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Drug-Induced Osteonecrosis of the Jaws

How to Diagnose,
Prevent, and Treat It

Robert E. Marx, DDS, FACS

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Prevent, and Treat It

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Dedication

Indeed, a dog can be man's best friend. I have been blessed to have grown up with and lived my adult life with such dogs. Due to their shorter life span than ours, their love and loyalty too often fade with the years. To commemorate that love and loyalty as well as every lick in the face, I want to dedicate this book to them in the order that they were with me: Blackie, Teeka, Cinder, Cindy, Lillie, Lucky, Rusty, Odie, Bones, Ninja, Rocky, Tubby, and Libby and Copper, who are still with me and my wife.

Preface

Dead bone in the mouth, known as *drug-induced osteonecrosis of the jaws (DIONJ)*, is a problem that every dental and oral and maxillofacial surgeon faces. It is also a problem that every oncologist faces.

What was first recognized in 2003 and linked to bisphosphonates has been expanded to include RANK ligand inhibitors and antiangiogenic drugs. The numbers of DIONJ cases have accumulated into tens of thousands and have caused bone loss, infection, pain, and deformity in many individuals. DIONJ is a drug complication that has not gone away, nor is it likely to go away. Most of the responsibility in preventing and managing the complication of this medical drug therapy falls on the dental profession and its specialties.

This author has published two previous texts on DIONJ (2007 and 2011) identifying the biologic mechanism of bone necrosis, its pathophysiology, and suggestions on its management. This new text accepts and does not dwell on the known pathophysiology of DIONJ from each drug. Instead, it concentrates its attention on specific measures the clinician can practice to prevent DIONJ, to assess risk, to slow its progress, to prevent worsening it, and to resolve it when it does occur.

This text, with its case samples, outlines specific medical history questions to ask patients as well as specific caveats of the oral examination related to DIONJ identification and assessment. It also presents specific antibiotic protocols that have proven best in controlling secondary infection. A new and more useable staging system is introduced that will help the clinician in disease assessment and treatment planning.

For the osteoporosis/osteopenia patient, the effective use of drug holidays allows the dental and oral and maxillofacial surgeon to perform indicated procedures with greater safety. The newly discovered role of occlusion and occlusal trauma in initiating DIONJ has led to the before-unrecognized preventive value of occlusal adjustments, the splinting of teeth, and mouthguards.

It is hoped that this book will serve as a guide for each provider to lessen the impact of DIONJ on their patients while still maintaining the dental and reconstruction/rehabilitation services we are known to provide.

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Chapter 1

Understanding Drug-Induced Osteonecrosis of the Jaws



What is now most accurately termed *drug-induced osteonecrosis of the jaws (DIONJ)*¹ came upon the dental scene in 2003.^{2,3} Since then, there have been over 2,500 refereed articles published on it. Every specialty of dentistry has produced a position paper on it. Every drug company manufacturing one of the offending drugs has a warning in its advertising referring to “dental problems” or “jaw problems.” And most every practicing dentist has seen one or more cases.

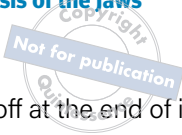
Although numerous other terms for DIONJ have been advanced, such as *medicine-related osteonecrosis of the jaws (MRONJ)*,⁴ *bisphosphonate-associated osteonecrosis of the jaws (BAONJ)*,⁵ and *chemo-osteonecrosis of the jaws (CONJ)*,⁶ among others, DIONJ is the most correct due to its identification of a cause-and-effect relationship, its acknowledgment that drugs other than bisphosphonates cause it, and because it is consistent with the term adopted by the World Health Organization and published by the American Medical Association ICD-10 code (M87.10).¹ Nevertheless, by any term, the dental profession has come to recognize the necrotic bone in either jaw as osteonecrosis caused by certain drugs.

How Do These Drugs Kill Jaw Bone?

The basic mechanism of the most common drugs known to cause DIONJ is that they are cellular poisons that affect bone remodeling and renewal. A few others cause DIONJ by affecting the blood supply to bone.

Bone is derived from osteoblasts, which secrete osteoid. These cells become entrapped in their mineralized matrix to become osteocytes, which have a life span of about 180 days. During this time, they secrete a protein called *osteoprotegerin*, which competes and inhibits RANK ligand (reactive activator of nuclear κ B ligand).⁷ Because RANK ligand is a natural activator of osteoclasts, this process resists bone resorption and maintains the bone during the 180-day life span of the osteocyte.

The basic mechanism of the most common drugs known to cause DIONJ is that they are cellular poisons that affect bone remodeling and renewal.



When the osteocyte ages or dies off at the end of its life span or from injury, its production of osteoprotegerin ceases, allowing RANK ligand to stimulate osteoclasts to resorb old dysfunctional bone, injured bone, or dead bone. This process is an evolutionary homeostatic process that maintains our skeletons in a healthy state, with bone capable of withstanding loads with proper elasticity and integrity.

