Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment

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Skeletal complications caused by osteoporosis or bone metastases are associated with considerable pain, increased mortality, and reduced quality of life. Furthermore, such events place a burden on health care resources. Agents that prevent bone resorption, such as bisphosphonates or denosumab, can reduce the risk of skeletal-related events and are widely used in patients with osteoporosis or bone metastases of cancer. Medication-related osteonecrosis of the jaw (MRONJ) is a rare, but potentially serious, adverse event associated with high cumulative doses of bisphosphonates or denosumab. However, MRONJ can be treated, and the likelihood of the development of this condition can be reduced through prophylactic dental care and the maintenance of good oral hygiene. Dentists, as part of a multiprofessional team, have a critical role in preventing MRONJ. This review describes the incidence and pathophysiology of MRONJ and provides guidance for dental practitioners with regard to the screening, prophylactic treatment, diagnosis, and management of patients with this condition. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;127:117−135)

Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon condition that can occur after exposure to agents used to prevent bone complications, such as bisphosphonates or denosumab, or treatment with other agents, such as angiogenesis inhibitors.[1] In the majority of cases, MRONJ manifests as exposed bone in the maxillofacial region (Figure 1), although non-exposed MRONJ has also been recognized (Figure 2).[2-5]

Bisphosphonates and denosumab are predominantly used to reduce the risk of skeletal complications in patients with bone loss, resulting from long-term cancer treatment or osteoporosis, and in patients with malignant bone disease.[6-8] Bisphosphonates are small molecules that dock in hydroxyapatite-binding sites on bone surfaces. When osteoclasts begin to resorb bisphosphonate-impregnated bone, the liberated bisphosphonates bind to farnesyl pyrophosphate synthase inside the osteoclasts, ultimately leading to apoptosis.[8-10] Denosumab is a fully human monoclonal antibody, which has a different mode of action from that of bisphosphonates. It targets and binds to the receptor activator of nuclear factor κ-B (RANK) ligand (RANKL); in doing so it prevents the activation of RANK on the surface of osteoclasts and osteoclast precursors. Inhibition of the RANKL−RANK interaction impedes osteoclast formation, function, and survival, thereby decreasing bone resorption.[11] MRONJ is more prevalent among patients receiving high cumulative doses of bisphosphonates or denosumab than in patients who receive lower doses.[12,13] The first cases

Statement of Clinical Relevance

Medication-related osteonecrosis of the jaw is a rare, but potentially serious, complication of treatment with bisphosphonates and denosumab. It is important for dentists to be aware of ways to identify and treat patients at risk of this condition.

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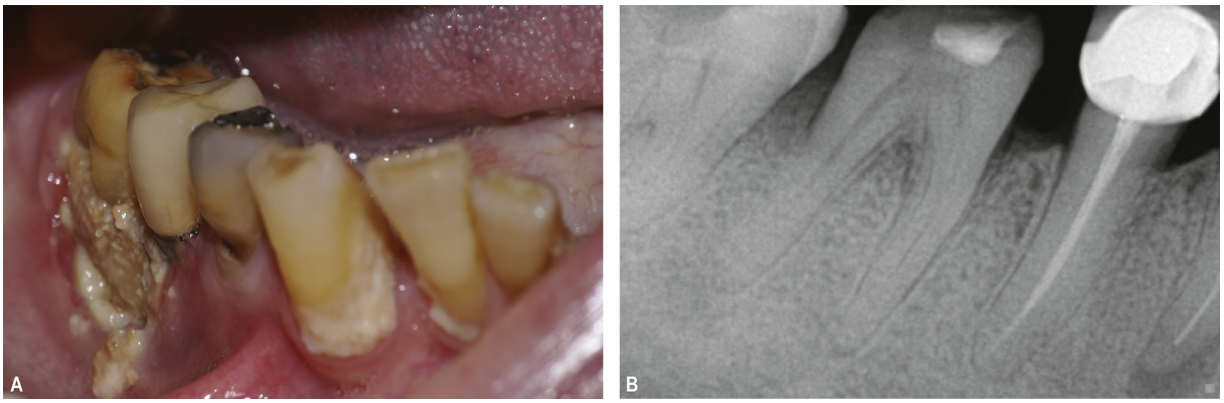


Fig. 1. Example of exposed medication-related osteonecrosis of the jaw. A patient receiving high-dose denosumab presented with pain of 6 months' duration on the right lower first molar. He was receiving antibiotics. **A,** Exposed bone and purulence was observed on the buccal alveolar bone area of the tooth consistent with osteonecrosis of the jaw, exposed type, before dental extraction. **B,** Panoramic radiography disclosed alveolar bone loss around the molar tooth. (Images courtesy of Professor Ourania Nicolatou-Galitis, Dental School, National and Kapodistrian University of Athens.)

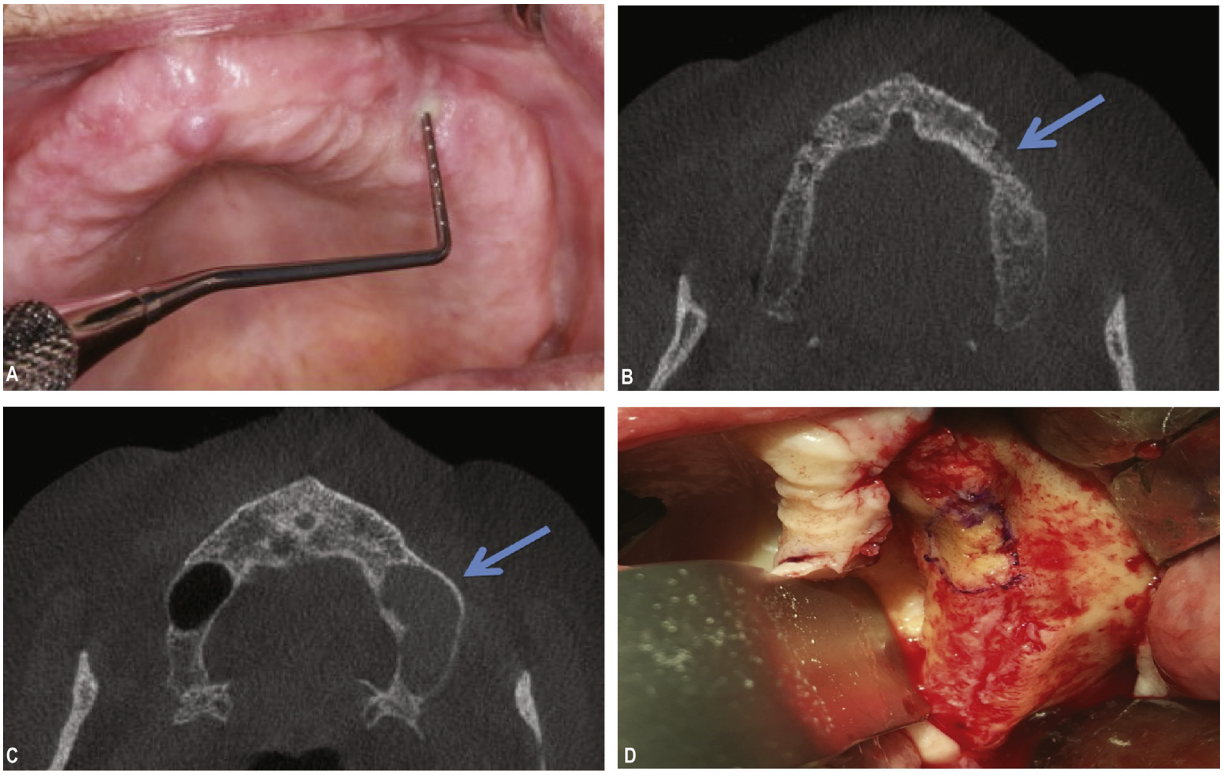


Fig. 2. Example of nonexposed medication-related osteonecrosis of the jaw. **A,** A patient receiving high-dose denosumab presented with pain in an apparently normal edentulous left maxilla. A droplet of pus was seen on palpation and bone was probed through a fistula. **B, C,** Cone beam computed tomography showed sequestrum at regions 24 and 25 *(arrow)* and infection in the left maxillary sinus. **D,** Perioperative view showing osteonecrosis outlined on the bone surface. Uneventful healing was accomplished. (Images courtesy of Dr. Morten Schiødt, University Hospital of Copenhagen. Published with the permission of the Danish Dental Journal; Schiødt M, et al. Medicinrelateret osteonekrose i kæberne—oversigt og retningslinjer. *Tandlægebladet.* 2015;119:918-930.)

