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Medication-Related Osteonecrosis of the Jaw

Important Clinical Considerations

Bard J. Levey, D.D.S.; Franklin Garcia-Godoy, D.D.S., M.S., Ph.D.

ABSTRACT

Medication-related osteonecrosis of the jaw (MRONJ) is a challenging condition for dental practitioners. Despite an abundance of published literature on this topic, widespread clinical awareness and recognition are still not common, as clinicians still do not recognize the common, early presentations of this disease. This has been shown in different studies conducted in different parts of the world.^[1-4] This paper highlights the important clinical considerations for practitioners to evaluate.

Technology can make us better dentists, as collaboration between dentists in different offices, with different specialties, even in different countries is now possible by posting clinically relevant details, radiographs, scans and photos with the push of a button. One recent posting on a Facebook group for dentists (with over 45,000 members worldwide, whose purpose is to allow dentists to share clinical information with, and receive feedback from, a broad network of their peers) included a case history and photos involving a patient with a mysterious “piece of bone sticking out of the gums on the distolingual of #18.” The dentist was looking

for diagnostic help. Studies conducted in different parts of the world have also shown the lack of solid knowledge of treatment of MRONJ.^[1-4]

Of the many responses received for this posting, not one person asked if this patient was currently, or had ever, received bisphosphonate treatment. A respondent finally posed this question. The author of the post, not surprisingly, stated they did not know and “would have to check.”

It is not an understatement to point out that the very low positive predictive value for the recognition of MRONJ continues to force many patients to endure unnecessary complications and suffering and, therefore, the clinical importance to highlight this issue. The didactically obvious definition of MRONJ is not inherently obvious to the wet-fingered general dentist. Especially in its early stages, necrosed bone does not present labeled as such, and its recognition can easily be mistaken for many other more commonly seen clinical findings. The delay in accurate diagnosis then delays proper treatment.

There are few, if any, dental diagnoses that are more potentially devastating and debilitating than undiagnosed and untreated medication-related osteonecrosis of the jaw (MRONJ). And yet, despite an abundance of published literature on this topic, widespread clinical awareness and recognition are still not common, as clinicians still do not recognize the common, early pre-

sentations of this disease. It is important for the practicing dentist to view any patient who has received bisphosphonate treatment as being “at risk.”

A thorough recent review article by Kim et al.^[5] highlighted key points of medication-related osteonecrosis of the jaw (MRONJ). This paper further summarizes the topic based on the Kim et al. paper, and will highlight the critical clinical implications for a practicing dentist.

Bisphosphonate medications work by essentially inhibiting the function of osteoclasts. Bisphosphonates have varying potencies, with newer (second and third) generation iterations being more potent than first-generation bisphosphonates (which do not contain nitrogen). The clinical significance of drug potency in development of MRONJ, as would be expected, shows that bisphosphonates with higher potency create a higher risk for development of MRONJ. Similarly, bisphosphonates used intravenously create increased risk for MRONJ when compared with those taken orally. The risk for development of MRONJ not only increases with drug potency, but also with route of intake, dosing and duration of treatment.

While the diagnosis of MRONJ is seemingly straightforward (necrosed maxillofacial bone lasting more than eight weeks in a patient with no history of radiation treatment who is receiving, or has received bisphosphonate treatment), as previously noted, there is a major disconnect between the scientific literature and awareness by the practicing dentist, which adversely affects prevention and/or early diagnosis of MRONJ.^[1-4]

In their consensus update paper on MRONJ prevention and diagnosis, Campisi, Mauceri, Bertoldo, et al.^[6] suggest the following to enhance the practitioner’s diagnostic ability:

- 1) Evaluate not only past and current bisphosphonate medications, but also consider any history of other anti-resorptive agents or medications with anti-angiogenic actions.
- 2) Realize that not all MRONJ cases are preceded by invasive dental treatments. Periodontal causes and spontaneous cases occur.
- 3) Understand that pain may not be a part of the MRONJ diagnosis.
- 4) With proper diagnostic imaging, MRONJ can be suspected even before exposed bone occurs.
- 5) Do not hesitate to prescribe the proper radiological exam (Pan, CT and/or MRI) when there are any possible clinical signs of MRONJ, even in the absence of exposed bone or fistulas.
- 6) Realize that MRONJ can initially present like many common dental issues (think endodontic and periodontal), or it can present as what appears to be the worsening of an existing condition.
- 7) Use CT imaging every six months to monitor MRONJ after undertaking treatment.

Taken together with these suggestions designed to enhance the practitioner’s diagnostic acumen, the summary of findings produced by Kim et al.^[5] will serve as an additional, important treatment planning guide for the practicing dentist, with the goal of reducing the potentially devastating outcomes inherent in MRONJ.



