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Pathophysiology of Osteonecrosis of the Jaws

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INTRODUCTION

Osteonecrosis of the jaw (ONJ) was defined as exposed, necrotic bone in the maxillofacial region for at least 8 weeks in patients receiving an antiresorptive medication for primary or metastatic bone cancer, osteoporosis, or Paget's disease, without history of radiation therapy to the jaws [1, 2]. Recently, the AAOMS revised the definition to include exposed bone, or bone that can be probed through an intraoral or extraoral fistula in patients on antiresorptive or antiangiogenic medications [3]. The addition of "probed bone" to the case definition is of clinical significance since frank exposed bone is not always seen, even though it is notably necrotic and radiographically similar.

The staging of the disease is based on severity of symptoms and extent of clinical and radiographic findings [3]. The 2009 and 2014 AAOMS position papers outline the disease stages including Stage 0, where there is no frank bone exposure [2, 3]. Chronic exposed, necrotic bone, inflammation, swelling, pain and radiographic changes are some of the more common clinical findings. ONJ can present as subtle, commonly overlooked Stage 0, as exposed bone without any pain or signs of infection (Stage I), as exposed bone with associated infection, pain, swelling (Stage II), or as extensive disease that forms in large segments of the maxilla or mandible with extraoral fistulae, involvement of vital structures, or pathologic fracture (Stage III).

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Treatment strategies range from conservative local wound care to aggressive resective surgery of all necrotic bone. Conservative strategies include systemic antibiotics, oral antibacterial rinse, and debridement of loose necrotic bone that no longer has soft tissue coverage. Recent literature demonstrates that disease prevention with dental exams and treatment before initiating antiresorptive therapy is the most effective method to decrease ONJ incidence [4]. In the conservative management of patients with active ONJ, the treatment goal is focused on preventing disease progression rather than reversal of the process [4–7]. Any procedures that remove soft tissue and/or expose bone, including extractions, are generally avoided when a conservative treatment plan is followed. More invasive treatment strategies may include local curettage and debridement, en bloc resection, flap advancement and resective surgery [8–10].

PROPOSED HYPOTHESES OF MRONJ PATHOPHYSIOLOGY

The first ONJ cases were reported in 2003 and 2004, and although significant progress has been made in our understanding of the disease, much more work needs to be done to completely explain its pathophysiology [11, 12]. Many hypotheses have been proposed, which have sparked empirically-based treatment modalities. Since it is unlikely that one single hypothesis can explain the pathophysiology of ONJ, as it is indeed multifactorial, it is also unlikely that one treatment modality will be successful in all patients. Moreover, since ONJ is a relatively newly described disease entity, as more clinical and preclinical evidence becomes available, it is apparent that our hypotheses and treatment approaches will need to be continuously modified.

HYPOTHESIS 1: BONE REMODELING INHIBITION

Osteoclast activity is tightly regulated by RANK/RANKL/OPG signaling, where an increase in RANKL or decrease in OPG lead to increased bone resorption. In cancer states, tumor cells release growth factors or cytokines, which in turn stimulate osteoblast RANKL release, causing increased bone resorption, and subsequently increased tumor cell presence and growth [13]. Because of their direct effects on osteoclasts, antiresorptives significantly decrease skeletal-related complications, relieve severe bone pain, and correct hypercalcemia in patients with malignant diseases [14–18].

BPs have direct effects on osteoclasts to significantly attenuate bone remodeling [19, 20] and decrease skeletal-related complications in patients with malignant diseases or osteoporosis [14, 15, 20]. Osteoclast differentiation and function play vital roles in bone healing and remodeling at all skeletal sites, but osteonecrosis of the jaws only occurs in alveolar bone of the maxilla and mandible [21]. Alveolar bone may demonstrate an increased remodeling rate as compared to other bones in the axial or appendicular skeleton, which may explain the ONJ predilection in the jaws [22, 23]. However, other studies have failed to confirm differences in bone turnover between the mandible and femur by bone scintigraphy, while the maxilla did show increased bone turnover; administration of BP or denosumab did not change the turnover rate of any bones [24]. Interestingly in mice, fluorescent-labeled BPs demonstrate preferential accumulation in sites of tooth extraction or dental disease, where bone turnover is increased. This is why increased uptake may predispose such sites to higher

