Universitas
ODONTOLOGICA

Vol. 40
Rolling volume, January-December
2021

ISSN: 2027-3444 (online) | ISSN: 0120-4319 (print)

Artículos

Medication-Related Osteonecrosis of the Jaw, a Hidden Enemy. An Integrative Review*

Osteonecrosis maxilar por medicamentos, un enemigo oculto. Una revisión integradora

Osteonecrose maxilar induzida por medicamentos, um inimigo oculto. Uma revisão integrativa

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DOI: https://doi.org/10.11144/Javeriana.uo40.mroj

Received: 12 april 2021
Accepted: 14 december 2021
Published: 17 december 2021

Abstract:

Background: Drug-induced osteonecrosis of the jaw (ONJ) is a serious complication associated with prolonged use of antiresorptive (e.g., bisphosphonates and denosumab) and antiangiogenic drugs (e.g., bevacizumab and sunitinib) in patients with osteoporosis or cancer. With this situation, a progressive infection of the maxillary or mandibular bone and later an avascular necrosis of the bone occurs. The incidence of ONJ is higher in people with cancer who are frequently received high doses of antiresorptive drugs intravenously. Risk factors associated with antiresorptive or antiangiogenic therapy have been identified to possibly contributing to the onset of ONJ. **Purpose:** To review and analyze the current available therapeutic options to treat at-risk patients or who already have ONJ. **Methods:** In this integrative review of the literature, publications were searched in the ScienceDirect, PubMed, SciELO, and ResearchGate databases between 2003 and 2020. The search terms were "bisphosphonate-associated maxillary osteonecrosis," "maxillary osteonecrosis associated with medication," and "maxillary osteonecrosis." **Results:** 64 articles were selected in which extractions are identified as the main risk factor for developing ONJ (52 % to 61 %). A second factor identified was the spontaneous appearance of bone necrosis lesions. **Conclusions:** It is important to implement preventive measures in medical and dental care before, during, and after antiresorptive and antiangiogenic treatments to minimize the risks of ONJ in patients.

Keywords: angiogenesis inhibitors, antiresorptive medicines, bisphosphonates, cancer, denosumab, dental extractions, dentistry, neoplasms, oncology, osteonecrosis, osteoporosis.

Resumen:

Antecedentes: La osteonecrosis maxilar por medicamentos (ONM) es una complicación grave asociada al uso prolongado de medicamentos antirresortivos (como bifosfonatos y denosumab) y antiangiogénicos (como bevacizumab y sunitinib) en pacientes con osteoporosis o cáncer. Se producen una infección progresiva del hueso maxilar o el mandibular y, en consecuencia, una necrosis avascular del hueso. La incidencia de ONM es mayor en personas con cáncer a quienes se les administran frecuentemente altas dosis de antirresortivos por vía endovenosa. Se han identificado factores de riesgo asociados a la terapia antirresortiva o antiangiogénica que pueden contribuir a la aparición de ONM. **Objetivo:** Revisar y analizar las opciones terapéuticas disponibles actuales para tratar pacientes con riesgo o que ya presentan ONM. **Métodos:** En esta revisión integrativa de la literatura se realizaron búsquedas de publicaciones en las bases de datos de ScienceDirect, PubMed, SciELO y ResearchGate realizadas entre 2003 y 2020. Los términos de búsqueda fueron "osteonecrosis maxilar asociada a bifosfonatos", "osteonecrosis maxilar asociada a medicamentos" y "osteonecrosis maxilar". **Resultados:** Se seleccionaron 64 artículos en los que las exodoncias se identifican como el principal factor de riesgo para desarrollar ONM (52 % - 61 %). Un segundo factor identifi cado fue la aparición espontánea de lesiones de necrosis ósea. **Conclusiones:** Es importante implementar medidas preventivas en la atención médica y odontológica antes, durante y después de los tratamientos con antirresortivos y antiangiogénicos para minimizar los riesgos de ONM en los pacientes.

Palabras clave: antiangiogénicos, antirresortivos, bifosfonatos, cáncer, denosumab, exodoncias, inhibidores de la angiogénesis, neoplasmas, odontología, oncología, osteonecrosis, osteoporosis.

Resumo:

Antecedentes: A osteonecrose da mandíbula induzida por medicamentos (ONM) é uma complicação grave associada ao uso prolongado de medicamentos antirreabsortivos (como bifosfonatos e denosumabe) e antiangiogênicos (como bevacizumabe e sunitinibe) em pacientes com osteoporose ou câncer. Ocorre infeção progressiva do osso maxilar ou mandibular e,

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consequentemente, necrose avascular do osso. A incidência de ONM é maior em pessoas com câncer que frequentemente recebem altas doses de drogas antirreabsortivas por via intravenosa. Fatores de risco associados à terapia antirreabsortiva ou antiangiogênica que podem contribuir para o aparecimento de ONM foram identificados. **Objetivo:** Revisar e analisar as opções terapêuticas atuais disponíveis para tratar pacientes em risco ou que já possuem ONM. **Métodos:** Nesta revisão integrativa da literatura, foram pesquisadas publicações nas bases de dados ScienceDirect, PubMed, SciELO e ResearchGate entre 2003 e 2020. Os termos de busca foram "bifosfonato-associado maxilar osteonecrose", "maxilar osteonecrose associada a medicação" e "maxilar osteonecrose". **Resultados:** foram selecionados 64 artigos nos quais as extrações são identificadas como o principal fator de risco para o desenvolvimento de ONM (52% - 61%). Um segundo fator identificado foi o aparecimento espontâneo de lesões de necrose óssea. **Conclusões:** É importante implementar medidas preventivas na assistência médica e odontológica antes, durante e após tratamentos antirreabsortivos e antiangiogênicos para minimizar os riscos de ONM nos pacientes.

