Pathophysiology of Osteonecrosis of the Jaws

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KEYWORDS

• Osteonecrosis of the jaws (ONJ) • Bisphosphonates • MRONJ • Antiresorptive • Pathophysiology

KEY POINTS

- Osteonecrosis of the jaw (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 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.

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 disease, without history of radiation therapy to the jaws.[1,2] Recently, the American Association of Oral and Maxillofacial Surgeons (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 because 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 1); as exposed bone with associated infection, pain, or swelling (stage 2); 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 3).

Treatment strategies range from conservative local wound care to aggressive resective surgery

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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 examinations 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 MEDICATION-RELATED OSTEONECROSIS OF THE JAW 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. Because 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, because 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 receptor activator of nuclear factor kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (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]

Bisphosphonates (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 ONJ occurs only in alveolar bone of the maxilla and mandible.[21] Alveolar bone may demonstrate an increased remodeling rate as compared with 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; although 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.

Because 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 with 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 zoledronic acid (ZA).[31]

ONJ prevalence in patients treated with BP or denosumab appears similar.[39,40] BPs bind to