of MRONJ were reported in 2003; in patients receiving the bisphosphonates pamidronic acid or zoledronic acid, Marx reported 36 cases of painful bone exposure in the mandible and/or the maxilla.[14] After an association between bisphosphonate treatment and MRONJ had been established, cases linked to denosumab treatment began to emerge in 2010.[15,16] Prospective phase III clinical studies have indicated that the

incidences of MRONJ in patients with bone metastases treated with zoledronic acid or denosumab are similar.[17,18] In addition, MRONJ is also associated with anticancer agents,[19] including classic chemotherapy agents,[20,21] angiogenesis inhibitors,[22] tyrosine kinase inhibitors (TKIs),[23,24] inhibitors of mammalian target of rapamycin,[25] and immunotherapeutic agents.[19,26,27]

Since the early reports of MRONJ, a growing body of evidence has been published on the causes, pathophysiology, prevention, and management of this condition.[1,28-32] The pathogenesis of MRONJ is likely to be multifactorial and can involve a synergistic effect between local infection/trauma and decreased bone turnover after exposure to bisphosphonates or denosumab. Different mechanisms may be involved in the development of MRONJ in association with other agents. The importance of localized dental and periodontal infection in the development of MRONJ has been highlighted in recent animal experiments, which supported the findings from radiologic, histologic, microbiologic, and clinical studies.[33-37] Furthermore, evidence suggests that such infections may precede the appearance of necrotic bone.[38]

Dentists of patients receiving bisphosphonates or denosumab have a pivotal role in the prevention and early diagnosis of MRONJ. In recognition of this, American Society of Clinical Oncology and Cancer Care Ontario made the following recommendation: "A dental assessment is recommended, where feasible, before commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with before starting treatment, if possible."[39] General dental practitioners need to have an improved awareness and understanding of this rare complication; however, concise tools that can assist decision making at the point of care are lacking.[40]

This review is divided into 2 sections:

Part 1: This part aims to summarize the rationale for the use of bisphosphonates and denosumab, to put the risk of MRONJ into context, and to present practical guidance for dentists on the prevention, diagnosis, and treatment of MRONJ.

Part 2: This part highlights the critical role that dentists, as part of a multiprofessional team with other health care professionals, can play in optimizing prevention, early treatment, and management of MRONJ.

PART 1

Rationale for treatment with bisphosphonates or denosumab

Diseases that affect bone can have debilitating effects on patients' lives by predisposing them to such events as fractures and other bone complications. These events can have a negative impact on morbidity, ability to work, and social activity.[41-43] Furthermore, fractures and other skeletal complications can place a considerable burden on health care resources.[44]

Osteoporosis

Estimates suggest that globally, approximately 200 million people have osteoporosis and that 9 million fractures occur each year (including 1.6 million hip fractures, 1.7 million forearm fractures, and 1.4 million vertebral fractures).[45,46] Therefore, it is not surprising that osteoporosis has a significant socioeconomic impact, primarily as a result of increased mortality and the financial and health-related quality of life (HRQoL) burdens associated with fractures.[45,47] Hip fractures have a particular association with mortality.[48] All-cause mortality within the first 3 months after a hip fracture is reported to be 5.75-fold higher in women and 7.95-fold higher in men than in age- and gender-matched control populations.[48] In addition, hip fractures are also associated with substantial health care resource utilization. A US study reported that after adjustment for confounders, osteoporotic fractures led to the second longest length of hospital stay (6 days; 95% confidence interval [CI] 5.9−6.0 days) and the highest average total hospital charges ($47,386; 95% CI: $46,707−48,074) of the 6 common health problems analyzed.[44] Furthermore, the functional burden of osteoporosis-related fractures can extend for years after the event.[43]

Efficacy of both low-dose oral bisphosphonate and low-dose denosumab treatments in reducing the fracture rate in osteoporosis has been clearly demonstrated in the clinical trial setting.[49-51] In practice, however, the effectiveness of oral osteoporosis treatments is limited by poor levels of adherence by patients to their treatment regimen. This has been attributed to lack of understanding in patients about their condition and the associated fracture risk, as well as concerns about adverse events (AEs), such as MRONJ.[52,53] In contrast, real-world evidence suggests that in postmenopausal women with osteoporosis, adherence to subcutaneous (SC) or intravenous (IV) antiresorptive treatments is higher and in the range 81.6% to 95.3%.[54,55] Another study showed that adherence to 6-monthly SC denosumab treatment was significantly higher compared with adherence to weekly alendronic acid tablets among women with osteoporosis.[56] Low-dose bisphosphonates (e.g., zoledronic acid 5 mg IV once per year and alendronic acid orally 10 mg once daily) are approved for the treatment of osteoporosis in postmenopausal women, patients receiving long-term systemic glucocorticoid therapy, and men at high fracture risk (Table I).[9,57-59] Low-dose denosumab (60 mg SC every 6 months) is approved for the

Table I. Agents commonly used to prevent skeletal-related events

Agent	*Low dose*						*High dose*	
	Osteoporosis							
	Postmenopausal women	*Men*	*Glucocorticoid-induced*	*Paget disease of bone*	*Cancer treatment–induced bone loss*	*Tumor-induced hypercalcemia*	*Prevention of SREs in patients with bone malignancies*	*Giant cell tumor of bone*
Alendronic acid[57]	70 mg PO once weekly or 10 mg PO once daily	10 mg PO once daily	10 mg PO once daily					
Ibandronic acid[58,80,81]	150 mg PO once monthly or 3 mg IV once every 3 months					Single dose of 4 mg IV (severe) or 2 mg IV (moderate)	6 mg IV once every 3–4 weeks or 50 mg PO daily in patients with breast cancer	
Pamidronic acid[82]				180–210 mg in either 3- or 6-unit doses		15–90 mg (depending on plasma calcium level) as single dose or over 2–4 infusions	90 mg every 4 weeks	
Risedronic acid[59,97]	5 mg PO once daily or 35 mg PO once weekly	35 mg PO once weekly	5 mg PO once daily	30 mg PO once daily for 2 months				
Zoledronic acid[9,79]	5 mg IV once yearly	5 mg IV once yearly	5 mg IV once yearly	Single dose of 5 mg IV		Single dose of 4 mg IV	4 mg IV once every 3–4 weeks	
Denosumab[11,60,78]	60 mg SC once every 6 months	60 mg SC once every 6 months			60 mg SC once every 6 months		120 mg SC once every 4 weeks	120 mg SC once every 4 weeks plus additional 120 mg SC doses on days 8 and 15 during first month

IV, intravenous; *PO,* per os; *SC,* subcutaneous; SRE, skeletal-related event.

treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures (see Table I).[60]

Cancer treatment–induced bone loss

Bone loss is a well-established risk associated with hormone ablation in prostate or breast cancer, although chemotherapy, radiotherapy, and TKIs may also play a role in dysregulating bone remodeling.[61] Cancer treatment–induced bone loss (CTIBL) is associated with an increased risk of fractures,[62] which can be reduced with bisphosphonates or denosumab. In a phase III trial, adjuvant low-dose denosumab treatment significantly increased the time to first clinical fracture, compared with placebo, in postmenopausal women with breast cancer receiving aromatase inhibitors (hazard ratio [HR] 0.50; $P < .0001$).[63] A meta-analysis of 15 randomized trials revealed significant fracture reduction in patients receiving androgen deprivation therapy treated with bisphosphonates at various doses (relative risk [RR] 0.80; $P = .005$).[64] In the Hormone Ablation Bone Loss Trial, men with nonmetastatic prostate cancer receiving denosumab had a significantly lower rate of new vertebral fractures after 36 months of treatment compared with those who received placebo (1.5% vs 3.9%).[65] Denosumab is approved for the treatment of bone loss associated with hormone ablation in men with prostate cancer who are at increased risk of fractures (see Table I) and in patients with breast cancer who are at risk of osteoporosis resulting from treatment with hormone therapy.[60] No bisphosphonates are approved for the treatment of CTIBL, and little comparative data exist regarding the efficacy of denosumab versus bisphosphonates in this setting.