Figure 1. Taken 11-2-16.



Figure 2. Taken 3-6-18.

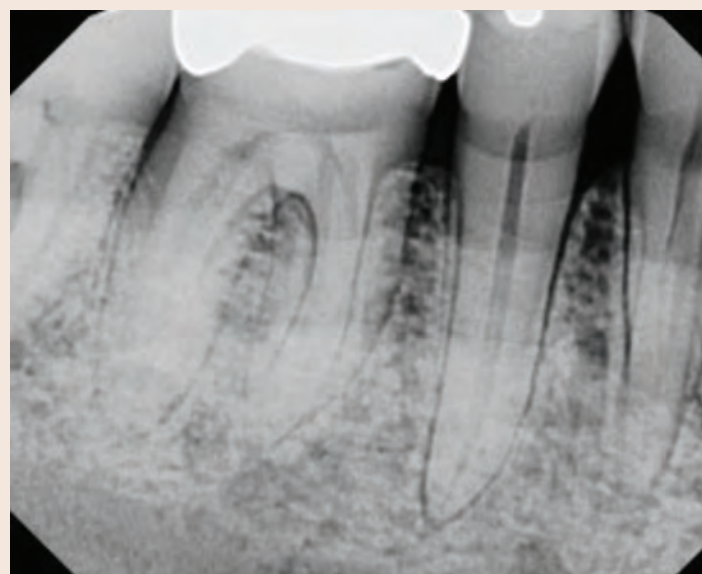


Figure 3. Taken 3-6-18. Note bony changes area #30, mimicking common periodontal pathology.

Orthodontic Considerations

- 1) For patients at risk of developing MRONJ, consider orthodontic tooth extrusion instead of extraction.^[7]
- 2) There is general consensus that patients at risk for MRONJ undergoing orthodontic treatment should expect increased treatment times, poor root parallelism (as some studies show that primarily tipping movements are possible), extra monitoring (more frequent appointments) due to the lighter than normal forces being applied.^[8]
- 3) With respect to retention, retainers must be fabricated to only cover the hard tissue, with no soft-tissue impingement for patients at risk for the development of MRONJ.^[9]
- 4) There is not one single reported case in which orthodontic treatment caused osteonecrosis of the jaw.^[5]

Endodontic Considerations

- 1) The periapical radiolucent lesions of MRONJ can mimic lesions of endodontic origin.^[1] Therefore, as clinicians, we must be very wary of these lesions in patients at risk for developing MRONJ and be certain that the lesion is actually of endodontic origin before endodontic treatment is initiated.^[10]



Figure 4. Taken 3-6-18. Exposed, necrotic bone #29-31 lingual.

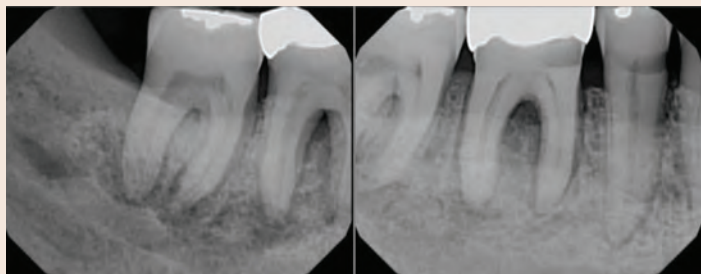


Figure 5. Taken 8-27-18. Progression of BRONJ. Note again how apical and furcal lesions areas mimic endodontic and periodontal pathology.

- 2) Careful medical history is therefore needed to know if the patient is at risk for developing MRONJ.^[11,12]
- 3) The rubber dam clamp poses a soft-tissue impingement risk that can be related to the development of MRONJ.^[13]
- 4) Bisphosphonate medications can, possibly, increase the risk of internal and external root resorption.^[14,15]
- 5) There is no evidence to suggest that bisphosphonate treatment decreases endodontic success.^[16]
- 6) Always choose conventional endodontic options vs. extraction in patients at risk for MRONJ.^[5]

Periodontal Considerations

- 1) There is an interesting potential “dual role” of bisphosphonate medications in periodontics. On one hand, the inhibition of osteoclastic activity can be used to “prevent the progression of periodontitis.” However, up to 84% of osteonecrosis of the jaw patients have periodontitis.^[17]
- 2) Improved home care and subgingival scaling can delay the onset of MRONJ by as much as 15 months.^[18] Consider pre- and postoperative chlorhexidine rinses (qid x 2-3 weeks pre- and postop), as well as antibiotic coverage pre- and postop (Augmentin 1 tab q 8-12 h x 6 days, starting the night before treatment or 1 g amoxicillin q 8h x 6 days).
- 3) Regular use of bisphosphonates has been shown in multiple studies to prevent periodontal bone loss.^[19-23]