Palavras-chave: antiangiogênico, antirreabsortivos, bifosfonatos, câncer, denosumabe, extrações, inibidores de angiogénese, neoplasias, odontologia, oncologia, osteonecrose, osteoporose.

INTRODUCTION

Maxillary osteonecrosis is a bone pathology that was first identified in the 19th century in Europe. Initially, it was an occupational disease that affected workers in white phosphorus factories that produced matches. The first case was reported in Vienna in 1839 (1) and the cause was the vapor generated by the phosphorus and the lack of protection measures, which caused necrosis of the maxillary bones, and was named maxillary phosphonecrosis. In 1922, the first article on maxillary osteonecrosis related to radiotherapy or osteoradionecrosis (ORN) was published. It is one of the most severe complications of radiotherapy in the treatment of head and neck cancer. Clinically, there is mucosal ulceration with exposure of necrotic bone from trauma and is rarely spontaneous. Eighty-one years after the first ORN report, a study of maxillary osteonecrosis appears again, in which Robert E. Marx described 36 clinical cases of patients who received treatment with ibandronate and zoledronate (bisphosphonates) (2). Bisphosphonates were initially developed to treat bone metabolic disorders such as osteoporosis to prevent pathological fractures. Subsequently, they were used to treat bone metastases from breast cancer, prostate cancer, multiple myeloma, and hypercalcemia.

Seventeen years after Marx's publication, several studies have been published by researchers in dentistry and medicine. Unfortunately, drug-related osteonecrosis of the jaw (ONJ) continues to increase. More than 90 % of cases of maxillary osteonecrosis have been seen in cancer patients due to high doses antiresorptives (bisphosphonates and denosumab) and antiangiogenics (bevacizumab, sunitinib). Its physiopathogenesis has not yet been fully resolved. Associated risk factors such as the use of corticosteroids, diabetes mellitus, periodontitis and extractions can increase the occurrence of ONJ (1,2,3,4,5,6,7,8,9,10,11,12).

With the constant emergence of new drugs to treat cancer and their possible effects on the maxillary bones, as well as the increase in the use of antiresorptive drugs in cancer and osteoporosis patients, it is considered important to conduct current reviews of the evidence so that the ONM no longer be a hidden enemy. An early referral by the treating health professional can reduce the incidence of ONJ, as well as complications in patients who may be susceptible to them and avoid surgical interventions, if the patient has started antiresorptive or antiangiogenic therapy. This study aimed to review ONJ in the literature from different areas: pathophysiology, diagnosis, risk factors, clinical manifestations, treatment protocols, and clinical and radiographic management.

MATERIALS AND METHODS

An integrative review of the literature was conducted by searching the ScienceDirect, PubMed, SciELO, and ResearchGate databases, from 2003 to 2020, covering publications in English and Spanish. The search terms

were "bisphosphonate-associated maxillary osteonecrosis," "drug-associated maxillary osteonecrosis," and "maxillary osteonecrosis." Descriptions of clinical cases, retrospective and prospective studies and systematic reviews were considered. Initially 1,230 titles were obtained of which 62 articles discussing the relationship between extractions and oral infection in the etiopathogenesis of ONJ and that were aimed at the clinical practice of the general dentist and the specialist were chosen. Animal studies and other articles that did not meet the requirements or did not contain sufficient information were excluded. It is evident that extractions are the main risk factor for developing ONJ (52 % - 61 %). The second factor is the spontaneous appearance of bone necrosis lesions.

FINDINGS AND DISCUSSION

Osteoradionecrosis of the Jaws

ORN is produced by radiation therapy leading to infection and bone exposure. The healing function of both soft tissue and bone is impaired by hypovascularization in the irradiated area. It can be spontaneous or due to trauma, for example, an extraction. The most frequent site of appearance is the jaw. As ORN progresses, pain, dysesthesia, or anesthesia develop. It is considered one of the most serious complications in patients with head and neck cancer. Claudius Regaud documented it for the first time in 1922, describing the susceptibility of the maxillary bones to necrosis, due to the combination of infection and radiotherapy in the treatment of intraoral carcinomas (3). In 1926, James Ewing published an article on three clinical cases showing bone changes due to remarkably high applications of radiotherapy in cancer patients; he called it radiation osteitis, giving importance to tissue changes and decreased vascularity, which increases the likelihood of infection and subsequent bone necrosis. Ewing suggested administering radiation in low doses (4). In 1941, Frank Kanthak described Ewing's histological findings of the cellular damage generated in the bone due to radiotherapy and that produces alteration and devitalization. In addition, considerable reaction occurs in the vascular supply of the bone; the blood vessels tend to harden and eventually become sclerosed. He concluded that the conditions responsible for necrosis of the jaws are irradiation, infection, and trauma (5).