Skeletal-related events in patients with malignancies involving bone

Bone is a common destination for metastases from primary solid tumors, particularly those originating in the breast or the prostate.[66] Studies suggest that 68% of patients with prostate cancer and 73% of patients with breast cancer had bone metastases at postmortem examination; and that 95% to 100% of patients with multiple myeloma (MM) eventually develop bone lesions during the course of the disease.[67] Bone metastases from solid tumors and bone lesions in MM frequently lead to skeletal-related events (SREs) (defined as pathologic fracture, radiation to bone, surgery to bone, and spinal cord compression),[68] which place a considerable burden on patients and health care resources.[69-72] Indeed, evidence has shown that without the prophylactic use of bisphosphonates or denosumab 21% to 39% of patients with bone metastases experienced a pathologic fracture and that around 18% to 32% required radiotherapy for alleviation of bone pain.[73-75] Treatment with high-dose denosumab or zoledronic acid has been shown to offer clinically relevant delays in the time to onset of SREs, to lower the risk of subsequent SREs, to reduce pain, and to maintain HRQoL in patients with bone metastases, and to reduce the risk of skeletal complications caused by MM.[7,76,77] High-dose therapy with zoledronic acid (4 mg IV every 3–4 weeks), ibandronic acid (6 mg IV every 3–4 weeks or 50 mg orally once daily [patients with breast cancer only]), and denosumab (120 mg SC every 4 weeks) are approved for the prevention of SREs in patients with advanced malignancies involving bone (see Table I).[78-81] High-dose zoledronic acid, pamidronic acid, and denosumab (in the United States, Europe, and other parts of the world) are approved for the prevention of SREs in patients with MM.[79,82,83]

Giant cell tumor of bone

Giant cell tumor of bone (GCTB) is a rare primary bone tumor with an incidence of approximately 0.1 to 1 per 1 million people per year, typically affecting young adults.[84] In the majority of cases GCTB is benign, and metastasis is unusual. However, GCTB can be locally aggressive, and benign tumors may transform into malignant high-grade sarcoma.[85] Locally aggressive GCTB may require substantial surgical resection and impact significantly on bone stability.[84-87] In clinical trials, high-dose denosumab treatment prevented tumor progression, induced primary tumor reduction, increased bone formation, and reduced pain in patients with GCTB.[88-91] High-dose denosumab is approved for the treatment of adults and skeletally mature adolescents with GCTB[78]; no bisphosphonates are licensed for this indication (see Table I). We regard minimizing the risk of MRONJ in patients with GCTB as being particularly important because the favorable prognosis, positive disease control offered by denosumab, and the young age of the people affected may lead to high cumulative exposure to denosumab. We also suggest that prevention strategies should follow the same principles as those used in patients with metastatic bone disease.

Hypercalcemia of malignancy

Hypercalcemia is a serious complication of malignant disease, which occurs most commonly in patients with advanced-stage cancers.[92] It is a condition that can cause end-stage organ damage, such as acute kidney injury, and serious symptoms, including cardiac dysrhythmias, anorexia, confusion, constipation, lethargy, malaise, and nausea.[93] Bisphosphonates have been the standard of care for patients with hypercalcemia of malignancy for some time, with zoledronic acid (4 mg IV single dose) generally being the agent of choice despite the associated risk of renal impairment.[94] In a

phase II single-arm trial, however, denosumab was shown to be effective in treating patients with hypercalcemia who relapsed after treatment with bisphosphonates or were refractory to the treatment.[95] In light of these findings, high-dose denosumab is also approved in several regions (other than Europe) for the treatment of hypercalcemia in this patient group.[11]

Paget disease of bone

Paget disease of bone is a chronic metabolic bone disorder, which manifests as excessive and disorganized bone formation.[96] Symptoms include pain, neurologic effects resulting from nerve compression, and hearing loss; furthermore, the disease may be associated with heart failure and hypercalcemia.[96] High biochemical remission rates have been reported in patients with Paget disease after treatment with low-dose bisphosphonates (approximately 75%−95% at 6−12 months after treatment).[96] Zoledronic acid (5 mg IV, single dose) and risedronic acid (30 mg orally daily for 2 months) are approved for the treatment of patients with Paget disease of bone (see Table I).[9,59,97] There is lack of robust data on the risk of MRONJ in patients with Paget disease who are treated with bisphosphonates, but it is believed to be very low, based on the doses used for this indication.[96] The role of denosumab in Paget disease has not been established at this time, but data suggest that mechanisms other than RANKL may also be important in this disease.[98]

Other risks associated with bisphosphonates or denosumab agents

The risk of some AEs other than MRONJ associated with the use of bisphosphonates and denosumab varies with the dose and duration of treatment. Bisphosphonates are nephrotoxic[99] and are associated with upper gastrointestinal irritation (when used orally), acute-phase responses, and an increased risk of atrial fibrillation.[100] More rarely, patients may be at increased risk of hypocalcemia and ocular inflammation.[101,102] Denosumab is associated with AEs other than MRONJ, including hypocalcemia and musculoskeletal pain.[103,104] The risk of developing hypocalcemia as a result of treatment with bisphosphonates or denosumab can be reduced by intake of sufficient dietary or supplemental calcium.[105,106]

Risk factors for MRONJ

The dominant factor when assessing the likelihood of development of MRONJ is the cumulative exposure of the patient to bisphosphonates or denosumab, considering both the dose per treatment and the number of administrations given from the start of the treatment.[78,79,107] To date, however, no clear threshold below which MRONJ does not occur has been identified. A secondary consideration should be the relative potency of the agents used. An indirect comparison of 9 agents found that zoledronic acid, denosumab, or teriparatide had the highest probability of being the most efficacious treatment for reducing fracture rates in postmenopausal women with osteoporosis.[108] Denosumab has been shown to be more effective than zoledronic acid in increasing bone mineral density and inhibiting bone remodeling in postmenopausal women with osteoporosis who had previously received oral bisphosphonates, and in preventing SREs in patients with cancer that had metastasized to bones.[108-110] Data from the osteoporosis setting showed that the effects of bisphosphonates on bone can continue for up to 3 years after the last administration because of accumulation in the bone matrix.[111] In contrast, denosumab does not accumulate in bone and exerts a more transient effect on the inhibition of bone resorption.[112] This is reflected in the elimination half-life of denosumab and may rationalize the numerically shorter time to MRONJ resolution among patients with bone metastases from solid tumors or bone lesions caused by MM observed for denosumab compared with zoledronic acid in three phase III trials (median 8.0 vs 8.7 months).[60,78,113] The mean denosumab elimination half-life was 28 days for doses of 120 mg every 4 weeks (high dose) and 26 days for a dose approximating to 60 mg every 6 months (low dose).[60,78,113] The pharmacokinetic profiles of the zoledronic acid and denosumab are reflected in the pharmacodynamic effects of each drug. In postmenopausal patients who have low bone mass and who discontinued denosumab having received 60 mg every 6 months for 24 months, bone mineral density returned to levels similar to those recorded at baseline 12 months after treatment cessation, whereas the levels were maintained with zoledronic acid.[114]

