

## Clinical Setting and Decision-Making

### Osteonecrosis in the context of denosumab — Perspective of the bone metabolism specialist and the maxillofacial specialist

#### Case report:

A 77-year-old postmenopausal woman, menopausal since age 53, was referred from primary care. She was diagnosed with osteoporosis in another region 6 years ago. The T-score of the densitometry at that time was T-2.8 in the spine, T-3.5 in the femoral neck, and T-3.3 in the total hip. She initially received risedronate, which had to be discontinued due to poor GI tolerance after 1 year on therapy and was then switched to a 6-month regimen of denosumab.

In her personal and family medical history, the patient is hypertensive with good control, while her mother suffered a hip fracture at age 86.

The patient reported that after a dental manipulation, consisting of an extraction and placement of two implants performed 7 months ago, she began experiencing pain and lack of healing in the mandibular area. Her dentist diagnosed osteonecrosis, and since then, she has not had another denosumab injection. After implant removal and local treatment with platelet-rich plasma, her symptoms have improved.

The current densitometry T-score is -2.5 in the spine, -3 in the femoral neck, and -2.8 in the total hip.

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## VIEW OF THE BONE METABOLISM SPECIALIST

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The presented case is the archetype of a patient with osteoporosis, with a high risk of fracture, treated with a 6-year regimen of antiresorptive agents, with some efficacy in terms of bone mass and without having experienced fractures during this period. However, she has experienced a rare but characteristic treatment-related complication: osteonecrosis of the jaws (ONJ), although the timing of the dental extraction concerning the denosumab dose is not specified.

A holistic view of the case suggests addressing the local complication, already treated by her dentist, and more importantly, the subsequent clinical management of her osteoporosis.

A global view of the problem may be useful, beyond the particularities of the case presented, to provide a perspective on most cases that may arise.

## BONE METABOLIC DISEASE AND DENTAL HEALTH

Dental implications in bone metabolic diseases are a common finding: from the loss of teeth, which is part of the first clinical descriptions of osteoporosis—it is a cardinal manifestation in hypophosphatasia—the association with hypoplastic teeth and the high frequency of caries and destruction of teeth in osteogenesis imperfecta, occlusion alterations in Paget's disease or osteopetrosis, and various complications in primary hyperparathyroidism and renal osteodystrophy (1).

However, what has most transcended in clinical practice in recent years is a very rare complication called osteonecrosis of the jaws (ONJ), associated with antiresorptive treatment in patients with osteoporosis, mainly bisphosphonates (BP) and denosumab. It is important to distinguish from cancer patients who use the same drugs at much higher doses and have a notably higher incidence rate (2).

## OSTEONECROSIS AND OSTEONECROSIS OF THE JAWS (ONJ)

It may seem paradoxical that osteonecrosis can appear in any bone, such as bone infarcts or sequestration, asymptomatic when located in central areas of the bone,

or having a joint impact if they occur near a joint, as in avascular necrosis of the hip or humeri, but they are not more frequent with antiresorptive treatment and are even used to slow progression (3,4). They are nothing like the antiresorptive-related ONJ.

Possibly the cardinal factor of this difference is that the jaws are located in a septic fossa, separated only by the oral mucosa. Chronic inflammation of the gingival mucosa will cause alveolar bone loss, as in patients with inflammatory arthritis, ONJ weakens the epithelial barrier, and perhaps also alters vascularization (5,6). Hence, additional risk factors for drug-induced ONJ—besides antiresorptives—include diabetes, alcohol consumption, corticosteroid use, immunosuppressants, vascularization inhibitors, smoking, and poor dental hygiene (7).