Therefore, the clinician should understand that the mandible and the maxilla are not static and are turning over daily. In fact, the alveolar bone of the jaws

The alveolar bone of the jaws turns over at a rate that is 10 times faster than that of long bones,⁸ which is why DIONJ always begins in the alveolar bone.

turns over at a rate that is 10 times faster than that of long bones,⁸ which is why DIONJ always begins in the alveolar bone. As such, the most vulnerable areas of the jaws are those areas where bone turnover is the greatest—ie, extraction sockets, the posterior lingual areas around mandibular molars, the maxillary alveolus and floor of the sinus above the maxillary molars, areas of alveolar bone surgery, areas of chronic occlusal overloading, and the surface of tori.⁹

Femur fractures

This understanding of bone turnover and bone remodeling also predicted the midshaft femur fractures resulting from osteoporosis drugs first reported in 2008 and now recognized frequently by orthopedic surgeons.^{10,11} This complication of DIONJ-causing drugs is now warned about by the drug companies.

The femur is the longest bone in the human skeleton. As we walk or run, we plant our feet so that the tibia/fibula and joints absorb the compressive forces. However, the femur flexes somewhat at its midshaft during this process as the knee bends. This creates an increased demand for bone remodeling and renewal in the midshaft areas, which after long-term use from many of the DIONJ-causing drugs results in a unique midshaft fracture due to the brittleness of the old unrenewed bone in that location (Fig 1-1).

Risk Factors for DIONJ

Unfortunately, drug companies and most position papers have published related “risk factors” that are not really risk factors for DIONJ at all. Publications have claimed that obesity or smoking,¹² anemia,¹³ diabetes,¹⁴ and many other common human habits and maladies cause DIONJ; however, these things do not actually cause osteonecrosis unless the individual has also been taking one of the drugs known to cause osteonecrosis. These are not risk factors by themselves. Therefore, the clinician examining or treating patients taking drugs that have



FIG 1-1 Atypical fracture of the femur caused by extended use of alendronate (Fosamax).



FIG 1-2 (a) DIONJ from alendronate in a patient treated for osteopenia. (b) DIONJ from denosumab in a patient treated for osteoporosis.

been known to cause DIONJ should keep in mind the seven critical aspects of risk described in the next section.

The drug itself

The only risk factor for DIONJ is the drug itself. The degree of the risk is related to the potency of the drug, the dose of the drug, the frequency that it is taken, the length of time the individual has taken the drug, its mechanism of action, and when the last dose was taken.

The only risk factor for DIONJ is the drug itself.

1. Potency

The potency of oral bisphosphonates taken for osteoporosis is well known and is determined relative to the first bisphosphonate introduced: etidronate. Relating the potency of etidronate as 1, tiludronate is 50 times as potent, risedronate and ibandronate 1,000 times as potent, and alendronate 5,000 times as potent. The potency for subcutaneous denosumab, a RANK ligand inhibitor for osteoporosis, is not known as compared to bisphosphonates. However, from its mechanism of action and its track record of DIONJ, it is at least as potent as alendronate when prescribed for osteoporosis and even more potent than zoledronate when administered for cancer patients. In fact, alendronate and denosumab are responsible for over 97% of DIONJ cases in the noncancer patient treated for osteopenia/osteoporosis (Fig 1-2 and Table 1-1).

Table 1-1 Percentage of DIONJ cases in noncancer patients caused by various osteoporosis drugs (N = 211)

Drug	Dosage	N	%
Alendronate	70 mg per week	129	61%
Denosumab	60 mg every 6 months	76	36%
Risedronate	35 mg per week	4	2%
Ibandronate	150 mg per month	2	1%
Raloxifene	NA	0	0%
rhPTH 1-34	NA	0	0%
rhPTH 1-80	NA	0	0%
Vitamin D + calcium	NA	0	0%

This twofold higher dose underscores the danger of alendronate as a major risk factor for DIONJ.

2. Dose and frequency

While the dose of oral risedronate is 35 mg/week and the dose of oral ibandronate is 150 mg/month, which averages out to be 35 mg/week, the dose of oral alendronate is 70 mg/week. This twofold higher dose underscores the danger of alendronate as a major risk factor for DIONJ. Denosumab for the osteopenia/

osteoporosis patient is a fixed dose of 60 mg administered subcutaneously every 6 months (see Table 1-1).