Typically, MRONJ develops following a local infection of, or trauma to, bone or soft tissue. Recent data have shown that localized periodontal or dental disease may precede the appearance of MRONJ (Figure 3).[38] Furthermore, alveolar bone necrosis has been documented at the time of dental extraction (Figure 4), and bacterial diversity within necrotic bone is representative of periodontal microflora.[34,115] Dentists should be aware of the risk of MRONJ when considering invasive procedures (e.g., tooth extraction or implant placement) and in case of pressure sores from ill-fitting prostheses or significant inflammation/infection.[116-118] A study in patients with MRONJ has shown that even after treatment with doxycycline and metronidazole, total bacterial level at the site of the jaw lesion was higher than that observed in a control population of orally healthy individuals.[119] However, several other factors have also been associated with an increased risk of MRONJ, including use of other cancer therapies

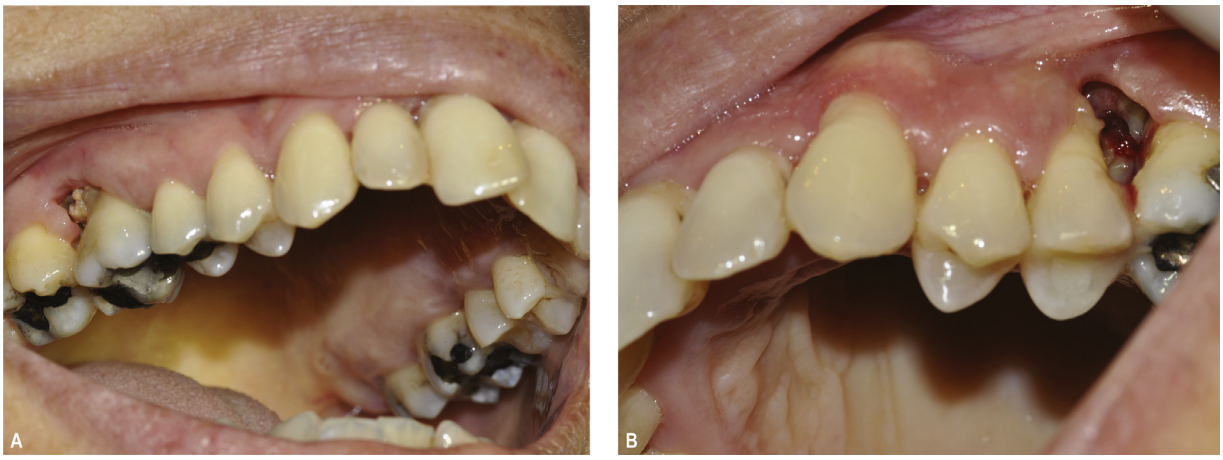


Fig. 3. Periodontal disease followed by medication-related osteonecrosis of the jaw. A patient receiving high-dose zoledronic acid and an angiogenesis inhibitor presented with pain, swelling, and tooth mobility, which was previously assessed and managed as periodontal disease. **A, B,** Clinical examination revealed exposed necrotic bone around the maxillary right and left molars. (Images courtesy of Professor Ourania Nicolatou-Galitis, Dental School, National and Kapodistrian University of Athens, Greece.)

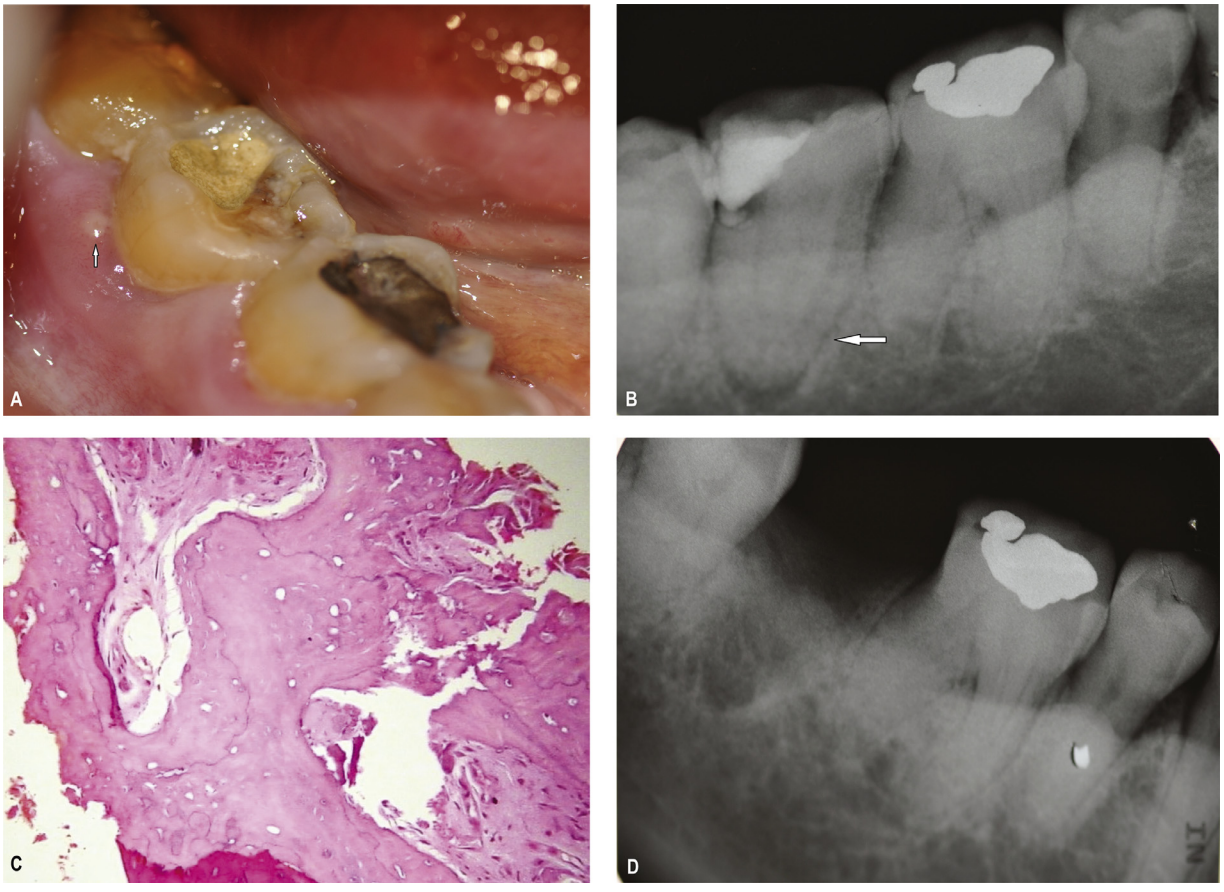


Fig. 4. Necrotic bone at the time of extraction. A patient receiving high-dose zoledronic acid presented with pain in mandibular molar. **A,** A fistula and purulence were observed clinically *(arrow)*. **B,** Periapical radiolucency was seen on radiograph *(arrow)*. **C,** Necrotic bone was observed on histology at the time of dental extraction. **D,** Postextraction socket healing and bone remodeling was observed 2 months later. (Images courtesy of Professor Ourania Nicolatou-Galitis, Dental School, National and Kapodistrian University of Athens, Greece.)

