pain, infection with fractures, extra-oral fistula or osteolysis extending to the inferior border of mandible or sinus floor.

We briefly review the action of bisphosphonates, outline the evolution, summarize the prognosis through exposing three case series with clinical and radiological presentations, and discuss implications of risk factors in inducing ONJ.

Clinical case 1

Chief Complaint: Stage III ONJ, symptomatic exposed necrotic bone.

A 60 year-old woman experienced jaw problems that began six months earlier with spontaneous deep jaw pain in the left posterior edentulous mandible. Her family dentist referred her to the department of Oral Surgery of the Saint Joseph University after having detected an extended exposed bone with pus discharge. The patient mentioned that over

the three preceding months, she developed severe pain combined with episodes of swelling and enhancement in jaw volume. She revealed having undergone Alendronate (Fosamax 70 mg/week) treatment for the past three years for osteoporosis that was interrupted seven months previously. Extraoral examination showed an asymmetrical face on angle region that was red and extremely painful on palpation. Intraorally, an extended exposed bone was depicted. The panoramic radiograph showed extensive osteolysis in the left molar area, with the beginning of a disruption of the inferior border extending to the mandibular angle region (Figure 1).

The Cone Beam radiograph showed that both the buccal and lingual cortices are osteolytic (Figures 2 - 4), with erosion



Figure 1: Panoramic view, osteolysis is evident in the left molar area, with beginning of a disruption of the inferior border extending to the mandibular angle region.

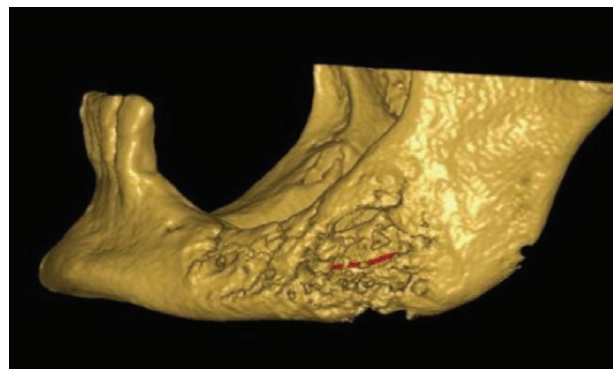


Figure 2: Cone beam 3D buccal view, showing destruction of bone involving the lower alveolar nerve.

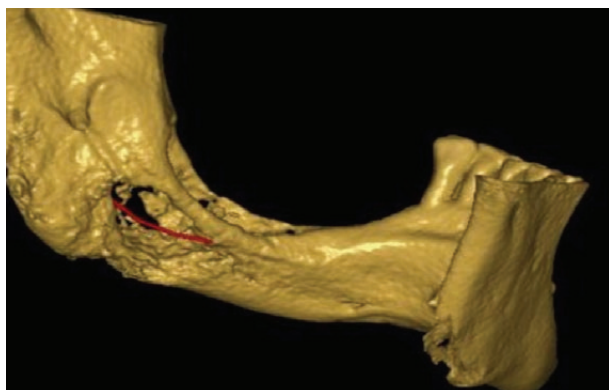


Figure 3: Bone destruction extending to the lingual side of mandible and showing the lower alveolar nerve passing through the lesion.

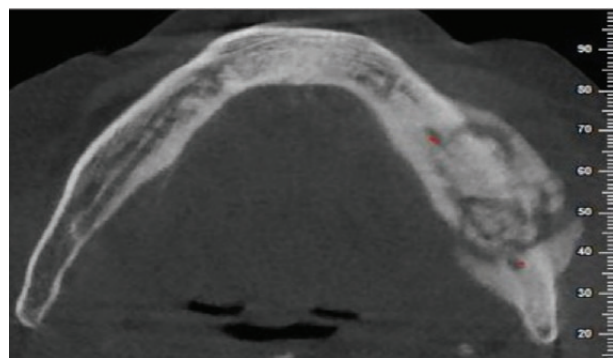


Figure 4: Occlusal view showing osteolysis extending to buccal and lingual plate with high risk of fracture and lower alveolar nerve involvement.