3. Half-life

One of the major distinctions between bisphosphonates and denosumab is their half-life in bone. All bisphosphonates become irreversibly bound to the mineral matrix in bone with a half-life of 11.2 years.¹⁵ The affinity of bisphosphonates for bone is so great that when an osteoclast dies from ingesting a bisphosphonate and bursts, it releases the bisphosphonate. The bisphosphonate molecules are then rapidly reincorporated into adjacent bone. It is this cumulative buildup of bisphosphonate molecules in the more actively turning over alveolar bone that causes DIONJ from these drugs and targets the jaws.⁹

Denosumab does not become bound to bone and has a half-life of only 26 days.¹⁶ However, its high potency and therefore its equal risk of causing DIONJ compared to alendronate is due to its mechanism of action affecting the very development of osteoclasts in the bone marrow.¹⁷

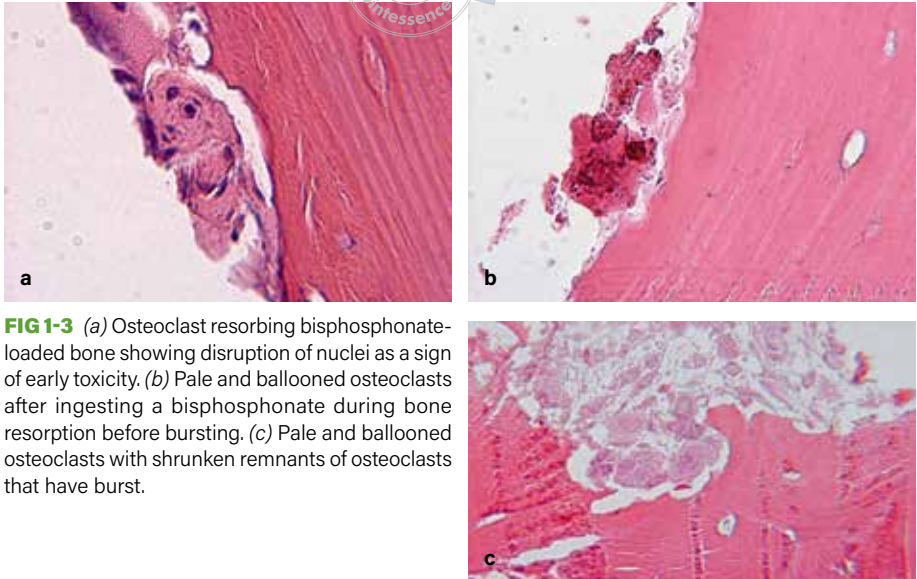


FIG 1-3 (a) Osteoclast resorbing bisphosphonate-loaded bone showing disruption of nuclei as a sign of early toxicity. (b) Pale and ballooned osteoclasts after ingesting a bisphosphonate during bone resorption before bursting. (c) Pale and ballooned osteoclasts with shrunken remnants of osteoclasts that have burst.

4. Mechanism of action

All bisphosphonates are cellular poisons that inhibit the cytoplasmic enzyme farnesyl synthetase required by nearly every cell.¹⁸ The reason why osteoclasts are more greatly affected is that they ingest a high concentration of the bisphosphonate that accumulates into bone as they go about resorbing it. Essentially, the osteoclast is singled out because it is the cell that comes into contact with the greatest concentration of a bisphosphonate, and the jaws are singled out because of their constant need for osteoclast-mediated bone turnover due to occlusion and denture wearing. Other less frequent but noted complications from bisphosphonates such as esophagitis¹⁹ and renal tubular necrosis²⁰ are also due to these tissues coming into contact with a greater concentration of bisphosphonates than other tissues.

Nevertheless, bisphosphonates' main toxicity is focused on the adult osteoclast as it resorbs bone that has accumulated a high concentration of bisphosphonate, with much less effect on developing osteoclasts in the bone marrow or circulating osteoclasts (Fig 1-3). That is, the main driving force of bisphosphonate toxicity is its half-life in bone and its accumulation from continuous dosing due to its irreversible binding to the mineral matrix of bone.^{21,22}

The mechanism of action of denosumab in DIONJ is its inhibition of RANK ligand²³ (Fig 1-4a). However, RANK ligand is not only required to stimulate the adult osteoclast to resorb bone but is also required in nearly every maturation step of the osteoclast from the mononuclear bone marrow osteoclast precursor