BP doses and increase susceptibility to BP effects. Although this may not demonstrate a general increase in bone turnover in the jaws, it does show a localized increase in potentially future ONJ sites [25]. The increased bone resorption in the setting of dental disease, coupled with the thin overlying mucosa and a direct pathway through the periodontal ligament with the external environment, make the jaws a suitable breeding ground for ONJ to develop.

Since the primary mechanism of BPs and denosumab is to inhibit osteoclast function by different mechanisms, it is not surprising that altered bone remodeling is the leading hypothesis for ONJ development [26–29]. Importantly, the prevalence of ONJ in patients receiving denosumab and BPs is not significantly different [30–32]. Moreover, animal studies demonstrate a similar rate of periosteal bone deposition, histologic necrosis, and bone exposure when rodents with periodontal or periapical disease or tooth extractions are treated with zoledronate as compared to RANKL inhibitors [21, 33–35]. These human and animal studies highlight the central role of bone remodeling suppression. To combat the effects of bone turnover suppression, withdrawing antiresorptive medications before tooth extraction of surgical procedures is often advocated to potentially reduce the risk of ONJ [3, 36–38]. However, no controlled studies confirm the reduction or reversal of ONJ after a “drug holiday.” Only one clinical report demonstrates a 40% resolution after discontinuing denosumab and 30% after discontinuing ZA [31].

ONJ prevalence in patients treated with BP or denosumab appears similar [39, 40]. BPs bind to exposed hydroxyapatite and incorporate into the bone matrix, where they are retained with a half-life of many years [41–43]. With the advent of denosumab, which does not incorporate into the bone matrix, the half-life is significantly shorter at 32 days maximum [44, 45] and rapid reversibility of its antiresorptive effects [46]. Interestingly, our recent animal study demonstrates faster normalization of TRACP-5b levels after discontinuation of RANKL inhibitor OPG-Fc, a surrogate to denosumab, as compared to zoledronic acid [47]. In addition, radiographic and histologic indices of ONJ returned to levels of control animals after withdrawal of OPG-FC, whereas ZA-treated mice still demonstrated ONJ features [47]. If these data can be validated in controlled clinical studies, they may support the rationale for drug holidays in the management of ONJ patients. They may also demonstrate that discontinuing denosumab vs. bisphosphonate therapy prior to surgical intervention offers faster recovery of normal bone homeostasis.

Another factor that points to the central role of osteoclastic bone resorption in ONJ pathophysiology is the effect of parathyroid hormone (PTH). Initial case reports in osteoporotic patients and animal studies simulating osteoporosis demonstrate the improved healing of extraction sockets and ONJ lesions with administration of parathyroid hormone, possibly due to its ability to improve bone homeostasis, by directly stimulating osteoblastic function and indirectly increasing osteoclastic bone resorption [48–51].

HYPOTHESIS 2: INFLAMMATION & INFECTION

The fact that only 0.8–12% of patients on systemic antiresorptives for malignant disease develop ONJ [3, 52–56], although this may be underestimated [57, 58], points to additional inciting factors beside antiresorptives that contribute to ONJ. Valuable information can be gained from patients with ONJ and their coexisting risk factors. Tooth extraction is generally

the most common inciting event associated with ONJ, but teeth in adults are almost always extracted because they have periapical or periodontal infections or inflammation [3, 57, 59, 60]. Animal models of inflammation and infection have been developed to parallel the clinical presentation of ONJ with associated dental pathology, and have consistently shown that both inflammation/infection and a systemic antiresorptive are sufficient for ONJ development [21, 33, 34, 61–65].