The first description of ONJ was as an occupational disease in workers with white phosphorus in 1906, such as ceramic decorators who “sharpened” the tips of their brushes with their mouths: phosphonecrosis (formally phosphorus necrosis of the jaw) (8). Subsequently, osteonecrosis associated with local radiotherapy in head/neck tumors is described: radiation osteonecrosis (9). The common denominator of both was the enormous extent of necrosis, abscess formation, and fistulization towards the skin, with severe deformities and very poor prognosis. This consideration is relevant since even today images of these processes are used to teach patients what ONJ can be. In the chapter of historical anecdotes, we should mention that in medical treatment approaches, PENTO therapy was included in these cases—pentoxifylline, tocopherol (to mitigate the vascular component), and clodronate (to improve the bone component) (10), later excluding the bisphosphonate (11).

It was not until 2003 that BP-related ONJ (BRONJ, in international literature) was described, in a patient with multiple myeloma on high doses of pamidronate, with more than 8 weeks of bone exposure in the gingival area (12). Afterwards, the term evolved to antiresorptive-associated osteonecrosis, upon realizing that a potent antiresorptive such as denosumab could also cause the disease, and finally, drug-induced osteonecrosis of the jaws (DIONJ), upon noting an increased risk associated with other drugs unrelated to osteoporosis treatment (13). Of note, the differential diagnosis of the maxillary lesion, beyond concomitant drug use, which includes maxillary sinusitis, deep dental caries, alveolar osteitis, gingivitis and periodontitis, periapical abscess, sarcoma, and chronic sclerosing osteomyelitis (7).

## OSTEONECROSIS OF THE JAW ASSOCIATED WITH ANTI-OSTEOPOROTIC DRUGS

The flood of publications on the subject, more than 4700 entries on PubMed, has not been accompanied by a reasonable improvement in the prevention and

treatment of ONJ. The cause is the low incidence rate of this condition, which is also a reason for the discrepancy seen between dental/maxillofacial professionals and osteologists regarding the stochastic component of its appearance (despite recognizing risk factors, perhaps the most relevant being dental interventions). This results in the practical absence of controlled clinical trials on its prevention and/or treatment. As an example, in the excellent critical review by the European Calcified Tissues Society, published in 2022, despite using 254 bibliographic references, the management algorithms often use verbs such as consider, discuss... and very general measures for both osteoporosis and cancer patients, before or during antiresorptive treatment (2).

In our routine clinical practice, we struggle with the most widespread classification of drug-induced ONJ by the American Association of Oral and Maxillofacial Surgeons (2), which, basically includes:

1. "At risk": All asymptomatic patients on drugs with bone effects (reasonable for potent antiresorptives, such as bisphosphonates, denosumab, questionable for romosozumab, yet unacceptable for estrogens, SERMs [raloxifene/bazedoxifene], or even teriparatide).
2. Stage 0: No clinical evidence of necrotic bone, but there are nonspecific symptoms or clinical/radiological findings (any oral symptom in patients on therapy).
3. Stages 1 (exposed bone or fistula without symptoms), 2 (exposed bone or fistula and signs of inflammation), and 3 (with spread beyond the alveolar bone or pathological fracture or extraoral fistulization), which would not be debatable
4. Non-exposed variant (not widely accepted and excluded in the latest updates): unexplained presence of pain in the jaws, fistula, swelling, loose teeth, or mandibular fracture diagnosed after excluding common jaw diseases known to cause similar signs (14).

This classification may be responsible for the different perceptions of incidence between dental professionals and doctors related to bone metabolism.

## WHAT IS THE RISK FOR OSTEOPOROTIC PATIENTS AND THE DIFFERENT DRUGS?

There is a notable dispersion in incidence data depending on its source, even with geographical variations, and in the way it is expressed.

For oral BPs, the incidence rate is estimated to be between 1/10,000 and 1/100,000 patient-years of treat-

ment (15), from 0.01 % up to 0.06 % for oral BPs (2), and with an increase after the fourth year of exposure to up to 0.23 % (16), without a clear increased risk for IV BPs (zoledronic 0.9/10,000 patient-years) (13,17), despite some clinical practice guidelines considering it higher risk (18), possibly due to the influence of increased risks seen in cancer indications (19).

In the case of denosumab, the incidence rate in the pivotal study was 5.2/10,000 patient-years, and at 10 years, 35/100,000 patient-years, or 0.30 % (12).