Prosthodontic Considerations

Risk factors for prosthodontic treatment for patients who have or are currently receiving bisphosphonate treatment are generally related to tissue impingement and mucosal trauma. “Even a mucosal trauma from a denture can trigger MRONJ.”^[24]

For Removable Partial Dentures:

- 1) Avoid over-extension of prosthetic flanges.^[25]
- 2) Advise patient to wear RPD less than 8-12 hours/day.^[25]
- 3) Avoid (remake or reline) poorly fitted prostheses.^[26]
- 3) Use soft-tissue liners.^[27]
- 4) Perform more frequent soft-tissue checks (every four months or less).^[25]

For Fixed Prosthodontics:

Soft-tissue management is of utmost importance, as at least one study of 128 patients showed 5 developed MRONJ under the pontic of a fixed partial denture.^[28]

- 1) Avoid encroachment of biologic width during preparations.^[25]
- 2) Do not damage long junctional epithelium.^[25]
- 3) Supragingival margins whenever possible.^[25]

While it seems intuitive not to place dental implants into an area of previous MRONJ, no studies have given scientific rationale.^[29]

Oral and Maxillofacial Surgery

Dental extractions are the number-one risk factor for development of MRONJ.^[30-34]

Even for a patient on an oral bisphosphonate (x five years), with a drug holiday of three months, a case study showed development of MRONJ after extraction.^[35]

Common risk factors for developing MRONJ:^[36-40]

- 1) Age
- 2) Long history of bisphosphonate use
- 3) Tissue trauma

Common precautions include:

- 1) Systemic antibiotics (pre- and postoperative)
- 2) Antibacterial rinses
- 3) Partial thickness flaps
- 4) Postop plasma-rich growth factor
- 5) Drug holiday

Actinomyces are a common bacteria found in tori removal specimens in patients with MRONJ, but there is not yet any proven relationship between the disease and the bacteria. Of note, no surgical procedures, other than tori removal and extractions, have been documented as causing MRONJ.^[5]

TABLE 1

Compilation of preventative and treatment options for patients who have already or who will receive bisphosphonate therapy

- Drug Holiday—Delay the start of or stop use of BP 3 months before and after planned dental treatment.
- Switch to non-nitrogen BP (etidronate, clodronate).
- Smoking cessation.
- Subgingival scaling and improved oral hygiene- 2 weeks before any planned treatment.
- Remove “hopeless teeth” (ie., teeth with prognosis less than 2 years) before BP therapy begins whenever possible.
- Adjust or remake poorly fitting prostheses prior to initiation of BP therapy, or as soon as you can afterward.
- Rinse with 1.2% Chlorhexidine once/day x 2-3 weeks pre treatment.
- Pre/Post-treatment antibiotic- Augmentin 1 tab q 8-12 h x 6 days starting the night before treatment or 1 g Amoxicillin q8h x 6 days have both been used successfully.
- Platelet-rich growth factor- postop; PRGF into extraction socket covered with autologous fibrin and sutured.
- Hyperbaric oxygen therapy.
- Remove exposed necrotic bone as soon as possible.
- Simplified extraction protocol—1 tooth at a time, taking care when grinding sharp bony edges to not lift the periosteum.

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Implants

The prominent themes were that bisphosphonates in general are risk factors in implant surgery and that oral bisphosphonates are less of a risk than those given intravenously.

- 1) Numerous case studies show MRONJ occurring after implant placement or removal.^[29,41-43]
- 2) MRONJ has been shown to occur even when there is a long interval between taking bisphosphonates and placing an implant.^[45]
- 3) MRONJ has been reported to occur even if the bisphosphonates are taken after implant placement, although evidence shows that patients taking bisphosphonates either concurrently with implant placement or prior to implant placement show a much more rapid development of MRONJ, compared with patients who start bisphosphonates treatment after implant placement has already occurred.^[46]
- 4) Evidence exists showing that symptomatic patients who stop taking bisphosphonates get relief of symptoms, and some tissue healing has been observed.^[47]



Figure 6. Taken 12-3-18. More exposed necrotic bone is clinically evident.



Figure 7. Taken 2-19-19. Pathological fracture right mandible.