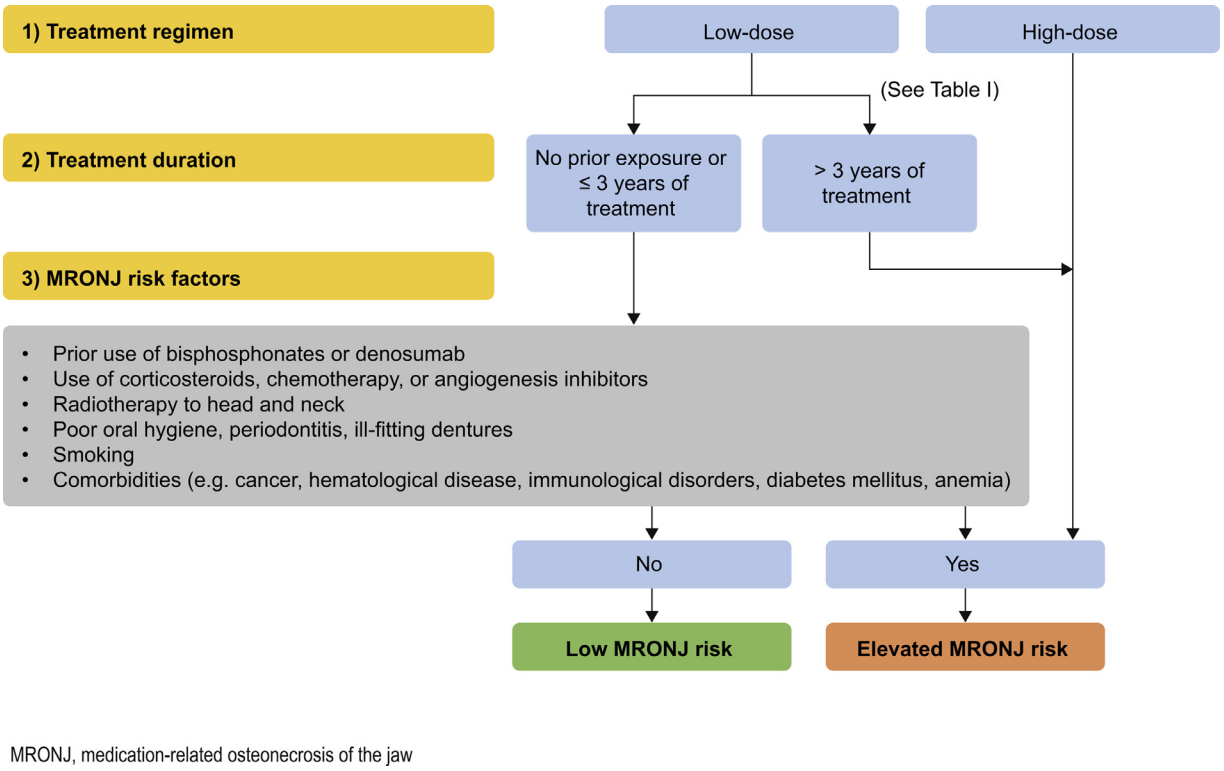


Fig. 5. Risk factor flowchart for medication-related osteonecrosis of the jaw (MRONJ).

and/or corticosteroids; smoking; poor oral hygiene; and comorbidities, such as anemia, diabetes mellitus, and renal failure (Figure 5).[22,24,26,29,59,120] In particular, the concomitant use of antiresorptives with agents that inhibit angiogenesis—that is, the formation of new blood vessels as part of tumor growth and spread—has been suggested to increase the likelihood of development of MRONJ, as recently reported in patients with advanced kidney cancer.[121]

Incidence of medication-related osteonecrosis of the jaw with bisphosphonates or denosumab therapy

The frequency of MRONJ is intrinsically linked to the cumulative exposure to, and potency of, the agent used to prevent SREs.

Low-dose therapy

It is important to keep the risk of MRONJ in context. The incidence of MRONJ associated with bisphosphonates or denosumab (60 mg every 6 months) therapy at low doses is regarded as being slightly higher than that in the general population (0.001−0.01% vs <0.001%).[1] In the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) pivotal fracture trial, there were no reports of spontaneous MRONJ after 3 years of treatment with zoledronic acid (5 mg, annually). Two cases of potential MRONJ were identified by a search of the trial database of AEs, followed by expert adjudication; one in the placebo group (n = 3852) and one in the zoledronic acid group (n = 3862).[122] Women receiving aromatase inhibitors for hormone-receptor positive breast cancer (n = 1711) were treated with low-dose denosumab in the phase III ABCSG-18 (Adjuvant Denosumab in Breast Cancer) trial; no positively adjudicated cases of MRONJ were reported in this study.[63] Thirteen cases of MRONJ were reported in an open-label extension of the phase III FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) study, which included 4550 postmenopausal women with osteoporosis receiving treatment with low-dose denosumab (60 mg every 6 months) for up to 10 years. The risk of MRONJ increased with duration of exposure to denosumab (0.04% at 3 years, 0.06% at 5 years, and 0.44% at 10 years).[51,60]

High-dose therapy

Greater than 90% of cases of MRONJ occur in patients with cancer receiving high doses of IV bisphosphonates or SC denosumab (120 mg every 4 weeks).[123] A phase III study compared the use of zoledronic acid (4 mg every 4 weeks) with that of denosumab (120 mg every 4 weeks) for the treatment of bone metastases in 1776 patients with advanced cancers (other than prostate or breast cancers). Treatment was received for a median duration of 7 months. Results showed that

positively adjudicated MRONJ occurred at rates of 1.3% in patients treated with zoledronic acid and 1.1% in those treated with denosumab (high dose). The authors noted that among those who experienced ONJ, 81% were exposed to ONJ risk factors during the study.[18] Two other double-blind phase III trials evaluated the safety and efficacy of high-dose denosumab or zoledronic acid in patients with prostate or breast cancer and bone metastases.[17,124] The incidences of MRONJ in patients with metastatic castration-resistant prostate cancer in year 1 and year 2 were 1% and 1% in the zoledronic acid group (median duration on study 11.2 months), and 1% and 2% in the denosumab group (median duration on study 12.2 months).[124] Among patients with advanced breast cancer, the incidence of MRONJ at years 1, 2, and 3, were 0.5%, 1.2%, and 1.4%, respectively, in the zoledronic acid group and 0.8%, 1.9%, and 2.0%, respectively, in the denosumab group.[17] Data from a 2-year, open-label extension of the phase III trials described above, in which patients either continued with denosumab or were switched to denosumab from zoledronic acid, provide more information on the longer-term risk of MRONJ. The incidence of MRONJ (adjusted for patient−year exposure) among those who received denosumab throughout the study was 1.1% in the first year, 3.7% in the second year, and 4.6% thereafter, highlighting the increased MRONJ risk with longer treatment.[104] In a phase III study that evaluated the efficacy and safety of denosumab compared with zoledronic acid in delaying bone complications in patients newly diagnosed with MM, the patient−year adjusted incidence of positively adjudicated MRONJ at the end of the double-blind treatment phase was 2% during the first year of treatment, 5% in the second year, and 4.5% per year thereafter.[11,77] A risk−benefit analysis of denosumab versus zoledronic acid was carried out on the basis of combined data from 5723 patients with bone metastases. The study found that 212 patients need to be treated with denosumab for 1 year to incur 1 more event of MRONJ, compared with zoledronic acid. In contrast, 7 patients need to be treated with denosumab for 1 year to prevent one additional SRE, compared with zoledronic acid.[113] Overall, the benefit provided by antiresorptive therapy outweighs the risk of development of MRONJ in the settings of both osteoporosis and oncology.[30,125]