Robert Marx in 1983 explained that the irradiation, infection, and trauma sequence should be replaced by one more indicative of the cellular and metabolic changes, which are basic in the pathophysiology of ORN: irradiation, hypoxia, hypovascularity and hypocellularity of the tissues (principle of 3H), tissue deterioration, and lack of wound healing (6). This sequence gives a clearer view of the pathophysiology of ORN and to begin to understand the pathophysiology of ONJ.

Medication-Related Maxillary Osteonecrosis

As mentioned above, Marx in 2003 (2) reports on the appearance of avascular osteonecrosis in the jaws of 36 patients treated with intravenous bisphosphonates and who underwent dental procedures. Initially, he called it bisphosphonate-associated maxillary osteonecrosis because it was exclusive to this drug. But in 2014, Ruggiero, *et al*. (7) changed the terminology after finding cases in the scientific literature of maxillary osteonecrosis due to other drugs such as denosumab, an antiresorptive drug that, like the bisphosphonate, inhibits osteoclast function. It has also been seen in antiangiogenic drugs that function as inhibitors of the vascular endothelial growth factor (VEGF). Then it was called ONJ and antiresorptive and antiangiogenic drugs were associated with it.

Antiresorptive drugs are used in patients with osteoporosis and cancer. Antiangiogenic agents are used to treat patients with age-related macular degeneration (8) and in cancer patients. Many dentists and medical doctors have little or no knowledge of this pathology. Physicians sometimes prescribe antiresorptive

medications to patients without having diagnostic tests for osteopenia or osteoporosis. In other situations, they prescribe them longer than standard time, which generates an effect contrary to the desired one (9). That is why it is important to know the different medications that can induce ONJ.

Antiresorptive drugs are divided into two groups:

a) Bisphosphonates. There are nitrogenous (pamidronate, ibandronate, risendronate, zoledronate, and alendronate) and non-nitrogenous (etidronate, tiludronate, and clodronate). Both nitrogenous and non-nitrogenous bisphosphonates are taken up by osteoclasts and damage their bone remodeling mechanism. They can be administered orally (alendronate, etidronate, tiludronate, risendronate, and ibandronate) or intravenously (pamidronate, ibandronate, and zoledronate), the last route being the most powerful. They can remain in the bone for prolonged periods (10).
b) Monoclonal antibodies (denosumab). They function as inhibitors of RANK ligand (RANK-L). Denosumab binds to RANK-L, prevents interaction with RANK, and inhibits osteoclast differentiation, activation, and survival. It is administered subcutaneously every six months and its effect decreases when the drug is discontinued (11).

Indications to use bisphosphonates (12):

- Osteoporosis
- Paget's disease
- Malignant hypercalcemia
- Breast, prostate, and lung cancer
- Multiple myeloma
- Metastatic bone diseases

Indications to use denosumab (13):

- Osteoporosis
- Malignant hypercalcemia
- Multiple myeloma
- Breast and prostate cancer
- Giant cell bone tumor

Antiangiogenic drugs (bevacizumab and sunitinib) are VEGF inhibitors. They bind to VEGF-A to inhibit cell proliferation by blocking the signal through VEGF-R1 and R2 and preventing new blood vessel formation in malignant tumors (14). Bevacizumab is the most used and, in combination with paclitaxel (chemotherapeutic), is more effective in fighting tumors than independently (15). In addition, antiangiogenic drugs are tyrosine kinase inhibitors and direct inhibitors of endothelial cell activation (16).

Pathophysiology of ONJ

The pathophysiology of ONJ has been studied for years; however, it has not yet been fully understood. Bones are constantly remodeling due to osteoblast-osteoclast activity to maintain the integrity and strength of the skeleton. An imbalance of this activity affects mineral bone density and generates bone disorders such as osteoporosis, bone metastases, and other diseases. Antiresorptive medications decrease pathologic fractures, pain, and possible vertebral compression. The mechanism of action of these medications varies. Osteoclasts absorb bisphosphonates, which alters their chemotactic function and their binding to bone, suppresses the mechanism of bone resorption, and induces apoptosis. Denosumab interacts with the RANK-RANK-L-OPG (osteoprotegerin) pathway by binding to RANK-L and preventing preosteoclast maturation

and differentiation, which ends up in osteoclast apoptosis. With both drugs, bone remodeling is affected. The high doses given to a patient and the prolonged time of the treatments decrease the ability of the bone to heal in the event of tissue trauma or bone exposure, which generates bone necrosis in the affected area (7,11).

Thus, why is osteonecrosis more frequent in the jaws than in other bones of the body? Five main theories have been proposed that would explain the exclusive location in the jaws: inhibition of bone remodeling; microbial oral inflammation and infection; immunosuppression; soft tissue toxicity; and inhibition of angiogenesis (11,17,18,19,20). It is likely that a combination of these factors facilitates the development of ONJ; however, inhibition of bone remodeling and angiogenesis are the most frequently cited theories.