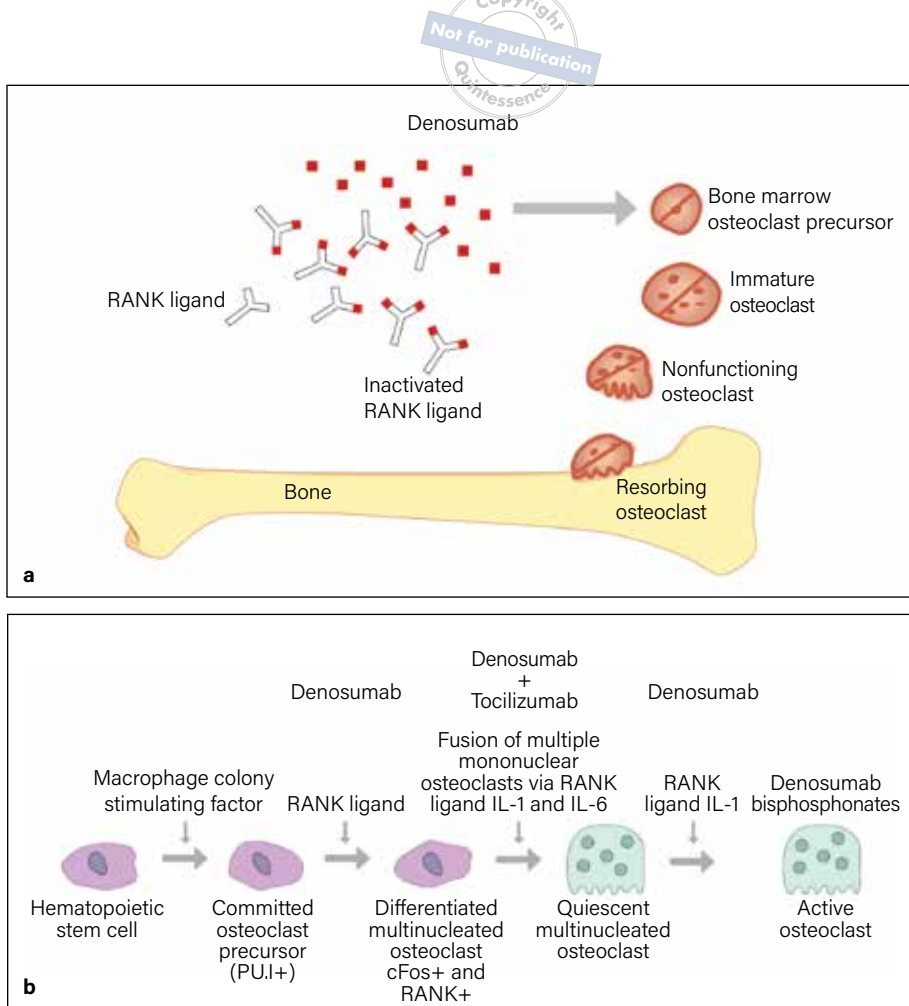


FIG 1-4 (a) Denosumab's inhibition of RANK ligand affects the mononuclear osteoclast precursors in the bone marrow, the developing osteoclasts in the bone marrow, the maturing osteoclasts, and the adult multinucleated osteoclasts. (b) Because RANK ligand is required in most phases of osteoclast development and maturity, RANK ligand inhibitors like denosumab have a profound negative effect on bone remodeling and renewal.

Table 1-2 Dosing risks of DIONJ after exposure to osteoporosis drugs

Drug	Risk begins	Mean dose for DIONJ
Oral alendronate (70 mg)	104th dose	240 doses
Intravenous zoledronate (4 or 5 mg)	4th dose	9 doses
Subcutaneous denosumab (60 mg every 6 mos)	4th dose	8 doses
Subcutaneous denosumab (120 mg/mo)	2nd dose	3 doses



to the multinucleated functioning osteoclast^{9,24} (Fig 1-4b). It is this potent effect on the developing and circulating osteoclasts as well as the adult osteoclasts that make denosumab (60 mg every 6 months) a significant risk factor for DIONJ in the osteopenia/osteoporosis patient and an even greater risk factor when it is administered at 120 mg/month for cancer patients.

5. Length of time of drug use

Certainly the length of time the drug has been used relates to an increased risk. With bisphosphonate use, this increased risk comes from the accumulation of bisphosphonate molecules in bone over the time in which it has been taken due to its long half-life in bone. For denosumab, which has a short half-life of just 26 days, this increased risk relates to its multifocal inhibitory effects on developing osteoclasts in the bone marrow, the circulating osteoclasts in blood, and the adult osteoclast trying to resorb bone, thereby depleting the osteoclast population and reserves.

6. Route of administration

Bisphosphonates in the treatment of osteopenia/osteoporosis are mostly prescribed as oral drugs. However, the intravenous (IV) drug zoledronate, which is mostly used for cancer patients with bone metastasis, is also used for osteoporosis at a different dose and frequency, that is, 5 mg IV once per year. Whether for the treatment of osteopenia/osteoporosis (60 mg every 6 months) or cancer metastasis (120 mg/month), denosumab is always administered subcutaneously.