Comparatively, a study attributes a risk of 4.5/10,000 patient-years with oral BPs vs 28.3/10,000 patient-years with denosumab, although two-thirds of the patients from this study had been on oral BP treatment before the addition of denosumab (16,20).

For romosozumab, despite its modest antiresorptive effect, initial data estimate an incidence rate between 0.02 % and 0.03 % (13), derived from the presence of 1 case in the clinical trial vs placebo (21) and 1 case in the sequential treatment group with alendronate (22).

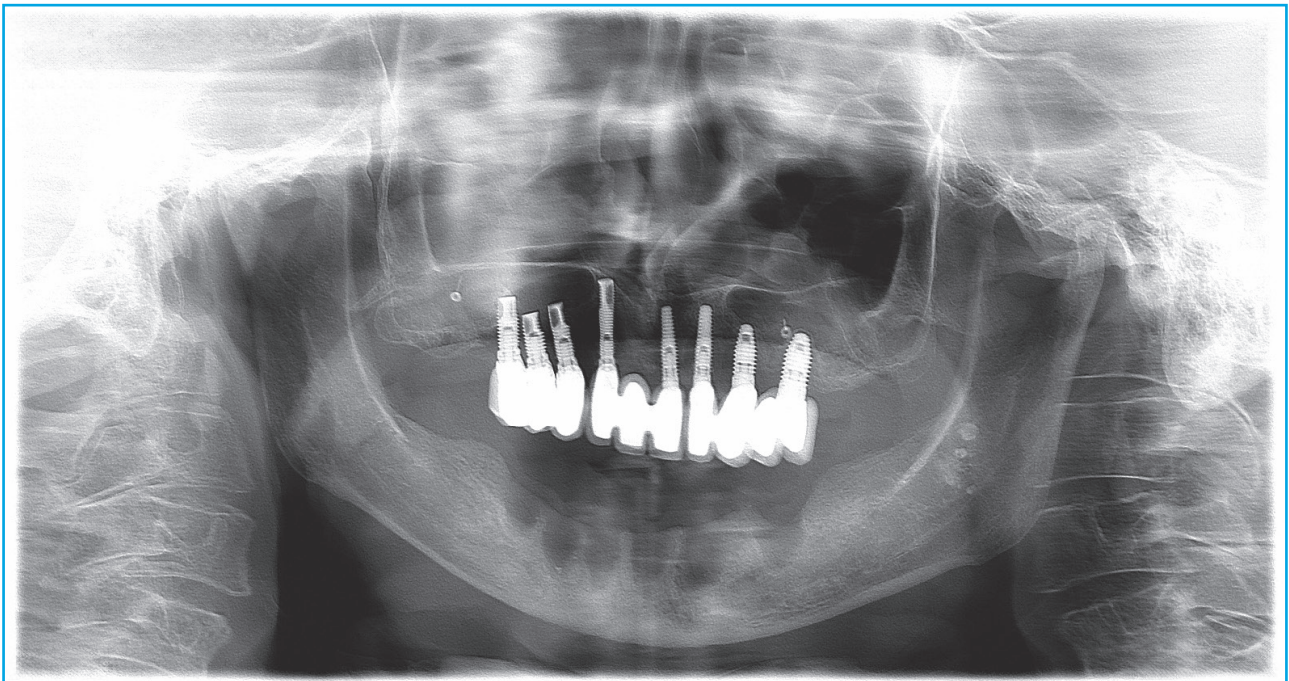
## PREVENTIVE MEASURES FOR DRUG-INDUCED ONJ IN OSTEOPOROTIC PATIENTS

It is universally recommended to explore the oral cavity to promote the best possible dental condition before starting potent antiresorptive treatment (2,23,24), although this consideration should include:

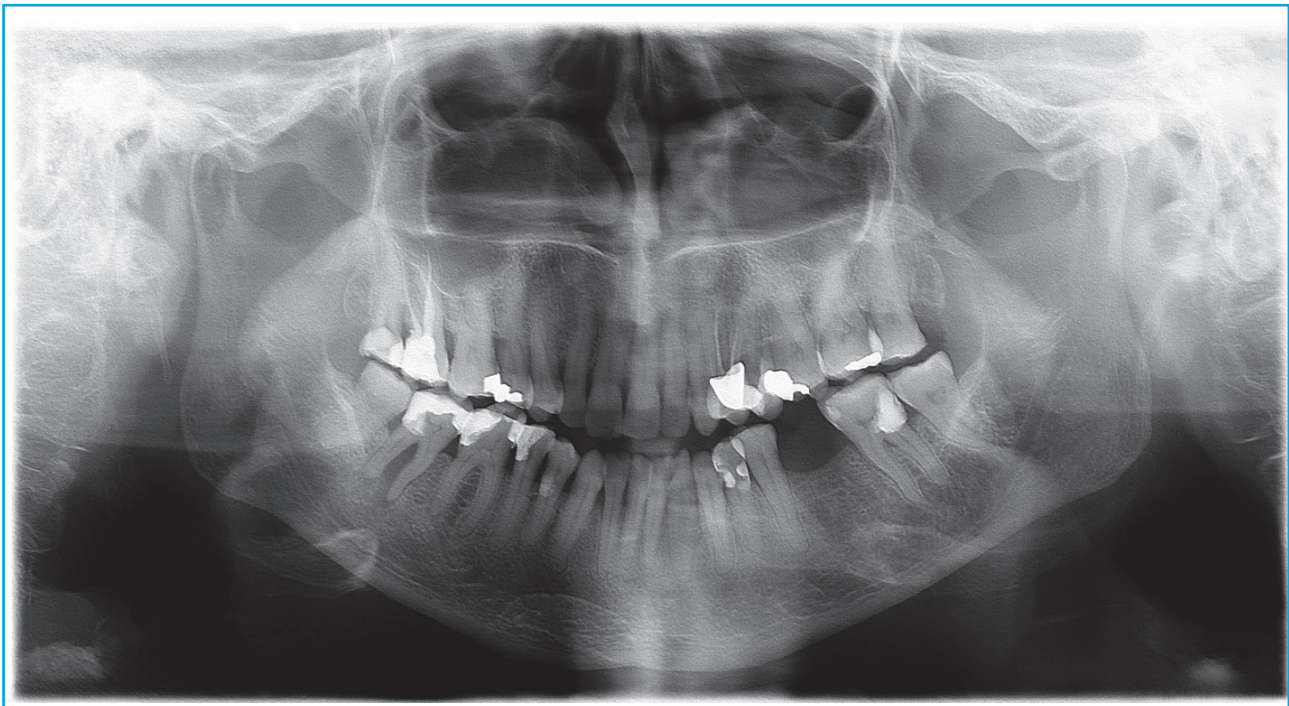
- Advising the dental professional about the patient's short-term fracture risk to avoid excessively prolonged dental sanitation, especially in patients with recent fractures and very high fracture risk for whom, for whatever reason, anabolic treatment is not possible.
- Advising the patient about possible dental treatment options, beyond the potential adverse effect of starting antiresorptive treatment. It is not uncommon for theoretically very efficient dental treatments (dental implants) to be suggested for patients who, due to their osteoporosis, do not have sufficient alveolar bone to support the implants and may "lose" them without the use of antiresorptive treatment (Fig. 1), considering alternatives such as bridges, removable prostheses, etc. (Fig. 2).

If the patient is already on antiresorptive treatment, we must advise both the patient and the dental professional that extractions or implants are not contraindicated due to this condition, despite 50 % of dentists believing otherwise (25). The ineffectiveness of determining CTX to predict the risk of osteonecrosis (2,23,24) and, regarding whether to temporarily suspend antiresorptive treatment, the key data are the





**Figure 1.** A 69-year-old woman with severe osteoporosis (lumbar spine: -5; femoral neck: -3.2; total hip: -3.6 T), dorsal kyphosis with 2 grade II vertebral fractures. She was referred due to the loss of 6 dental implants in the mandible, and mobility of 2 implants in the maxilla. The patient, untreated for osteoporosis, had been undergoing the implant process for 14 months, including bone grafting to elevate the maxillary sinus. Is this treatment justified?