Tooth extractions performed due to periapical or periodontal infections are the main cause of ONJ in which impaired healing with inflammatory infiltrate in the alveoli, bone exposure, and necrotic areas is observed histologically. Inflammation due to bacterial oral infection is a particularly important risk factor in the development of ONJ (21). According to Khan, *et al*. (15), polymorphonuclear cells and bacterial aggregates are always observed in necrotic tissue. The bacteria stimulate bone resorption and contribute to bone necrosis. Seddghizadeh, *et al*. and Kumar, *et al*. (22,23,24) have commented on the association between microbial biofilm and ONJ. Kalyan, *et al*. (25) describe how the oral microbiome can be an opportunistic factor and not the cause of ONJ.

Thus, periapical and periodontal infections with or without extractions increase the risk of ONJ because they can alter the function and number of osteoclasts and become an aggravating factor in the pathophysiology of ONJ (20). However, good oral hygiene and periodontal maintenance are beneficial to prevent ONJ in patients who are going to start treatment with antiresorptive agents (26).

Diagnostics

A patient is considered to have ONJ if they have three conditions (7,17,27):

a) Previous or current medical treatment with antiresorptive and antiangiogenic drugs.
b) Exposed necrotic bone in the maxillofacial region for more than 8 weeks.
c) No history of radiotherapy or metastatic disease in the jaws.

Common clinical conditions such as caries, neoplastic processes in the jaws, sinusitis, periodontal abscesses, periapical and temporomandibular disorders, and any lesion in the alveolar mucosa that causes regional pain (e.g., an ulcer) should be excluded (28).

Clinical Signs

There are clinical signs that could indicate the onset or an already established pathology of ONJ. They include pain, swelling, redness, or other signs of gum infection, gums or sockets that do not heal after treatment, dental mobility, numbness or sensation of jaw heaviness, drainage, and bone exposure (20,29). However, the diagnostic criteria must always be considered to avoid confusion with other pathologies such as ORN or neoplasms in the jaws.

To estimate the prognosis of patients who have used oral or intravenous antiresorptive agents and antiangiogenic drugs, the American Association of Oral and Maxillofacial Surgeons (AAOMS) in a 2014 position paper, proposes a staging system based on the clinical and radiographic findings (7) (table 1).

TABLE 1
ONJ Staging System Proposed by the AAOMS (7)

Stage	Characteristics
At risk	There is no apparent necrotic bone in patients who have used oral or intravenous bisphosphonates.
0	There is no clinical evidence of necrotic bone; there are unexplained symptoms (e.g., pain and swelling) and radiographic changes (sclerosis).
1	Exposed necrotic bone or fistula to bone in an asymptomatic patient and without evidence of infection.
2	Exposure of necrotic bone or intraoral fistula to bone associated with infection, pain, and erythema in the region of exposed bone, with or without purulent drainage.
3	Exposure of necrotic bone or a fistula to bone in patients with pain, erythema, and infection and one or more of the following conditions: exposed necrotic bone extending to the alveolar bone region (lower border and ramus of the mandible, maxillary sinus, and zygomatic bone) resulting in pathologic fracture, extraoral fistula, or oroantral or orosinusal communication.

Risk Factors

A broad knowledge of the risk factors that are associated with the development of ONJ allows monitoring and surveillance of patients who are medicated with antiresorptive or antiangiogenic drugs. Three groups of key factors are presented: potential, oral, and triggers.

Potential Risk Factors (7,19,20,30,31,34)

- Intravenous route of administration increases risk (higher potency than oral bisphosphonates)
- Prolonged treatment with antiresorptives
- Concomitant cancer treatment
- Corticosteroid administration
- Diabetes mellitus
- Alcohol and smoking

Oral Risk Factors (7,30,31,32,33,34).

- Extractions
- Tooth infection (periapical abscess)
- Periodontal disease
- Peri-implantitis
- Poorly adapted removable prostheses
- Palatal or lingual torus
- Surgical treatments (oral, endodontic, or periodontal implants)

Triggering Risk Factors

Tooth extractions are the greatest triggering risk factor for developing ONJ (52 % - 61 %) (7,26,34,35,36,37,38), hence the importance of performing a rigorous anamnesis by the dentist. The second factor is the spontaneous appearance of bone necrotic lesions. Periodontal disease (22,23,24,25,35) and trauma or pressure caused by total or partial prostheses in patients with a thin periodontal biotype (7,21,33,39,40) are other important triggering factors in the possible development of ONJ. The most frequent anatomical sites are the mandible with 73 % incidence and the maxilla with 22.5 %. The possibility of occurrence in both jaws simultaneously is 4.5 %. Figure 1 shows different studies in which tooth extraction was the highest risk factor (> 60 %). Spontaneous periodontitis and osteonecrosis presented high values, as did prosthetic trauma (25,29,32,34-36) (figure 1).