The difference between an oral and IV bisphosphonate is significant. An ingested oral bisphosphonate is poorly absorbed (ie, 0.68% in the gut). Therefore, there is a gradual accumulation of the oral bisphosphonate in bone. From the experience of the author, one must take an oral bisphosphonate for 2 years (104 doses) to begin to develop a risk for DIONJ, with the risk increasing with subsequent doses beyond that (Table 1-2). On the other hand, with IV zoledronate for either osteoporosis at 5 mg/year or for cancer at 4 mg/month, the risk for DIONJ begins with the fourth dose and increases with each dose beyond that. This early development of risk is because the IV route of a bisphosphonate loads the bone 140 times greater and faster than the oral route.⁹ The similar risk profile for a once-per-year IV bisphosphonate dosing versus a once-per-month dosing is due to the 11.2-year half-life in bone (Fig 1-5a; see Table 1-2).

The IV route of a bisphosphonate loads the bone 140 times greater and faster than the oral route.⁹

For denosumab, the subcutaneous route of administration is the same for osteopenia/osteoporosis patients as it is for cancer patients. Here the difference in toxicity is related to the dose (60 mg vs 120 mg) and the frequency of administration (once every 6 months vs once per month; see Table 1-2).

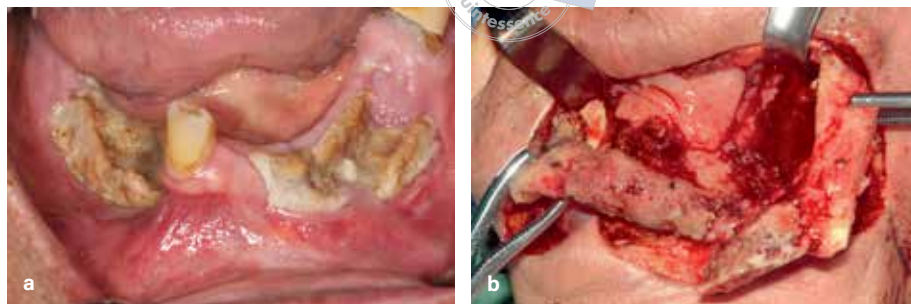


FIG 1-5 (a) Stage III DIONJ due to IV zoledronate at 5 mg/year after six doses. (b) Extensive Stage III DIONJ with a pathologic fracture due to denosumab administered as a replacement for zoledronate.

7. Heightened risk when denosumab follows a bisphosphonate

With the more recent marketing of denosumab and the known risks for DIONJ from bisphosphonates throughout the medical profession, many treating physicians have switched from a bisphosphonate to denosumab in both osteopenia/osteoporosis patients and cancer patients. However, the loading of alveolar bone with a bisphosphonate by either the oral or IV route followed by subcutaneous denosumab has resulted in a rapid development of a more extensive and more severe form of DIONJ with advanced staging (Fig 1-5b).

Initiating factors

Factors too often touted as risk factors are actually initiating factors. That is, these entities do not cause DIONJ by themselves, but the increased need for bone remodeling and renewal created by these factors can initiate DIONJ in a person taking or who has taken one of the known drugs that cause DIONJ.

Extractions

The greatest initiator of DIONJ is a tooth extraction (61%; Table 1-3).^{9,25} In a person within the risk category for DIONJ, the extraction of a tooth creates an

The greatest initiator of DIONJ is a tooth extraction.

increased need for bone turnover, which the alveolar bone may not be able to meet depending on the level of risk within the alveolar bone as discussed in this section. In some cases, the extraction occurs within

already necrotic bone that may not be overtly exposed. That is, in some cases the necrotic bone is only exposed by a subtle pinpoint fistula or through the furcation of a molar tooth or subtly via the periodontal ligament space before the tooth is extracted. Therefore, it may be best to say that an extraction is associated with

**Table 1-3** Associated indicators of DIONJ (N = 400)

Indicator	N	Percentage of cases
Tooth removal	244	61%
Spontaneous/occlusion	112	28%
Dental implant placement	20	5%
Periodontal surgery	20	5%
Other	4	1%

the identification of and diagnosis of DIONJ in 61% of cases, where in some cases the trauma from the extraction initiated it while in other cases the DIONJ was already present.

Traumatic occlusion/spontaneous

In the author's experience, about 30% of DIONJ seems to occur without any extraction of teeth or surgical intrusion into the alveolar bone. Although necrotic bone in the jaws may develop directly related to the potency and the length of time of taking the drug, on closer inspection most are seen to be related to traumatic occlusion. It is noted that 50% of DIONJ cases from any drug occur in the posterior lingual area of the mandible, where the wide occlusal table of molars and the axial loading of occlusal forces is directed onto the lingual cortex (Figs 1-6a and 1-6b).

DIONJ is often targeted to areas of selective occlusion due to missing teeth or restorations in hyperocclusion.