Figure 5: Draining fistula in the chin area below the inferior border of the mandible to the left of the midline, it has a central area of drainage surrounded by 2 cm area of erythema.

starting in the basal area. A conservative treatment based on quinolone (Ciprofloxacin 500 mg) and bicarbonate mouthwash, was conducted for one month. A sequestrum was isolated and removed after two months. Subsequently, contact with the patient was lost for one year, but we knew from her physician that the clinical symptoms were well controlled, even though she was still suffering from a 1 cm bone exposure without infection or clinical signs. No fracture of basal bone was noticed, showing an acceptable prognosis.

Clinical case 2

Chief Complaint: Stage III osteonecrosis of the jaw, swelling and drainage from the chin.

A 67 year-old male patient consulted the department of Oral Surgery of the Saint Joseph University, for an asymptomatic bone exposure causing halitosis and difficulty in masticatory functions. The patient mentioned that he had been undergoing treatment for osteoporosis based on zoledronic acid (Zometa 4mg/ month) intravenously for the past two years, and had since then endured spontaneous loss of all his teeth.

An extraoral examination showed a draining fistula in the chin area below the inferior border of the mandible to the left of the midline with a central area of drainage surrounded by 2 cm area of erythema (Figure 5).

The panoramic examination showed an extended sequestrum of the alveolar crest with remaining fractured basal bone. (Figure 6). The intraoral examination revealed a yellowish exposed bone extending from right to left in the molar region. All those findings suggested a bad prognosis. The patient was operated on under general anesthesia and the sequestrum was removed. Post operative examination showed clinically an exposed bone of 1.5 cm with no detected infectious symptoms.



Figure 6: Panoramic view showing the extended mandibular sequestrum, with fracture of basal bone.

Clinical case 3:

Chief Complaint: Stage III, spontaneous symptomatic exposed necrotic bone involving the sinus floor.

A 62-year-old woman presented in our private clinic with a history of breast cancer, diagnosed two years previously by means of an incisional biopsy. She received primary zoledronate (Zometa 4mg/ month) treatment intravenously with chemotherapy every six months.

Intraoral examination revealed the absence of the 16 tooth, with exposed fluctuant yellowish bone (Figure 7). The patient mentioned severe pain in the exposed maxillary area, with the spontaneous loss of tooth 16, four months prior.

Panoramic examination detected an osteolytic region in the right maxillary area, with congestion of the sinus (Figure 8).

No extraoral findings were detected. The C-terminal telopeptide (CTX) value was 180 pg/ml even with an evolving ONJ. Quinolone (ciprofloxacin 500mg, 2g/day) was prescribed for one month. An isolation of the sequestrum, with mobility of the 17 tooth was obtained. It was decided to remove the right maxillary second molar and sequestrum conservatively



Figure 7: Intraoral view showing spontaneous bone exposure after expulsion of tooth 1.6 in maxillary region

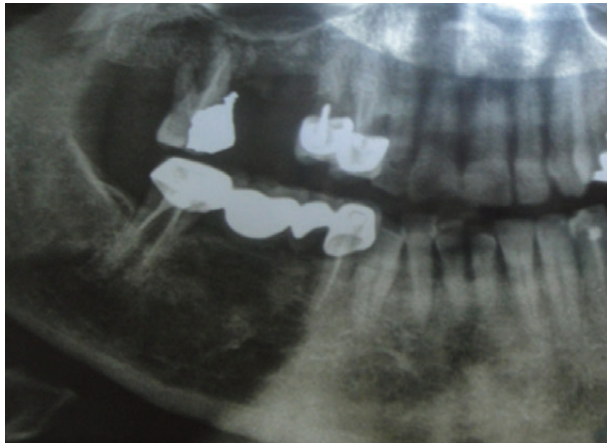


Figure 8: Bisphosphonates-induced osteonecrosis. Evident osteolysis and osteosclerosis.