Drug holidays

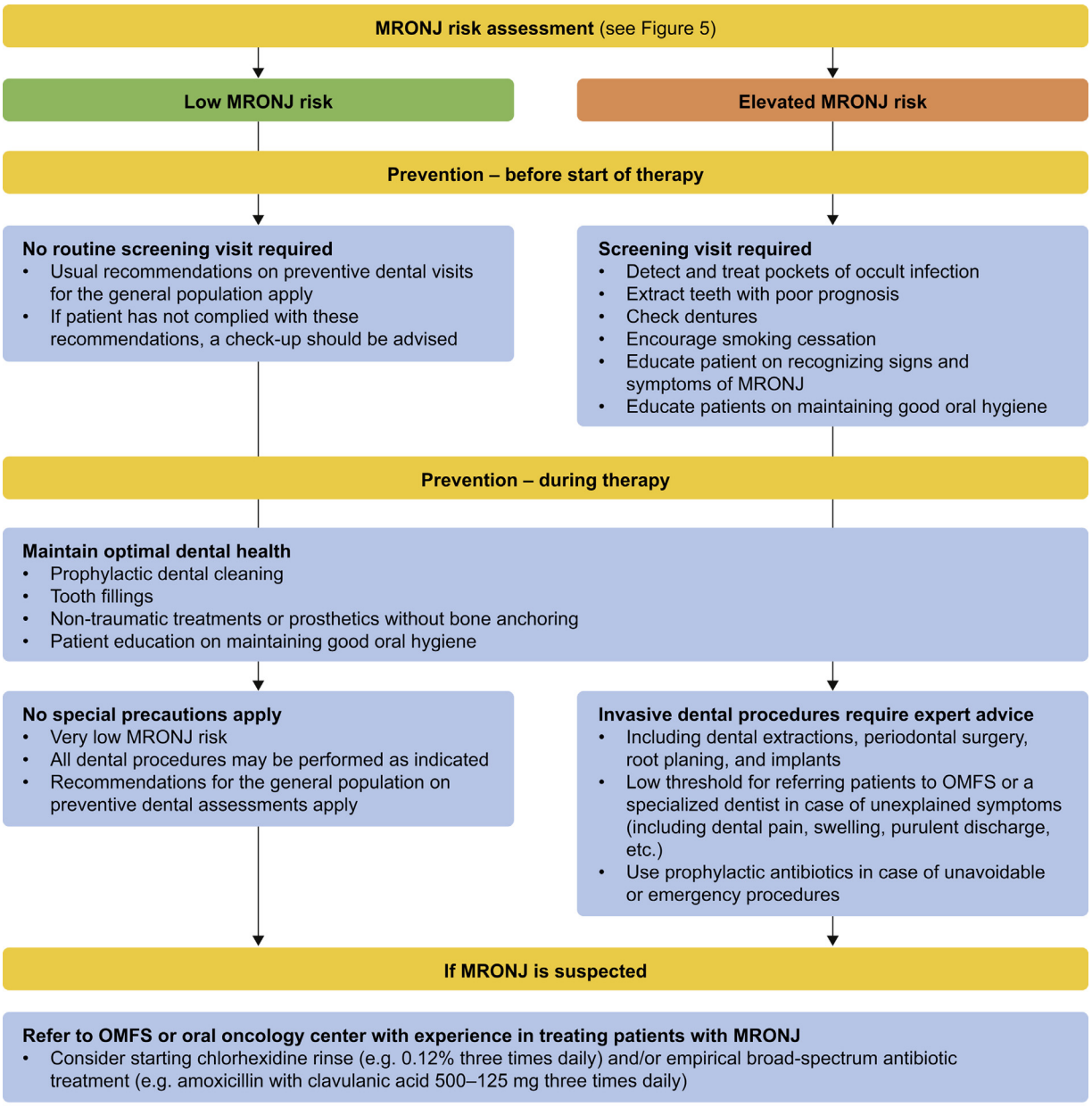
Opinions are divided with regard to the benefit of temporarily pausing treatment with bisphosphonates or denosumab in patients who are scheduled to receive invasive dental procedures (referred to as "drug holidays").[126] The increased risk of SREs during drug holidays must be balanced with the reduced risk of development of MRONJ on a case-by-case basis and should be discussed by a multiprofessional team. Evidence to support the benefit of drug holidays is lacking; however, a recent Japanese study found that treatment holidays before dental extraction did not reduce the risk of MRONJ in patients receiving oral bisphosphonates.[127] An American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper on MRONJ stated that a 2-month drug holiday before and after dental surgery in patients receiving oral bisphosphonates may be prudent, and an international ONJ task force recommended that treatment should be withheld after invasive dental surgery in patients receiving high-dose bisphosphonates or denosumab.[1,29] Of note, the authors of both sets of guidelines acknowledged that there is little evidence to support their recommendations, and the concept of drug holidays, thus, remains a contentious issue.

PART 2
Role of the dentist

Identifying patients at risk of MRONJ

Dentists have a pivotal part to play in minimizing patients' risk of development of MRONJ. Studies have shown that the risk of developing the condition can be substantially reduced if patients are assessed by a dental professional and preventive measures are taken.[1,30,120] The duration of low-dose bisphosphonate or denosumab exposure beyond which the risk of development of MRONJ is high varies among studies[120,128,129]; however, in our opinion, patients who have received low-dose therapy for less than 3 years or are scheduled to receive low-dose therapy and have no additional risk factors are regarded as being at low risk of development of MRONJ. In contrast, patients scheduled to receive high-dose bisphosphonates or denosumab, individuals who have received low-dose bisphosphonates or denosumab previously for 3 years or more, and those with MRONJ risk factors receiving low-dose bisphosphonates or denosumab are regarded as being at high risk of development of MRONJ (see Figure 5).

High-risk patients should undergo a thorough dental assessment, including dental radiography, before treatment with bisphosphonates or denosumab is initiated (Figure 6). The European Society for Medical Oncology has stated that "before zoledronic acid or denosumab therapy is initiated, patients should undergo an oral examination and appropriate preventive dentistry, and be advised on maintaining good oral hygiene."[7] Consequently, the patient should be referred to a dentist by the treating physician. A dental examination before treatment has also been recommended for patients with osteoporosis and other MRONJ risk



IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw; OMFS, oral and maxillofacial surgeon; SC, subcutaneous

Fig. 6. Management flowchart for medication-related osteonecrosis of the jaw (MRONJ).

factors by the British National Osteoporosis Guidance Group.[130] It is imperative that good channels of communication are established; data suggest that a lack of cooperation between physicians and dentists is related to an increased rate of fractures and MRONJ.[131] To assess MRONJ risk accurately, the dentist should ascertain the following information during initial discussions with the physician:

- Indication of bisphosphonate or denosumab therapy (osteoporosis or malignancy)
- Prior exposure to bisphosphonates or denosumab
- Time frame for initiating bisphosphonate or denosumab (Is there a window of opportunity for the dentist to perform dental procedures or is there a need to start therapy immediately?)
- Patient's prognosis (months or years) and general health status
- If any other agents with potential oral side effects are being used (e.g., chemotherapy, angiogenesis inhibitors, mammalian target of rapamycin inhibitors, TKIs, or corticosteroids)

- Who will discuss the risks of developing MRONJ with the patient
- Who will coordinate the follow-up of oral care

Alternatively, dentists may encounter patients being treated with bisphosphonates or denosumab who were not considered to be at high risk of MRONJ or did not undergo dental screening before treatment. In this situation, the dentist has the responsibility to evaluate the medical history and reassess the risk of MRONJ proactively before initiating invasive dental procedures, such as tooth extraction. The medical history should establish what dose of bisphosphonate or denosumab the patient is receiving, duration of that treatment, and if any other medications that are likely to increase the risk of MRONJ are being used. If in doubt about the risk of MRONJ, dentists should contact the treating physician and refer the patient to an oral and maxillofacial surgeon (OMFS) or an oral oncology center with experience in the management of patients with MRONJ.[132]

Prophylactic dental care before initiation of bisphosphonate or denosumab treatment

Prophylactic dental treatment should be carried out on all high-risk patients to minimize the probability of its development. Treatment should include extraction of partially embedded teeth; conservative endodontic and prosthodontic therapies of teeth with good prognosis; periodontal stabilization splints for teeth with grade 1 or 2 mobility in patients with good dental hygiene, and extraction of such teeth in patients whose dental hygiene is poor; and the identification and treatment of occult pockets of infection (see Figure 6).[29] All necessary oral surgery should be completed before initiation of treatment with bisphosphonates or denosumab.[29]

In our opinion, bisphosphonate or denosumab therapy should not be initiated before the mucosa has healed and adequate bone remodeling has occurred; this is unlikely to happen within 1 month of dental treatment. Educating patients on the signs and symptoms of MRONJ is also very important. Patients should be advised to return to the dentist and to inform their physician immediately if they experience any pain, swelling, or numbness associated with their teeth or gums.

During bisphosphonate or denosumab treatment

Invasive dental procedures should be avoided in high-risk patients unless dental infections are present that cannot be controlled using standard therapies. Elective dentoalveolar surgery, however, is not contraindicated in low-risk patients. Simple extractions and surgeries that do not involve osteotomy can be carried out on low-risk patients in the primary care setting. If in doubt about the risk of MRONJ development or if not confident in carrying out procedures on patients receiving bisphosphonates or denosumab, dentists should have a low threshold for referring patients to an oral oncology or oral and maxillofacial surgery center.