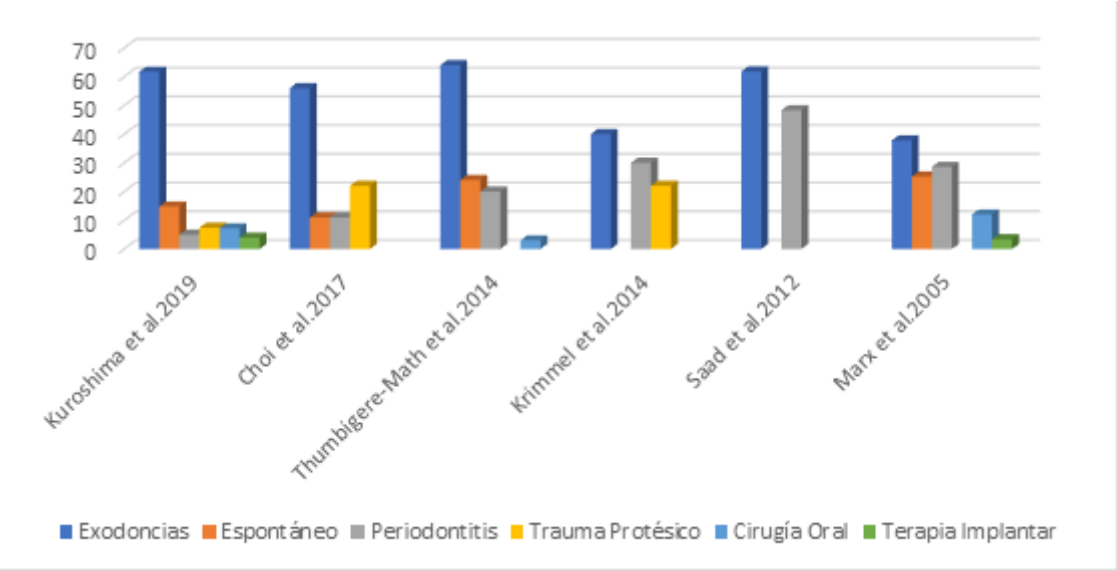

FIGURE 1
Triggering factors of ONJ identified in six studies (25,29,32,34,35,36)

Radiographic Signs

The clinical signs have been widely described in the literature, but there is little reference to the radiographic ones. With a timely diagnosis of radiographic lesions, ONJ will be easier to treat and maintain, since early diagnosis plays a significant role in the definitive treatment of this pathology. Different diagnostic images are used: orthopantomograms, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET/CT). Bone sclerosis is the first imaging manifestation diagnosed; there are changes in bone density and the patient may be asymptomatic. Dentists must be attentive to these changes in order to take the necessary preventive measures (41). It should be noted that these bone sclerosis changes can also be seen in patients with ORN, osteosarcomas, chronic suppurative osteomyelitis, or metastasis. Hence, it is important to perform a good initial diagnosis of the disease.

Dental Management

Before starting any treatment with antiresorptive or antiangiogenic agents, the treating physician should refer the patient to the dentist for a careful examination of the oral cavity in order to minimize the risks of ONJ. The clinical history, the intraoral and extraoral examination, and the anamnesis continue to be the most valuable tool for its diagnosis and that of any other pathology. In these times of multi-medication, it is essential that the dentist review the medication history with the treating physicians to obtain the necessary and reliable information. Sometimes, the patient does not know exactly what medications they are consuming and if the necessary measures are not taken, they could make big mistakes.

Intraoral examination must be rigorous to identify sites of probable infection. At a minimum, an initial panoramic radiograph should be ordered, as well as always performing a periodontal hygiene phase to reduce the bacterial load (biofilm) that the patient presents. All surgical periodontal treatment, surgical removal of multilobed lingual tori, extractions, and endodontics should be performed at least three weeks to one month before antiresorptive or antiangiogenic therapy. Likewise, active caries must be removed and affected teeth rehabilitated.

It is important to conduct motivation and oral hygiene education to avoid future infections. Also, oral rinses with chlorhexidine (0.12 % or 0.2 %), cetylpyridinium chloride, benzalkonium chloride, or other alcohol-free active ingredients should be used periodically.

Patients wearing full or removable dentures should have their flanks relieved to avoid pressure on the buccal and alveolar ridges. After starting treatment with antiresorptive or antiangiogenic drugs, periodontal checkups and maintenance should be performed every four months. If the patient started treatment with antiresorptive or antiangiogenic agents but was not previously referred to the dentist and requires some treatment, non-surgical endodontics should be indicated. Also, avoid extractions, although, if necessary, there should be premedication with antibiotics, curette the alveolus very well to induce bleeding, and suture well confronting the edges to obtain healing by first intention. If there are teeth with extensive caries, without mobility and they are not restorable, endodontic treatment should be performed, amputate the clinical crown, and submerge the roots to minimize the risk of ONJ. Before, during, and after any of these procedures, the patient should always perform oral rinses with chlorhexidine (0.12 % or 0.2 %) 2-3 times a day for a period of 2-3 weeks. Controls will be monthly during the first year and with x-rays (in the case of having performed extractions) every six months (7,11,21).