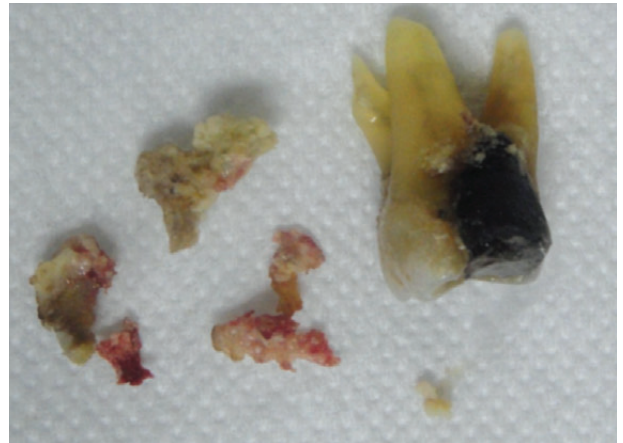


Figure 9: After extraction of tooth 17 with type 4 mobility and conservative curettage of sequestra.



Figure 10: After 5 months surgical reentry for removal of remaining sequestra.

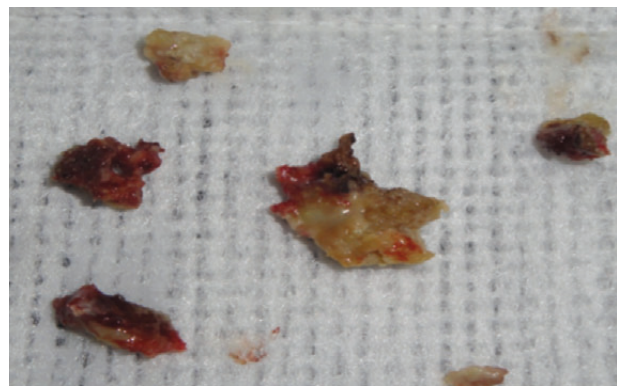


Figure 11: Macroscopic view, multiple sequestra were debried from the maxillary ONJ area.



Figure 12: Intraoral view, total and complete healing 8 months later.

(Figure 9); followed by further conservative surgery with curettage in order to remove other formed sequestra five months later (Figures 10 and 11). After eight months total healing of the mucosa and absence of any exposed bone was obtained (Figure 12).

Four months later, the CTX value evolved to 240 pg/ml following the total healing.

Discussion

Bones are in an inconstant state of remodelling. After menopause most women develop brittle, fragile bones that are easily broken. Bisphosphonates are subsequently prescribed to prevent the process by inhibiting osteoclast activity.

This complication prompts specialists around the world to reconsider when and how to prescribe bisphosphonates in order to predict the evolution and prognosis of ONJ. Many complications were noticed (Table II).

Osteochemonecrosis of the jaws always originates in the alveolar bone and early subclinical radiographic signs including sclerosis of lamina dura may be detected due to enhancement of mineralization in this zone.

The onset of ONJ is related to the potency, frequency, and duration of the specific bisphosphonate used.¹⁰ Zoledronic acid is considered the most potent bisphosphonate and is administered at the recommended dose of 5 mg/month, which may produce ONJ within three to twelve months.⁵

It would be unreasonable not to discuss the contribution

Table II: Complications of ONJ

The most noticed complications of ONJ are:
- Aggressive evolution
- Sequestrum
- Bucco-nasal and cutaneous fistula
- Pathological fracture
- No concordance between mucosal evolution and bone evolution

of comorbidity factors in the development of ONJ and in its prognosis as presented in the previous clinical cases. Comorbidity factors are divided into 2 categories: dental (occlusal trauma, acute periodontitis), and medical factors such as chemotherapy, steroids, methotrexate. Knowing those factors will help specialists to establish a strategy to improve the prognosis of ONJ and even to prevent it.