If invasive dental procedures are unavoidable, dentists should liaise with the treating physician to reassess MRONJ risk (as described above). In general, extractions can be carried out on patients at low risk of MRONJ (Figure 7) in the primary care setting, whereas those at high risk should be referred to an oral and maxillofacial surgery or oral oncology center with relevant experience.[117,133] To minimize the risk of MRONJ, use of an antimicrobial mouthwash should be recommended, and the use of systemic antibiotics before and/or after the procedure should be considered. The type and duration of antibiotic treatment will depend on the status of the tooth, the presence of dental or periodontal infection, and local guidelines. The choice of an antibiotic capable of penetrating bone is prudent, and penicillin, amoxicillin (with or without clavulanic acid), and metronidazole are the commonly used agents.[134] Tooth extraction wounds should be closed appropriately, and the postextraction healing process should be monitored closely; radiographic assessments of socket bone remodeling may also be required. Once the healing process is complete (i.e., when the wound has been covered by the mucosa), the patient's physician should be informed.[135]

Managing oral infections during treatment with bisphosphonates or denosumab

Special care is needed in patients who develop dental and/or periodontal infection while on treatment with bisphosphonates or denosumab. Delayed care and failure to resolve the infection can lead to dental extraction and an increased risk of development of MRONJ; however, extraction is an option if the tooth is preventing resolution of infection. If extraction is necessary, it is important that trauma be kept to a minimum.[117] After an extraction, sharp bony edges should be smoothed to facilitate closure of wounds, and biopsy of the alveolar bone to assess bone viability may be considered. Monitoring after tooth extraction should be thorough, and antibiotic prophylaxis is recommended.[135]

Diagnosis of MRONJ

Key signs and symptoms

It is important that dentists are confident in recognizing the signs and symptoms of MRONJ and are familiar with the staging system that has been established for this condition.[29] Pain and signs of infection are the most frequent symptoms reported by patients, but MRONJ can be asymptomatic. Conditions commonly confused with MRONJ include alveolar osteitis,

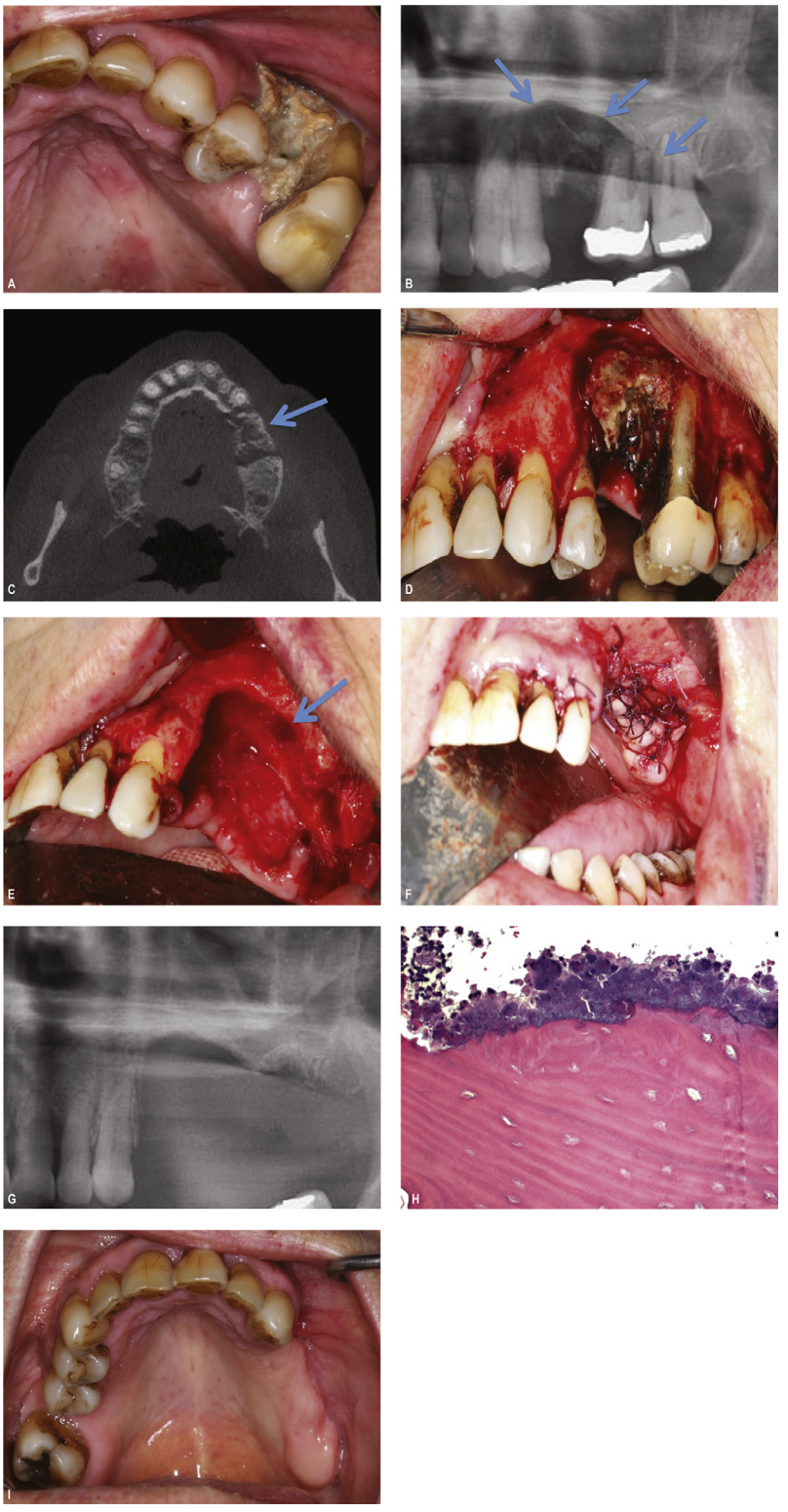


Fig. 7. Example of successful management of patient with medication-related osteonecrosis of the jaw. **A,** Patient receiving low-dose alendronic acid for more than 3 years presented with clinically exposed bone in region 24−26 of the right maxilla. Tooth 25 had been extracted 13 months before this photograph was taken. Teeth 24 and 26 were mobile. **B,** Radiologic findings. Section of panoramic radiograph of the patient showing nonhealing alveolus 25, and radiolucent process involving the alveolar process of region 24−27 *(arrows)* with central sequester. **C,** Cone beam computed tomography scan. A large sequestrum is seen corresponding to the upper left alveolar process *(arrow)*. **D,** Peroperative. Exploration showing demarcation of sequester. Note the grayish-

sinusitis, gingivitis and periodontitis, periapical pathology, odontalgia, atypical neuralgias, sarcoma, and chronic sclerosing osteomyelitis.[29]

In most cases, a diagnosis of MRONJ requires the following[29,136,137]:

- Current or previous treatment with bisphosphonates, denosumab, or antiangiogenic therapy
- An area of exposed bone, or bone that can be probed through an intraoral or extraoral fistula and has persisted for greater than 8 weeks
- No history of radiation therapy to the jaw or obvious metastatic disease of the jaw

It should be noted that there are certain caveats to these general principles. An 8-week observation period may be appropriate in cases of nonhealing postextraction sockets, but in many cases, the diagnosis is clear, and periods of observation are not necessary. Furthermore, there are increasing reports of nonexposed forms of osteonecrosis, which should also be included in the differential diagnosis.[3,4,138]

Diagnostic stages of MRONJ

The AAOMS has defined the stages of MRONJ to describe disease presentation and to facilitate the appropriate stratification of patients[29]:

- Stage 0—no clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms
- Stage 1—exposed and necrotic bone/fistulae that can be probed to bone, asymptomatic, no evidence of infection
- Stage 2—exposed and necrotic bone/fistulae that can be probed to bone, associated with infection
- Stage 3—exposed and necrotic bone/fistulae that can be probed to bone, associated with infection and additional complications

The staging of MRONJ remains a contentious issue—in particular, the nonspecific nature of stage 0 MRONJ and the definition of the disease itself. The dynamic nature of the staging system is also a matter of debate; for example, stage 1 MRONJ can become stage 2 after infection, and stage 2 disease can be downgraded to stage 1 after a brief course of antibiotics.