Inflammation/infection has been thought to play a role in ONJ, often occuring after extraction of teeth with advanced dental disease or around teeth with periodontal or periapical infection [3, 57, 60, 66]. In multiple myeloma and metastatic cancer patients, aggressive dental hygiene therapy reduces the incidence of ONJ [67, 68]. Further evaluation of histologic specimens detect bacteria on the exposed bone, including Actinomyces species [69, 70]. However, the question remains. Did the bacteria induce the infection and exposed bone, or did the exposed bone develop a bacterial biofilm? Recent studies have shed light on the complexity of biofilm, which include fungi and viruses in addition to the bacterial species [71, 72]. These multiorganism biofilms present challenges to therapy, and may require complicated strategies to eradicate the infection [73–75].

HYPOTHESIS 3: ANGIOGENESIS INHIBITION

Angiogenesis involves the formation of new blood vessels, and necrosis of bones such as the femur are usually of vascular etiology [76]. Bone becomes necrotic without adequate blood supply, as do most tissues, even in pathologic processes. Anti-angiogenic therapies are now widely utilized to inhibit tumor invasion and metastases, targeting vascular signaling molecules such as vascular endothelial growth factor (VEGF) [77]. Zoledronic acid is a known agent that reduces circulating VEGF levels in cancer patients in vivo and reduces angiogenesis in vitro [78–80]. Zoledronic acid inhibits proliferation and interferes with adhesion and migration of human endothelial cells [4, 78], which is thought to interrupt tumor invasion and metastases [4, 80]. In addition, all BPs, especially nitrogen-containing BPs, induce a statistically significant decrease in microvessel density in vivo [81].

Recently, new antiangiogenic therapies such as tyrosine kinase inhibitors and anti-VEGF monoclonal antibodies are associated with ONJ development [82–84]. For these reasons, the new AAOMS guidelines have recognized antiangiogenics as a contributing factor and modified the disease name to medication related ONJ (MRONJ) [85]. Moreover, the prevalence of ONJ is highest in patients with mulitiple myeloma, which is thought to be caused by concomitant antiangiogenic medications and steroids [86, 87]. Even though there is some evidence that antiangiogenesis is involved in the ONJ disease process, histopathologic studies have shown normal vasculature in post-mortem specimens [36]. Most importantly, denosumab has not been associated with antiangiogenesis [88]. Therefore, although unlikely to be central in the development of ONJ, antiangiogenesis is thought to be a significant contributor to the disease process.

HYPOTHESIS 4: SOFT TISSUE TOXICITY

An early hypothesis in ONJ pathophysiology was a direct soft tissue toxicity of BPs [89]. BP exposure, especially nitrogen-containing BPs, induces apoptosis or decreased

proliferation of cervical, prostate, and oral epithelial cells in vitro [81, 89–93]. In vitro studies also demonstrate that nitrogen containing BPs localize to epithelial tissue, as well as bone [94]. In addition, oral alendronate is associated with esophageal irritation, requiring special precautions for patients during administration [95]. However, this hypothesis has become less likely due to the lack of soft tissue toxicity reported with denosumab.

HYPOTHESIS 5: – INNATE OR ACQUIRED IMMUNITY DYSFUNCTION

A continued debate exists about the effect of alterned immunity on ONJ development. Tumor pathogenesis is often associated with an impaired immune function [96], and animal studies have implicated immune deficiency in the development of ONJ, while infusion of mesenchymal stem cells or T-regulatory cells prevents and alleviates ONJ-like lesions [97]. In addition, the highest prevalence of ONJ in patients with multiple myeloma, who receive steroids and anti-angiogenics as part of their chemotherapy regimen further points to a role of immune dysfunction in ONJ pathogenesis [87]. Additionally, in many animal models of ONJ, incidence and severity of disease increases with the presence of chemotherapy or steroids [6, 49, 63, 97, 98]. In patients on oral BPs, steroids are also a risk factor for ONJ [3, 60]. This points to the potential significant contribution of immunomodulators in the pathophysiology of the disease (Fig. 1).