Both the prognosis and evolution of ONJ may vary depending on many factors.

There is no detected difference in prognosis between provoked and spontaneous induced ONJ, nor between stage II and III since evolution may be dramatic and can leave some sequels, but can still be healed, as in Case 3. Furthermore, it might be affected by treatment adopted following already established recommendations.

Patients taking intravenous bisphosphonates compared to oral bisphosphonates have a poor prognosis since it differs in three ways.^{5,6,8} Firstly, longer duration of exposed necrotic bone; secondly, a more severe and extended exposed bone; thirdly, an interruption of oral bisphosphonate might improve the prognosis and maintain a better evolution into healing. Oral bisphosphonates-induced osteonecrosis of the jaw has a more favorable evolution with good prognosis.

A second means of assessing risk and determining

prognosis is through a serum test known as C-terminal cross-linking (CTX)⁷, which measures the rate of bone turnover and detects the suppression of bone renewal. Values more than 150 pg/ml is associated with normal bone remodelling of the jaws. This test is not considered accurate nowadays since there is also evidence that bone turnover may not be reduced in ONJ lesions as osteoclasts have been observed in ONJ lesions indicating active bone resorption at these sites and therefore high CTX.

Posterior mandible is more susceptible to develop ONJ due to high remodelling. Bisphosphonates treatment and suppression of bone remodelling with traumatic occlusion causes accumulation of microfractures which will lead to ONJ.⁹

A stronger focus should be directed on the effect of comorbidity factors on evolution and prognosis.

The most important factor affecting the evolution and therefore, prognosis, is using adequate conservative treatment since aggressive surgical treatment might lead to more exposed bone and therefore more risk of fracture and complications.

Given the gaps in knowledge that exist in relation to prognosis stratification and potential comorbidity factors, it is very difficult to propose a clear evidence-based prognosis measurement, and most of the available theories are empirically based. Further research is clearly needed in order to establish specific recommendations for treatment of osteochemonecrosis of the jaw, which will provide us a way to read the prognosis and evolution of this disease.

Conclusion

The jaw bones have a high blood supply and remodelling rate which may result in an increasing of bisphosphonates concentration in this area.

The goal of dental treatment for a patient who is currently receiving bisphosphonates therapy is to achieve and maintain optimum dental health, and in so doing, to prevent ONJ without initiating it. In patients already suffering from this complication, the aim is to stabilize or enhance the

Table III: Factors influencing ONJ prognosis:

Bad prognosis	Good prognosis
Intravenous bisphosphonates	Oral bisphosphonates
C-terminal telopeptide (CTX)<150pg/ml	C-terminal telopeptide (CTX)>150pg/ml
Mandible (Less vascularization)	Maxillary (More vascularization)
Cancer patients	Osteoporotic patients
Presence of comorbidity factors (dexamethasone, chemotherapy)	Absence of comorbidity factors
Stage II and III	Stage I and II
Surgical treatment of ONJ	Conservative treatment of ONJ

evolution and prognosis in order to have a complete healing.

Today the question remains - what is the prognosis of these lesion and how does it influence the patient's life? Some might live with exposed bone without any clinical symptoms, while others may suffer from infectious complications.

Determination of prognosis and evolution is still ambiguous and is correlated to many risk factors in association with bisphosphonate exposure, particularly individual bisphosphonate potency, the route of administration and cumulative dose.

The concern is that with more women ageing and taking bisphosphonates for longer periods of time, more cases of osteochemonecrosis of the jaw (ONJ) might develop, and with the absence of any clear treatment consensus, the prognosis of this pathology remains unclear.

This article reviews the findings, in three clinical cases, suggests strategies and outlines for depicting prognosis and evolution that may help us better understand and treat this condition.

However, better conducted clinical studies are required to evaluate the prognosis of osteochemonecrosis of the jaw.

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