In these same cases, the wear pattern and admitted bruxing habits of some patients is often seen as well (Fig 1-6c). Similarly, DIONJ is often targeted to areas of selective occlusion due to missing teeth or restorations in hyperocclusion (Figs 1-6d and 1-6e).

Chronic inflammation

No doubt chronic inflammation from untreated periodontal disease is an initiating factor or contributes to another initiating factor (ie, traumatic occlusion or an extraction to create DIONJ). Inflammation increases the osteoclast-mediated turnover rate of alveolar bone that causes the bone to die off if it is loaded with a bisphosphonate or if the osteoclast population is diminished by denosumab.

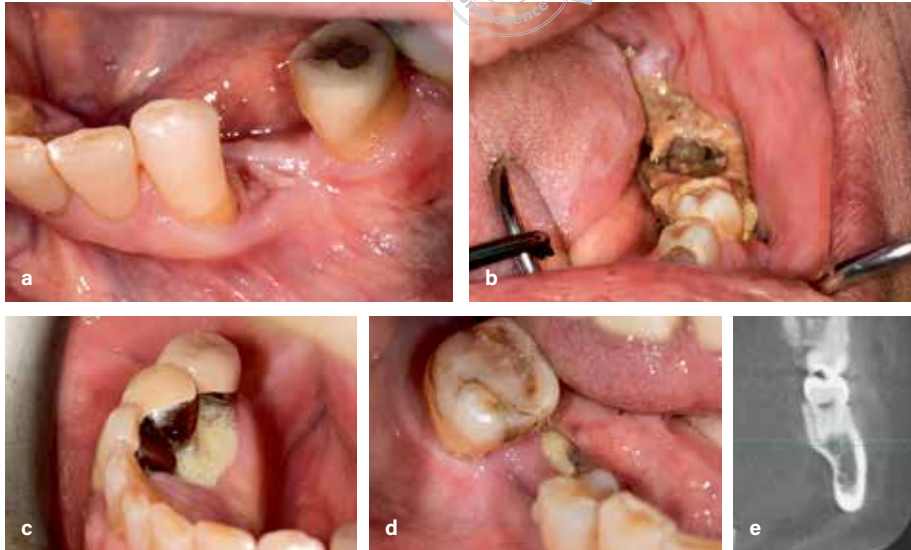


FIG 1-6 (a) DIONJ initiated after a periodontal osseous surgery. (b) DIONJ initiated by a tooth extraction. (c) Clinical DIONJ is most often seen on the lingual cortex opposite the molars. (d) DIONJ adjacent to the molar with obvious severe wear. (e) The axial loading of molars is directed on the lingual cortex and is responsible for the high incidence of DIONJ in that location.

Surgical intrusion into alveolar bone

Like tooth extractions, several dental procedures have been known to result in DIONJ (Fig 1-7a). Procedures such as alveolar bone biopsies (Fig 1-7b), crown lengthening (Fig 1-7c), osseous periodontal surgery, and the placement of dental implants (Fig 1-7d) have resulted in DIONJ by imparting a degree of trauma to the alveolar bone that in turn creates a need for bone remodeling and renewal, which these drugs inhibit.

Vulnerable sites

Areas of common occurrence of DIONJ have also been incorrectly labeled as risk factors. Once again, these areas do not develop necrotic bone by themselves. It

The most common vulnerable site is the posterior lingual cortex of the mandible.

is another underlying injury that causes these areas to become necrotic (ie, radiation, bisphosphonates, RANK ligand inhibitors, and more rarely antiangiogenic drugs). The most common vulnerable site is the posterior lingual cortex of the mandible (Fig 1-8a).



FIG 1-7 (a) Selective unilateral occlusion initiated this DIONJ. (b) DIONJ initiated by a bone biopsy. (c) DIONJ initiated by a crown lengthening procedure. (d) DIONJ initiated by the surgical placement of dental implants.



Another well-known vulnerable site is the surface of a torus (Fig 1-8b). Although we recognize that tori are hard mature outcroppings of compact bone, it is often unappreciated that they have a high turnover rate particularly at their surface. The vulnerability of tori to develop DIONJ is added to by the thin oral mucosa that overlays them. Additionally, in the author's experience, DIONJ develops in the mandible twice as frequently as in the maxilla.

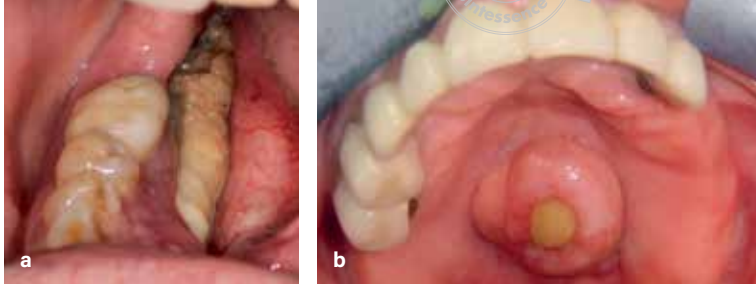


FIG 1-8 (a) The most common site for DIONJ is the posterior mandibular lingual cortex. (b) Tori are a frequent site for DIONJ.

