

PERSPECTIVES

Bisphosphonates: Sacrificing the Jaw to Save the Skeleton?

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Abstract:

Bisphosphonate-associated osteonecrosis of the jaw has drawn widespread attention and concern in the absence of evidence-based scientific information. There are hundreds of thousands of patients in the United States taking bisphosphonates for a variety of conditions including breast and prostate cancer, multiple myeloma, Paget's disease, and osteoporosis. Recent reviews in the *Annals of Internal Medicine* and *Lancet Oncology* have provided valuable summaries of this condition but also highlight the need for additional data. Bisphosphonate-associated osteonecrosis is, simply, exposed necrotic bone in the jaws of patients on bisphosphonates. Although the incidence is not yet clear, existing data suggest 6-10% of patients on intravenous bisphosphonates for cancer therapy will develop osteonecrosis of the jaw. This *Perspective* reassesses contributing factors that have been discussed in the literature, and also provides new thoughts regarding the targeted destruction of bones of the oral cavity versus other skeletal sites. Further research will help to identify individuals susceptible to osteonecrosis of the jaw and therefore facilitate prevention and effective treatment. Conditions such as osteonecrosis of the jaw highlight the need to consider oral-systemic links when treating patients and underscore the importance of communication between health care providers. *BoneKEy-Osteovision*. 2006 September;3(9):12-18.
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Bisphosphonate-associated osteonecrosis of the jaw, typically a rare occurrence, has drawn widespread attention, concern, and in some instances, paranoia. Hundreds of thousands of patients in the United States alone are taking bisphosphonates for a variety of conditions including breast and prostate cancer, multiple myeloma, Paget's disease, and osteoporosis. The medical and dental community is obliged to provide patients with evidence-supported information and both the pros and cons of therapeutic modalities in order for patients to make informed healthcare decisions. To date, studies relevant to osteonecrosis of the jaw associated with bisphosphonate treatment have centered on case reports and case series. Recent reviews in the *Annals of Internal Medicine* and *Lancet Oncology* have provided valuable summaries of this condition but also highlight the dearth of useful data (1;2).

Bisphosphonate-associated osteonecrosis has been defined as the "unexpected development of necrotic bone in the oral cavity of a patient receiving bisphosphonates treatment and who has not received radiotherapy to the head and neck" (1) or, very simply, exposed necrotic jaw bone. Bisphosphonates have been used for more than 10 years for a variety of metabolic bone diseases and cancers. They are synthetic analogues of inorganic pyrophosphate where the P-O-P bond has been replaced with a P-C-P non-hydrolyzable bond. Bisphosphonates bind divalent ions such as Ca(2+) and hence are targeted to bone. Nitrogen-containing bisphosphonates inhibit components of the intracellular mevalonate pathway and protein prenylation leading to defective osteoclast regulation that compromises the cytoskeleton, membrane ruffling, and protein trafficking and results in an induction of apoptosis. Bisphosphonates impact other

cell types as well, but to an extent that is less clear.

The incidence of bisphosphonate-associated osteonecrosis is not yet determined with certainty, but existing data suggest occurrence in 6-10% of patients on intravenous bisphosphonates for cancer therapy (2). The most devastating sequelae involve patients who do not recover from osteonecrosis and are relegated to living with exposed bone in the oral cavity.

Why the Jaw?

Anatomy: Circulation, and Soft and Hard Tissues

To date, nearly all reports of osteonecrosis associated with bisphosphonate therapy have involved the jaw. Exceptions include reports of cases involving the bones of the ear subsequent to a surgery of the external auditory canal (3) and concurrent pathology of other skeletal sites such as long bones and the hip, but the jaws are clearly the target skeletal site (4). The bones of the jaw are unique relative to other bones and hence may present differing responses to systemic factors. For example, it has long been controversial whether metabolic disturbances such as osteopenia and osteoporosis affect the oral cavity. Antiresorptive agents such as bisphosphonates and estrogens, and anabolic agents such as parathyroid hormone (PTH), have documented effects in the oral cavity and have been considered for the treatment of the bone resorptive condition of periodontal disease. However, to date, studies have not indicated clinically significant results and hence they have not reached clinical practice. Hence, the tie between oral bone and other skeletal sites remains enigmatic.

There are several characteristics of bones of the jaw that can be compared and contrasted to other bones of the human skeleton and that may predispose them to altered healing responses. Unlike the long bones and vertebrae, the maxilla and mandible form primarily via intramembranous bone formation, although

there are remnants of Meckel's cartilage in the mandible. The cortical bone of the mandible is particularly thick and somewhat thinner in the maxilla. The thickest cortical bone in the jaw is present in the premolar and molar region of the lower jaw, a site that is often cited to have osteonecrosis. In the maxilla, the outer cortical bone is perforated by many small blood vessels, whereas in the mandible, the cortical bone is dense, and relatively few small vessels perforate the bone. In the anterior region of both the maxilla and mandible, the alveolar supporting bone is thin and there is relatively little trabecular bone. The trabecular bone in the posterior areas of the mouth, and particularly in the mandible, displays functional adaptation. The trabeculae follow the direction of occlusal stress, typically in a horizontal pattern. The condyloid process, angle of mandible, and maxillary tuberosity are sites that may contain hematopoietic marrow in adults, but more commonly the jaw contains fatty marrow. In contrast, the vertebrae, ribs, and long bones contain red marrow. The presence of a hematopoietic environment is likely to be protective in the healing response of bone, and the lack thereof in the oral cavity may be a predisposing factor to adversity.