The dentist may be the first to identify signs and symptoms of MRONJ. In such cases, the patient should be referred to an oral and maxillofacial surgery or oral oncology center with experience in treating patients with MRONJ,[139] and the physician should be informed of the patient's symptoms and the possible treatments for and outcomes of MRONJ. Ideally, the physician will be able to recommend an OMFS or an oral oncologist who works in the same hospital to facilitate communication among care providers. The dentist will have to decide if and when to initiate treatment with chlorhexidine or broad-spectrum antibiotics. During the interval between the diagnosis and the appointment with the OMFS, antibacterial rinses can be started as soon as MRONJ is suspected, but antibiotics should be prescribed only when signs of infection are observed.

Treatment of MRONJ

There is no defined treatment algorithm, but findings from a systematic review of treatment strategies for MRONJ suggested that stage-specific treatment approaches have a sound scientific foundation.[126] The goal of MRONJ management should be control of infection, progression of bone necrosis, and pain.[29,120] If MRONJ occurs while a patient is receiving high-dose bisphosphonate or denosumab, the need for continuation of treatment should be discussed with all involved, taking into account the severity and evolution of MRONJ, the oncologic disease burden and activity, and the wishes of the patient.[140]

Conservative management

Conservative management approaches include maintaining optimal oral hygiene, eliminating active dental and periodontal diseases, and application of topical antibacterial mouth rinses and systemic antibiotic therapy, as indicated by local guidelines.[1] Such strategies may be used in cases where there is no obvious disease progression, uncontrolled pain, or discontinuation of bisphosphonate or denosumab therapy as a result of MRONJ.

green color of the necrotic process. **E,** Perioperative condition after removal of granulation tissue, involved teeth and necrotic bone until level of clinically vital bone. There is communication to the maxillary sinus *(arrow)*. **F,** Primary suture. The patient was treated with antibiotics for 10 days postoperatively. **G,** Postoperative radiograph. **H,** Histology showing empty osteocyte lacunae and accumulation of bacteria on the surface. **I,** The condition 1 month postoperatively showing complete healing. The patient is now free of symptoms and is considered cured from osteonecrosis. The missing teeth are replaced by a removable denture. (Images A-G and I, Courtesy of Dr. Morten Schiødt, University Hospital of Copenhagen. Reproduced with the permission of the Danish Dental Journal; Schiødt M, et al. Medicinrelateret osteonekrose i kæberne—oversigt og retningslinjer. *Tandlægebladet.* 2015;119:918−930; Image H, Courtesy of Professor Jesper Reibel, Department of Odontology, University of Copenhagen.)

Surgical management

Recent evidence suggests that surgery is effective in reducing pain in patients with MRONJ and ultimately leads its resolution.[141] Surgery is, therefore, indicated for patients with MRONJ whose disease does not respond to or is deemed unlikely to respond to conservative approaches.[141] The following surgical principles have been proposed for the removal of necrotic bone in this patient group: "A full-thickness mucoperiosteal flap should be high and extended to reveal the entire area of exposed bone and beyond to disease-free margins; resection of the affected bone should be extended horizontally and inferiorly to reach healthy-appearing, bleeding bone; sharp edges should be smoothed; and primary soft tissue closure achieved" through appropriate mobilization and suturing to facilitate tension-free mucosal healing (see Figure 7).[142]

In an observational chart review of 327 patients with cancer who were deemed to have MRONJ, 97% had received bisphosphonates and/or denosumab, 92% had received medication to treat the condition, and 31% had undergone surgery. Resolution of MRONJ during the study (as judged by the AAOMS criteria) was observed in 43% of evaluable patients, and improvement in MRONJ was reported in 19% of patients. The median time to MRONJ resolution was 7.3 months. Of note, almost half (47%) the patients in the study had undergone a tooth extraction during the study.[143]

Adjuvant treatment options

In addition to the established conservative and surgical treatment options, several adjuvant treatments for MRONJ have been investigated, including laser-assisted surgical debridement/low-level laser therapy and the application of ozone oil or platelet-rich plasma/platelet-derived growth factor to the surgical wound.[1,144,145] However, it should be noted that these techniques have yielded conflicting results and have not yet been assessed in prospective controlled clinical trials.

MRONJ and the need for multiprofessional teamwork

Although the benefits of treatment with bisphosphonates or denosumab are clearly established, MRONJ has emerged as an important safety consideration. To optimize the use of these agents in practice and to ensure appropriate focus on the risk of MRONJ, good collaboration is required among dentists, physicians, oral oncologists, OMFSs, and other health care professionals involved in a patient's care. Although it is important to be aware of MRONJ and understand which patients are most likely to be affected, dentists should also be aware of the educational materials available to them and not overestimate the risk of this condition and restrict dental care unnecessarily.[146] Moreover, lack of communication among care providers may result in misunderstandings regarding the reasons for, and the risks of, treatment with bisphosphonates or denosumab. Such misunderstandings may lead to conflicting information being given to the patient. This can ultimately jeopardize the patient's trust and adherence to the proposed treatment, leading to inferior health outcomes.

Developments in MRONJ treatment

MRONJ remains a topic for research and debate among the medical and dental communities. An improved understanding of how treatment with bisphosphonates or denosumab interacts with trigger events, such as oral infections or trauma, will help optimize the prevention and treatment of MRONJ.

The definition of MRONJ and, in particular, the diagnostic stages are subjects of ongoing debate. Specific and nonspecific radiographic features may be associated with clinical MRONJ, but imaging criteria have yet to be included in the formal definition of the disease. Further clarification regarding the definition of stage 0 MRONJ is required; its clinical relevance and benefit need to be clearly described in the MRONJ classification system. The precise definition of 'nonexposed' disease also needs to be established.[1,4,147,148] More research is needed on preclinical and clinical aspects of MRONJ, including further studies to confirm whether localized periodontal disease is an early form of MRONJ, and additional controlled trials should be conducted to establish the effectiveness of different treatment modalities.[149,150] There is also an urgent need to define the characteristics of the increasingly reported cases of osteonecrosis of the jaw related to medications without known antiresorptive properties.[151,152]

Patient-reported outcome data are needed, not only to help to establish which treatments are most effective but also to better understand the disease process. Although there is a higher risk of MRONJ in the oncology setting than in the osteoporosis setting, evidence suggests that the burden of disease may, paradoxically, be greater in the latter.[152] A study suggested that MRONJ may lead to a significant deterioration in oral HRQoL, as measured by the Oral Health Impact Profile 14, driven largely by pain/discomfort and anxiety/depression.[153] Outcomes reported by patients and members of a care team can also provide a useful insight into health-related behavior. Despite being a safety consideration associated with bisphosphonates and denosumab, MRONJ is not typically a focus of attention among patients, caregivers, or nurses, who rank it very low among factors that influence bone-protection treatment preferences.[154,155]

CONCLUSIONS

MRONJ is a rare, but potentially serious, AE associated with different therapies (including chemotherapy) and specifically with high-dose/long-term use of bisphosphonates or denosumab. The development of MRONJ may compromise treatment, thereby increasing the risk of pathologic fractures in those with osteoporosis and of fractures and other bone complications (SREs) in individuals with cancer. Minimizing the risk of MRONJ is critical, not only to prevent the pain and discomfort the disease can cause patients but also to maximize the benefit of treatment with bisphosphonates or denosumab. Dentists have a pivotal role to play in preventing MRONJ; through thorough assessment, prophylactic dental treatment, and close multiprofessional teamwork, the risk of developing this condition can be reduced. To that end, it is important that dentists are able to identify patients at risk, are familiar with the required prophylactic treatment recommendations, and are aware of the diagnostic criteria and management strategies for MRONJ.

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