Comorbidities

The many comorbidities often incorrectly labeled as risk factors also do not cause DIONJ by themselves. They certainly contribute to it by making DIONJ occur sooner or to become more extensive and severe when it does occur. Some of these comorbidities include diabetes, smoking, cancer, corticosteroids, chemotherapy, and immune-based diseases, among others.¹²⁻¹⁴

Definition of DIONJ

Despite its many names, the definition of DIONJ is mostly consistent among the position papers produced by various originations.^{5,26,27} A good working definition is this:

Exposed nonhealing bone in the mandible or maxilla that is present for more than 8 weeks in a person who received a systemic drug known to cause ONJ but who has not received a local tumoricidal dose of radiation to the jaws.

Staging of DIONJ

Staging systems for oral cancer,²⁸ lymphomas,²⁹ and osteoradionecrosis³⁰ identify the severity and extent of the disease and guide treatment decisions and prognosis. None of them include the subjective relation of pain, which is variable between patients and based on analgesic use. The following is a straightforward staging system for DIONJ developed by the author:

- **Stage 0:** Radiographic and/or clinical evidence of alveolar bone toxicity without bone exposure. This is often recognized as sclerosis of the lamina dura and widening of the periodontal ligament space. It is often noted symptomatically as



FIG 1-9 Sclerosis of the lamina dura and a widened periodontal ligament space.

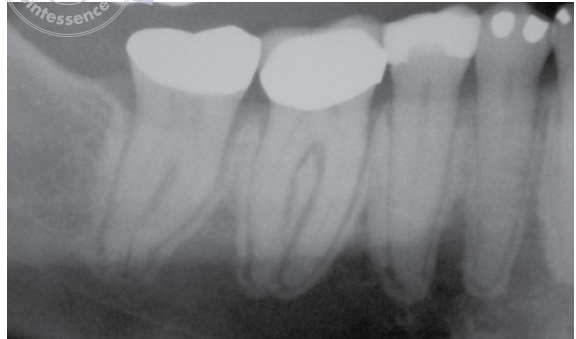


FIG 1-10 Stage I DIONJ.



FIG 1-11 Stage II DIONJ.



deep bone pain or tooth pain or tooth mobility not attributed to a more obvious cause (Fig 1-9). Stage 0 should be taken as caution that exposed bone may result if subjected to any one of the initiating factors discussed.

- **Stage I:** Exposed bone limited to one quadrant (Fig 1-10)
- **Stage II:** Exposed bone in two quadrants (Fig 1-11)
- **Stage III:** Exposed bone in three or four quadrants (Figs 1-12a and 1-12b) **OR** osteolysis to the inferior border of the mandible (Fig 1-12c) **OR** pathologic fracture (Fig 1-12d) **OR** extension into the maxillary sinus (Fig 1-12e)