There is a great deal of misinformation in the medical and dental fields about the adverse effects that these drugs can have on the maxillary bones. Prior to the start of treatment, there must be communication and multidisciplinary management with the different medical groups and the dentist, when it is determined that a patient is treated with antiresorptive or antiangiogenic drugs (7,21,42,43). The most important activity is to explain and inform patients about the minimal risk associated with these drugs, but also the elevated risk of not following the recommendations or conducting preventive measures (44,45,46).

Every dentist must consider that patients with osteoporosis under oral bisphosphonates are less likely to present ONJ than those who use intravenous antiresorptives (i.e., denosumab or bisphosphonates). Likewise, cancer patients are more likely to present ONJ due to the high doses and frequency with which they are applied (11,17,21,39).

The estimated incidence in patients with osteoporosis treated with antiresorptives is 0.01 % to 0.1 % (1-10 cases per 10,000). In cancer patients treated with antiresorptive or antiangiogenic agents, the incidence is 1 % (one case per 100) (21,47). Although the percentages may seem low, the risk is always high. Women are at greater risk than men due to a higher incidence of osteoporosis and breast cancer.

During drug treatment, the oral status should be monitored, the patient should practice good oral hygiene, and periodontal maintenance should be performed. This review should be periodic, if possible, every 3, 4, or 6 months (48,49,50).

High-risk patients should always receive prophylactic or previous dental treatment. The Ontario Cancer Care group and the American Society of Clinical Oncology issued the following recommendation in 2017: "Dental evaluation is recommended, when possible, prior to initiation of BF [bisphosphonates] and any outstanding dental or oral health problems should be resolved before starting treatment" (51)

On the other hand, the Scottish National Health and Education Service in its clinical guide recommends that before starting pharmacological treatment with antiresorptive or antiangiogenic agents, or as soon as possible thereafter, ensure that the patient is in the best possible dental condition, prioritizing preventive care. Higher-risk cancer patients should preferably undergo a comprehensive dental evaluation, performing dental treatments where necessary, before starting pharmacological treatment (47). The treatment proposed by the AAOMS in 2014, based on the various stages (7), is as follows (Table 2):

TABLE 2
Treatment of ONJ based on stage, according to the AAOMS (7)

Stage	Treatment
At risk	No treatment is necessary. Patient education.
Stage 0	Systemic management, including the use of antibiotics and analgesics.
Stage 1	Oral antibacterial rinses (0.12 % or 0.2 % chlorhexidine). Periodic clinical monitoring (every 15 days, monthly, or quarterly). Patient education and review of indications for continuing bisphosphonate therapy.
Stage 2	Treatment of symptoms with oral antibiotics. Oral antibacterial rinses (0.12 % or 0.2 % chlorhexidine). Pain control with analgesics. Debridement to relieve soft tissue irritation and infection. Infection control.
Stage 3	Oral antibacterial rinses (0.12 % or 0.2 % chlorhexidine). Antibiotic therapy and pain control with analgesics. Surgical debridement or resection for long-term relief of pain and infection.

The management of ONJ with several types of treatments is still under investigation. Medications such as teriparatide seem to be a possible solution (52). But side effects such as nausea, arthralgia, vomiting, psychological and, kidney problems may occur, which leads to discontinuation or interruption of treatment. Its use in the treatment of ONJ continues to be investigated (53).

It is not just about treating the patient with antiresorptive or antiangiogenic drugs; it is always imperative to take risk factors into account. If a patient has one or more of these factors, the probability of developing ONJ is higher. Figures 1,2,3 show clinical and radiographic aspects of patients with osteoporosis and cancer with ONJ generated by several factors.