**Figure 2.** A 66-year-old patient with 3 vertebral fractures, 6 years on denosumab treatment. Baseline BMD of -3.4 T in the lumbar spine and -2.3 T in the femoral neck (currently -2.4 and -1.9 T). Dental extraction without problems. Implant proposed with denosumab discontinuation. What if we opt for a bridge instead?

patient's fracture risk, as well as the non-association of the risk of ONJ with the qualitative/quantitative state of bone mass (26).

Temporary discontinuation of bisphosphonate treatment has not been shown to be useful in preventing the onset of ONJ (27) due to its pharmacokinetics and persistence in bone tissue. However, strategies, such as suspending oral BP for 4-8 weeks before extraction and reintroducing it once the oral mucosa has healed, may have an anxiolytic effect on the dentist and the patient and does not significantly increase the patient's fracture risk (28,29).

On the opposite pole is denosumab: its suspension entails a significant rebound effect, with an increased risk of fracture, even in the very short term (up to 1 month after the postponed scheduled dose), including multiple vertebral fractures if the patient has prevalent fractures (30,31). In this case, it is advised to perform the intervention (extraction/implant) in the intermediate period between 2 doses or at the end of the interdose period (32).

Needless to say, in the case of an acute dental problem that is unresponsive to medical treatment, with clinical persistence and patient suffering, that it is up to the patient to make the decision after receiving truthful information on the personalized risk, even signing an informed consent. It is unacceptable to "wait for a few weeks or months" for the sake of the dentist's peace of mind.

In any case, it is always advisable to take antiseptic measures during the surgical moment, including antibiotic prophylaxis (amoxicillin-clavulanic acid from the day before until completing 8 days in patients who accumulate multiple risk factors) and periodic chlorhexidine rinses, avoid multiple extractions in a single surgical act, and even suture the gingival mucosa after extraction (28,29).

## TREATMENT OF ESTABLISHED ONJ

Although the specific treatment of ONJ falls within the competence of the specialist in oral pathology, there are several alternatives and even meta-analyses on the subject (2,28,29,33). However, it is worth mentioning that if considering using teriparatide, absolute or relative contraindications of this treatment must be respected: hypercalcemia, active lithiasis, monoclonal gammopathy of undetermined significance, history of malignant neoplasms, or history of skeletal radiation (24).

In severe cases, surgical management remains the cornerstone of therapy. Antibiotics are the only medical complement with convincing evidence of benefit in DIONJ at present (13).

## MANAGEMENT OF OSTEOPOROSIS TREATMENT AFTER ONJ

This is undoubtedly the Gordian knot of the case presented and our routine clinical practice, and as in the above title, the only solution is that of Alexander the Great: cut the knot with a sword.

In terms of morbidity and mortality, the risk of ONJ cannot be compared to the risk posed by osteoporotic fractures. Therefore, patients with osteoporosis and high fracture risk should continue to be treated, even if they have had ONJ.

The key question would be: what is the likelihood of ONJ recurrence in a patient who has already had an episode of ONJ?

There is no relevant literature beyond a few specific case reports (34) on the possibility of ONJ recurrence when antiresorptive treatment persists. Yes, with zoledronic acid in indication and at oncological doses (35).

In the case of denosumab, there are some reports indicating recurrence in neoplastic disease (36), but in the Freedom study and its extension, out of the 11 patients who had ONJ, 8 continued with denosumab—in 7 cases ONJ healed—and no relapse was ever reported (37).