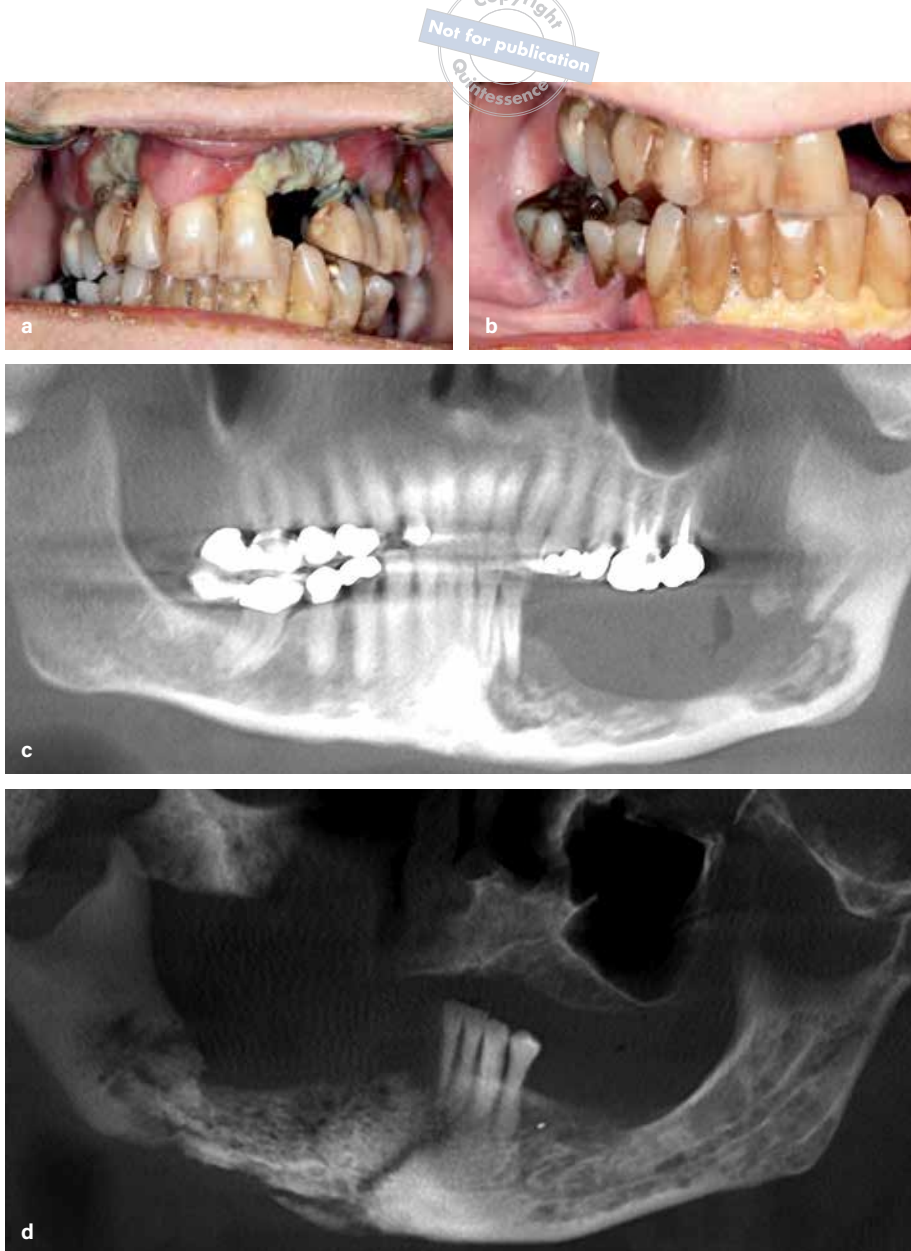


FIG 1-12 Stage III DIONJ. (a and b) Three separate areas of DIONJ. (c) Osteolysis to the inferior border. (d) Pathologic fracture. →

Antiangiogenic Drugs

Pertinent only to patients being treated for cancer are two other drugs known to cause DIONJ; bevacizumab³¹ and sunitinib.³² Bevacizumab is used in the treatment of lung cancer and is a direct inhibitor of vascular endothelial growth factor (VEGF).³³ It is usually administered IV based upon weight but most commonly 500 mg every



FIG 1-12 (cont) (e and f) Maxillary sinus involvement.

2 weeks. Reported cases of DIONJ from this drug and those observed by the author have mostly been Stage I and respond to discontinuation (drug holiday) with either stabilization, sequestration, or local surgical removal (Fig 1-13).

Sunitinib is a tyrosine kinase inhibitor mostly administered to patients with renal cancer and less commonly for gastrointestinal stroma tumors and pancreatic neuroendocrine tumors.³⁴ It inhibits several growth factors required by the cancer but seems to have its most profound effect on VEGF and therefore is mostly an antiangiogenic drug. Sunitinib has more reported cases of DIONJ than bevacizumab and produces more Stage II and Stage III presentations (Fig 1-14). It is an oral drug taken as a daily dose between 12.5 mg and 50 mg for nine 6-week cycles. Discontinuation of the drug seems to halt the progression of DIONJ, and most cases are either stabilized with exposed bone or require surgical removal including resections if extensive.



FIG 1-13 DIONJ caused by bevacizumab.

Not for publication



FIG 1-14 DIONJ caused by sunitinib.



FIG 1-15 DIONJ resulting from tocilizumab prescribed to treat rheumatoid arthritis.

Drugs prescribed for immune-based disease

In rare instances, the drug tocilizumab has caused DIONJ cases (Fig 1-15). Tocilizumab is an interleukin-6 (IL-6) inhibitor used to treat rheumatoid arthritis, giant cell arteritis, and some juvenile polyarthritis conditions.^{35,36} As an IL-6 inhibitor, it represents a specific inhibitor of immune-based inflammation but also an inhibitor of osteoclast development similar but not identical to denosumab as a RANK ligand inhibitor. The inhibition of IL-6 prevents the mononuclear precursor cells of osteoclasts from fusing together to produce a multinucleated cell and therefore stops the development of osteoclasts resulting in a risk for DIONJ.

Tocilizumab may be administered subcutaneously but is mostly infused IV at 4 mg/kg per week for 4 weeks followed by 8 mg/kg per week for another 4 weeks. Discontinuation of the drug halts the progression of DIONJ, but the few cases experienced by the author have been Stage III, requiring a resection.



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