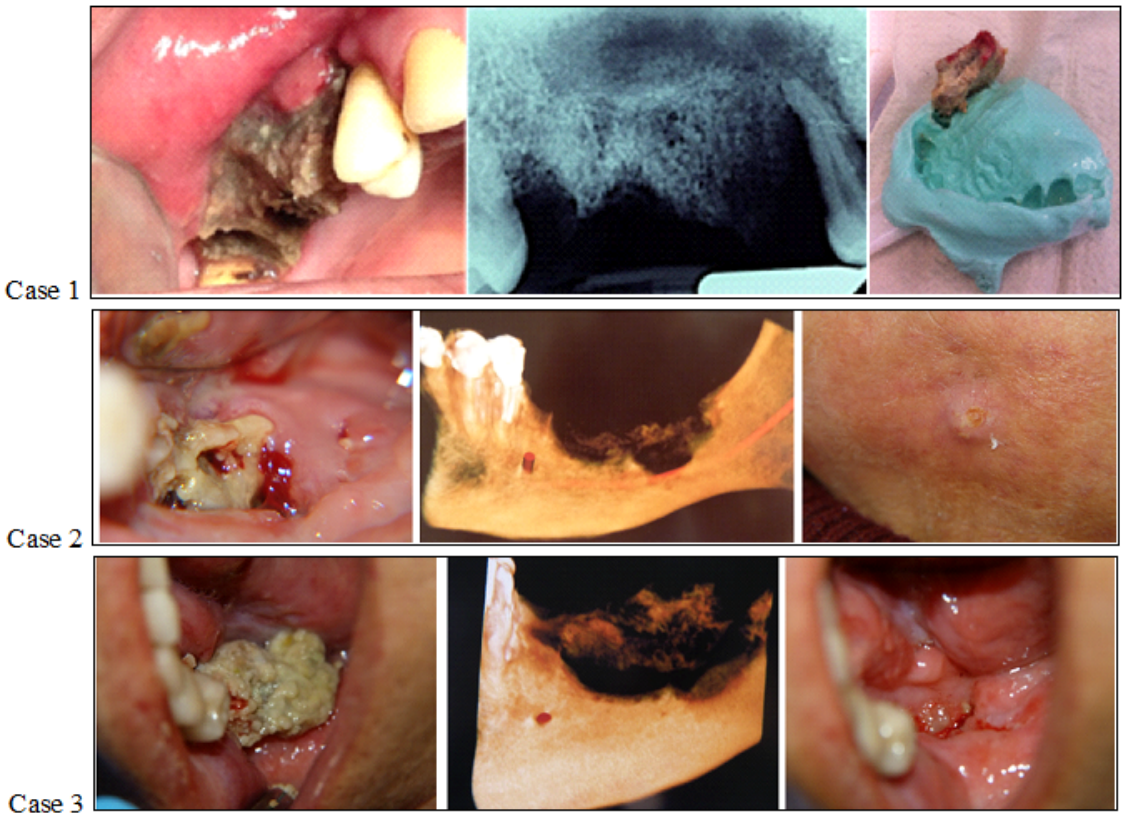

FIGURE 1

Characteristics of patients with osteoporosis and cancer with ONJ, cases 1-3

Case 1) Patient diagnosed with multiple myeloma undergoing treatment with antiresorptive agents with ONJ due to extractions. Alginate impression is taken and the alveolar bone is adhered to the material. It is a favorable situation for the patient because there is scar tissue and no infection. Case 2) Patient in treatment with antiresorptive drugs for osteoporosis with ONJ due to extractions and orofacial fistula. Case 3) Four months after conservative treatment with clindamycin 300 mg and chlorhexidine 0.2 %; note the bone sequestration and healing of the gingiva. Note: Images posted with permission from patients.

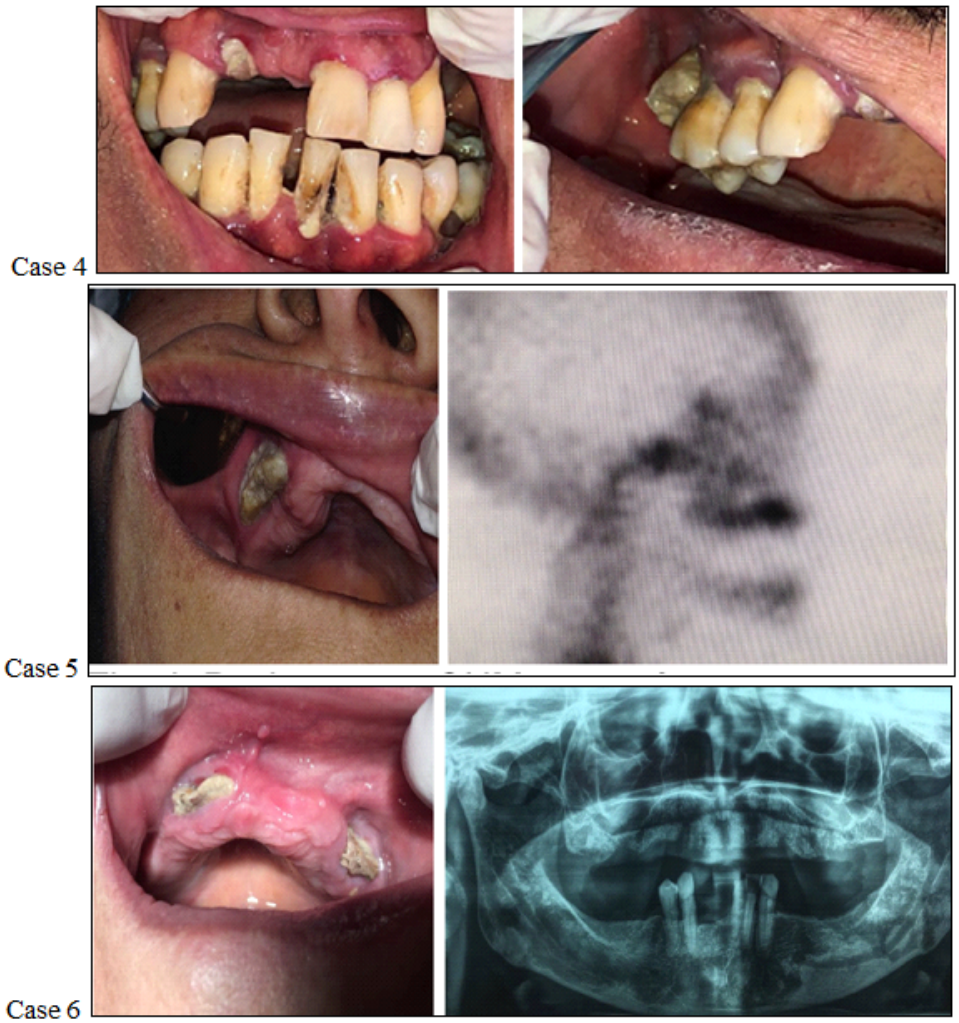

FIGURE 2

Characteristics of patients with osteoporosis and cancer with ONJ, cases 4-6

Case 4) Patient with pancreatic cancer, periodontitis, and ONJ in the upper right posterior segment. Case 5) Patient with spontaneous ONJ in the upper right posterior segment. Case 6) Presence of ONJ due to pressure from a total prosthesis in the upper jaw.
Note: Images posted with permission from patients.