In the case of patients treated with BP, if, as usual, they have been on therapy for 4 years or more, and their incidence of ONJ increases (15) due to the residual effect of accumulated BPs in the bone, we should calm down and space out the reintroduction of the drug (18 months in the case of risedronate and somewhat longer with other BPs [38] due to the residual protective effect against new fractures). Even in patients with very low BMD or coexistence with other notable fracture risk factors (e.g., corticosteroids, multiple fractures, etc.), a cycle of treatment with teriparatide can be interspersed beforehand (24).

In the case of denosumab, discontinuation results in a notable increase in remodeling, loss of bone mass, and an increased risk of fracture, especially if the patient had prevalent vertebral fractures (30,31). In this case, it is known that sequencing treatment with teriparatide is not efficient in the mid-term to contain the increase in remodeling and bone mass loss, with no data on whether this increases the risk of fracture (39). It is known that the transition to an oral BP is not sufficient if the patient has been on denosumab for more than two years, and even in terms of bone mass, the transition to iv zoledronic acid would not be sufficient (with higher theoretical risk of ONJ) (40). The transition to romosozumab due to its modest impact on remodeling and the attenuation of its bone-forming effect (besides some cases of ONJ with romosozumab) does not seem the most efficient al-



ternative either. Therefore, the best treatment to attenuate the rebound effect of denosumab discontinuation would be its reintroduction. There could be an option—in special cases of very high fracture risk or panic crisis after discussing it with the patient—to undergo a period of combined treatment (denosumab-teriparatide) and then, with the patient “stabilized,” consider continuing with only denosumab or transitioning to BP.

Exhausting the assumptions, if ONJ occurs in a patient on romosozumab, despite the lack of accurate data on how we should behave, assuming it is likely a patient with very high risk of fracture, it may be continued with the same treatment or, in the absence of contraindications, teriparatide can be used for up to 18-24 months before switching to an antiresorptive.

It goes without saying that if ONJ appears in a patient on teriparatide or SERMs, discontinuation is ill-advised, as there is no data on increased risk of ONJ and, despite its extreme rarity, there are cases of ONJ occurring without any treatment (41).

In conclusion, in the case at hand, the best treatment option would be to continue denosumab treatment, in addition to the local treatment of ONJ.

## VIEW OF THE MAXILLOFACIAL SPECIALIST

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Drug-induced osteonecrosis of the jaw (DIONJ) is a rare condition that primarily occurs in patients on IV bisphosphonates.

However, in a hospital like ours (Hospital Universitario La Paz), we see patients who present with osteonecrosis after prolonged treatment with oral bisphosphonates or denosumab. Typically, the development of symptomatic disease is accompanied by surgical manipulation involving the jawbone, especially when it results in bone exposure to the oral cavity, as it is the case after extractions. The case presented here is highly representative of this situation. On the one hand, an extraction was performed, and 2 dental implants were placed. As I mentioned, extraction exposes the bone to an oral cavity populated with potentially pathogenic microorganisms, and the placement of implants requires well-vascularized bone for the process of osseointegration to occur. Thus, we encounter the two situations implicated in the pathogenesis of osteone-

crisis: infection and vascularization changes, which in this case have resulted in mandibular osteonecrosis. Fortunately, the process seems to have been limited and affected only the bone in the implant area, leading to bone sequestration that was removed along with the non-integrated implants. At this point, the most important step is to thoroughly debride the underlying bone and ensure good soft tissue coverage. The use of platelet-rich plasma or growth factors can aid in healing.

In our experience, treatment with denosumab does not contraindicate the placement of dental implants. We usually prefer to first perform the extraction, ensure good mucosal coverage of the socket, and delay the placement of implants for about 10-12 weeks after the extraction. We always use preoperative antibiotic prophylaxis and postoperative antibiotic treatment if deemed necessary. Regarding the optimal timing for the procedure, considering that denosumab is administered semiannually, we recommend performing the procedures 4 or 5 months after the administration of the drug.

Finally, on the continuation of pharmacological treatment, one must weigh the benefits of the drug vs the risk of osteonecrosis. If the process has been localized with bone sequestration that has been removed and the bone has healed well, without evidence of disease progression, we believe that treatment could be continued.

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