- 5) It can take more than 60 months to develop MRONJ after implant placement, with the average time varying depending on the type of bisphosphonate medication: Zoledronic acid—16 months; pamidronate—50 months; alendronate—68 months.^[48]
- 6) Successfully osseointegrated implants have been shown to fail if bisphosphonates are taken. The suggestion is that occlusal forces on these implants, if excessive, can lead to bone necrosis, leading to MRONJ. This finding emphasizes the importance of controlling occlusal forces.^[49]
- 7) MRONJ can occur regardless of type of bone grafting material used.^[50]
- 8) At least one systemic review refutes the evidence cited in numerous case studies and concluded that bisphosphonate use does not increase the risk of developing MRONJ in implant patients.^[51] It was also pointed out that this systemic review did not “fulfill the quality assessment (AMSTAR).”

Treatments for MRONJ

Preventive Considerations

- Drug holiday (three months pre- and post-dental surgery)^[52,53]
- Stop smoking^[54]
- Stop steroid treatment^[54]
- Improve oral hygiene^[54]
- Remove hopeless teeth^[56]
- Adjust or remake poorly fitted prostheses^[55]
- Use of chlorhexidine rinses^[56]
- Pre- and postoperative use of antibiotics^[56-59]
- Switch medications to etidronate or clodronate^[60]

Nonsurgical treatment considerations


- Stage 1 ONJ—Chlorhexidine rinses or hydrogen peroxide rinses^[61]
- State 2 ONJ—Use of rinses as listed above and antibiotics^[61]
- Teriparatide injections^[62]
- Sifloxacin injections^[63]

Surgical Treatment Considerations

- For patients with stage 3 ONJ—Chlorhexidine rinses or hydrogen peroxide rinses, antibiotics and surgical debridement, as well as placement of reconstructive plate to prevent mandibular fracture^[61]
- Placement of tetracycline-soaked gelfoam into surgical wounds^[64]
- Tension-free closures^[65]
- Simplified extraction protocol (one tooth at a time)^[54]
- Grinding of bony sharp edges without lifting periosteum^[54]
- Resection and microvascular reconstruction^[66]

- Ultrasonic bone surgery^[67]
- Bone marrow stromal cells^[68]
- Platelet-rich fibrin^[69,70]
- Plasma-rich growth factors^[71]
- Nd YAG laser therapy^[72]
- Doxycycline fluorescence-guided Er:YAG laser ablation with Nd:YAG/diode laser biostimulation^[73]
- Visually enhanced lesion scope^[74]
- Ozone therapy^[75]

Conclusions

It is imperative that practicing clinicians be made aware of the potentially serious consequences that can accompany MRONJ and take early and definitive actions for patients who are at risk. Preventive measures, coupled with a proactive diagnostic mindset, will reduce the chance of life-altering side effects. 

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University at Buffalo School of Dental Medicine

Wed, Sept 21: 6-8pm, Hofbräuhaus Buffalo!

***NEW* Get 'Crafty' ...Sefan Ruhl, DDS, PhD, presents CDE & learning about craft beer at one of the area's best breweries!**
\$55 includes 2 CE credit hours, beer tasting & light snack

UB Implant Study Club Spring 2022-23, UB SDM, Thursdays, 6-9pm

Sept 29: Understanding & Applying Implant Occlusal Concepts
Marshall Fagin, DDS

Oct 20: Implants in the Head & Neck Cancer Patient
Vladimir Frias, DDS, MS

Nov 17: Horizontal Augmentation...Techniques & New Products, Sebastiano Andreana, DDS, MS

Dec, 15: CBCT in Implant Dentistry, Nicole Hinchy, DDS, MS

(Tent.) Spring 2023 dates: Feb 16, Mar 16, Apr 20, May 18

Annual new membership fee: \$1295, Returning member \$995

CE HRS: 3/meeting. Single meeting Nonmember \$225

Fri, Sept 30, 9am-4pm, Buffalo, NY

Implant Tx Planning Considerations & Techniques in Partially Edentulous Pts & Full-Arch Rehabilitations, Konstantinos Chochlidakis DDS, MS, FACP
UB Dental Alum or AO Member \$195, Nonmember \$225, CE HRS: 6

Wednesday Evening Lecture Series via 'live Zoom' meetings 6-8pm

Oct 12: **Ethical Missteps: How To Avoid 'Stepping In It'**, Joseph Rumfola, DDS & Sam Carocci, DDS

Oct 19: **Infection Control in Dental Practice: A Practical Approach**, Alyssa Tzetzto, DDS, MPH

Additional dates/topics & speakers TBA

Dentists/doctor \$45, RDH/DA \$35, CE HRS: 2

Thur, Nov 10, 7-9pm via Zoom

Orthodontic Trends & Industry Changes You Must Understand to Prosper in the Future, Chris Bentson, DDS

NYSSO Member N/C, Nonmember \$35, CE HRS: 2

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