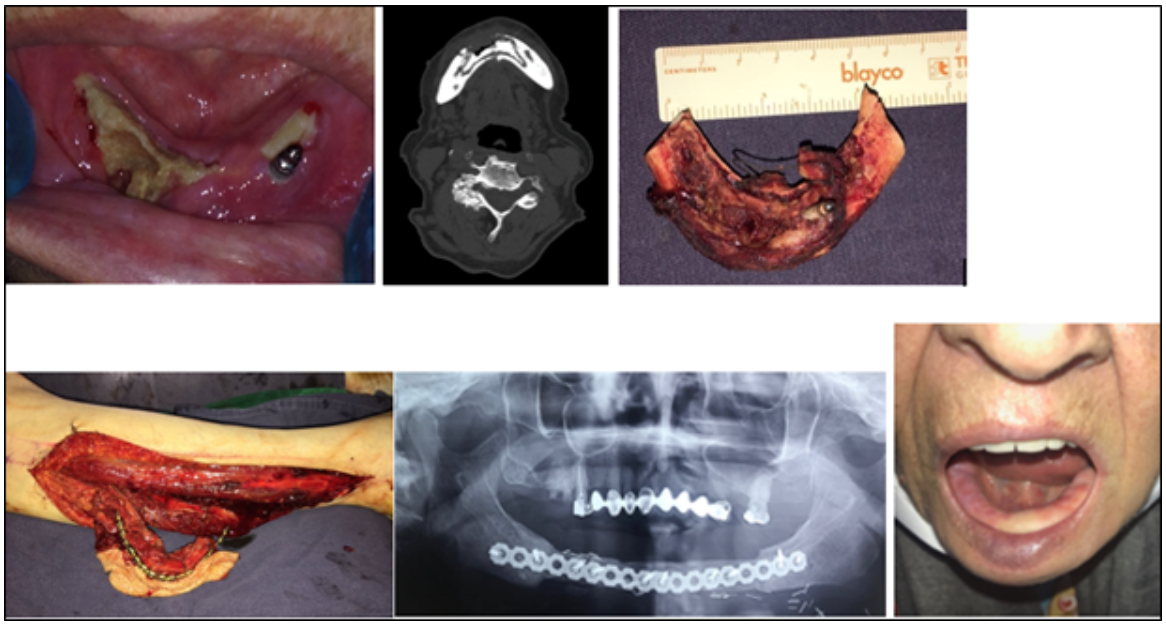

FIGURE 3
Characteristics of patients with osteoporosis and cancer with ONJ, case 7
Mandibulectomy and reconstruction with microvascularized fibular bone-myocutaneous flap due to ONJ in a patient with multiple myeloma.
Note: Images posted with permission from patients.

It is also important to know that cases of ONJ have been described in the literature due to the development of new drugs for the treatment of cancer and bone and autoimmune conditions. This situation could broaden the range in the classification given by Ruggiero, *et al*. in 2014 (7). The following are some of the drugs described in the literature:

- Anti TNF-alpha: adalimumab, infliximab, etanercept, certolizumab, golimumab, rituximab (54,55,56).
- Tyrosine kinase inhibitors: sunitinib, lenvatinib (57,58).
- Recombinant fusion protein: Ziv-Aflibercept (59).
- M-Tor inhibitors: everolimus (60,61).
- Folic acid antagonist: methotrexate (62,63,64).

Due to the wide range of medications related to ONJ and that remain unknown to the vast majority of clinical dentists, it is crucial to raise awareness among them of the risks to improve patient management (65).

CONCLUSIONS AND RECOMMENDATIONS

ONJ has become a serious complication in patients who, due to osteoporosis or cancer, undergo treatment with antiresorptive or antiangiogenic drugs, which compromises their quality of life.

Due to the growing treatments with these drugs, it is important to alert dentists to perform a thorough oral and radiographic review in order to identify the risk factors that can trigger ONJ. An early diagnosis can prevent or reduce the risk of this pathology. Conservative treatments are the best choice.

Medical doctor-dentist communication before starting antiresorptive treatments should always be a priority.

More research is necessary to establish guidelines that can improve the management and treatment of ONJ.

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Notes

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How to cite this article: Chediak-Barbur O. Medication-related osteonecrosis of the jaw, a hidden enemy. An integrative review. Univ Odontol. 2021; 40. https://doi.org/10.11144/Javeriana.uo40.mroj