CONCLUSION

ONJ is a multifactorial disease in patients with primary or metastatic bone malignancy or osteoporosis undergoing systemic antiresorptive therapy, where the pathophysiology has not yet been fully determined. Human and animal studies point to a combination of mechanisms, interacting with each other to increase the development and severity of the disease. The complexity of ONJ and the potential synergy of multiple pathways is depicted on the schematic diagram of Figure 1. Histologic bone necrosis is at the center of the disease process. Strong evidence points to antiresorptives in combination with trauma and/or inflammation/infection as key factors that are necessary and sufficient for ONJ development. Antiresorptives alone do not cause bone necrosis, but when combined with trauma such as a tooth extraction or inflammation/infection from periodontal or periapical disease, bone necrosis can occur. Necrotic bone in turn can lead to loss of soft tissue integrity, or clinical ONJ. Surgical intervention also results in direct disruption of soft tisseus and further complicates the disease. Case reports of exposed, necrotic bone with loss of soft tissue integrity have been associated with trauma or infection alone. Bone exposure propagates infection and inflammation in a positive feedback loop increase disease severity or extent. Further loss of soft tissue integrity leads to continued bone necrosis, and the cycle perpetuates.

Imunomodulators such as steroids or chemotherapy, as well as immunocompromised states from disease such as diabetes, and antiangiogenics are significant modifiers that may increase disease prevalence or severity when combined with inflammation/infection or trauma in the presence of antiresorptives. Again, reported cases of ONJ associated with steroids, chemotherapy, or anti-angiogenics alone are fewer in number. Bone necrosis does not always lead to bone exposure, which is why Stage 0 ONJ has received much attention in

recent years. Unless loss of soft tissue integrity occurs, frank bone exposure or Stage I, II, or III clinical ONJ is not diagnosed. Preliminary reports demonstrate that approximately Stage 0 ONJ often progresses to clinical bone exposure [99, 100]. However, it is unclear what determines progression in those patients. We anticipate that continued preclinical and clinical studies will shed light on the key players and significant modifiers in the development, severity, and progression, and resolution of ONJ. Understanding pathophysiologic mechanisms of ONJ will help explore targeted treatment interventions to reduce development and improve management of patients with established disease.

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KEY POINTS

- ONJ is a multifactorial disease in patients with primary or metastatic bone malignancy or osteoporosis undergoing systemic antiresorptive therapy, where the pathophysiology has not yet been fully determined
- The staging of Osteonecrosis of the jaw (ONJ) is based on severity of symptoms and extent of clinical and radiographic findings.
- Treatment strategies range from conservative local wound care to aggressive resective surgery of all necrotic bone
- The first ONJ cases were reported in 2003 and 2004, and although significant progress has been made in our understanding of the disease, much more work needs to be done to completely explain its pathophysiology.

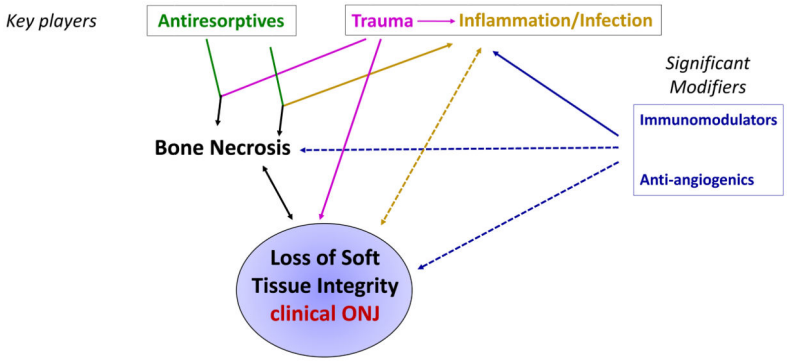

Figure 1.
The potential synergy of multiple pathways of ONJ