Since most cases of osteonecrosis occur after a surgical procedure or traumatic incident and often after tooth extractions, it is valuable to consider the wound healing process in the oral cavity. The healing of an extraction site involves a series of steps including the formation of a coagulum, which is replaced by a provisional connective tissue matrix followed by woven bone and finally lamellar bone and bone marrow (5). The coagulum forms within the first 24 hours and contains erythrocytes, platelets, and isolated neutrophils in a fibrin matrix, which is replaced by vascularized granulation tissue by three days. If a systemic agent such as a bisphosphonate reduces vascularity, it could compromise this stage of healing. By seven days, the provisional matrix is comprised of new blood vessels, immature mesenchymal cells, leukocytes, and collagen fibers. In the adjacent marrow spaces, osteoclasts increase in number and signal that remodeling is underway. This

should be a particularly vulnerable time for the action of an agent that inhibits osteoclasts. By 14 days, large amounts of new woven bone are found in the extraction site. This area is rich in cells and adjacent to newly formed blood vessels. By 30 days, this woven bone shows evidence of remodeling with increased osteoclastic activity here and on adjacent lamellar bone. By 90 days, the woven bone is being replaced by lamellar bone, and after 180 days, the site contains bone marrow with trabeculae of lamellar bone. As a result, a compromise in osteoclast function could render ineffective either early remodeling of the old lamellar bone or later remodeling of new woven bone, and perhaps contribute to necrosis. It is interesting to consider withdrawal of bisphosphonate administration during the time the woven bone is being generated such that this new bone does not take up bisphosphonate to the same extent. Although bisphosphonates would be released from the older surrounding bone, the woven bone would contain lower bisphosphonate levels and could be more amenable to remodeling during the phase of replacement of woven bone, making a vital trabecular and marrow apparatus more likely than a bone susceptible to necrosis.

One of the reasons often cited as a factor for the jaw being a favored site for osteonecrosis is blood flow. However, scientific studies comparing blood flow in the craniofacial region to other skeletal sites are lacking. Blood flow rates in rats have been reported to be low in the mandible and skull (3–7 mL/min/100 g) versus the pelvis, proximal tibia, and fibula (13–35 mL/min/100 g), but not unlike blood flow to the clavicle and radius (6–9 mL/min/100 g) (6). Hence, blood flow alone is not likely a predisposing factor for the predilection of osteonecrosis to the jaw.

Oral Cavity Infection and Microbiota

Unlike other skeletal sites, the oral cavity is an 'open growth system.' After surgery or trauma, the bones of the jaw are continually exposed to microorganisms. More than 500 different species of microorganisms are capable of colonizing the oral cavity, with

150 or more typically present in an individual at any particular time (7). Many of these microorganisms are beneficial, but many are associated with the induction of osteoclastogenesis. Since the epithelium in the oral cavity is thin and easily traumatized, the maxilla and mandible can be readily exposed to a plethora of bacteria that other skeletal sites do not typically see. Supporting this as a contributing factor, many of the case report studies have cultivated pathogenic microflora, and antibiotics are routinely recommended for the treatment of osteonecrosis. Still, many patients do not recover from osteonecrosis even with antibiotic therapy. However, if the vascularity is reduced to the site, the potential for the antibiotic to reach its target may be compromised.

The host immune response could certainly be a contributing factor in bisphosphonate-associated osteonecrosis of the jaw. The largest number of cases has been in patients on intravenous bisphosphonate therapy for various cancers. Some are on other therapies as well and hence likely have an altered immune system. The data on bisphosphonates focuses on their impact on osteoclastic cells; there is a paucity of data on the effects of bisphosphonates on other hematopoietic cells. Interestingly, alendronate has been shown to act on antigen-presenting cells to inhibit their proliferation and production of various cytokines (8). This aspect of bisphosphonate function may factor into the compromised healing associated with osteonecrosis of the jaw.

Osteoclasts and Osteoclast Defects

Osteoclasts are the main target cell of bisphosphonate action, and their differentiation, function, and lifespan are compromised by bisphosphonate use. Although osteoclasts are better known for their negative impact in pathologic situations like osteoporosis and skeletal metastasis, they are also necessary for many physiologic processes such as bone growth, tooth eruption, and normal bone remodeling. Bone turnover occurs at a normal rate on average of 10% per year and is thought to

be critical for maintaining quality of bone. Patients on long-term bisphosphonate therapy have more brittle bone and some reports suggest that their healing after fracture is compromised (9). Animals and humans with osteopetroses provide an informative genetic model to better understand the significance of osteoclasts. Humans with osteopetrosis often have osteomyelitis in the oral cavity, delayed tooth eruption, congenitally missing teeth, poor tooth mineralization, and early tooth loss (10). Osteomyelitis is often secondary to tooth extraction or trauma. Such findings suggest parallels between the condition of bisphosphonate-associated osteonecrosis and osteopetrosis-associated osteomyelitis.

Other Lessons from Similar Disease Profiles

Interestingly, history may be repeating itself regarding the high profile of the condition of osteonecrosis of the jaw. In a book entitled *"The 13th Element: The Sordid Tale of Murder, Fire and Phosphorus,"* John Emsley details the hazards of phosphorus used by manufacturing and match industries (11). In Chapter 6, "The Cost of a Box of Matches," he describes 'phossey jaw/phosphorus necrosis' as a common occurrence among match workers exposed to the vapors from white phosphorus. The results described included erosion of teeth and surrounding tissues to such an extent that individuals often lost their complete 'jaw' bones. The first case of phossey jaw appeared in the medical literature in 1838. Additional reports indicated that the disease was slow in onset, about five years from first exposure, and that it occurred in 1–10% of people exposed to phosphorus. Individuals who cut and dried the matches and those with dental caries seemed more susceptible to phossey jaw. The disease was attributed to breathing phosphorus fumes and continued absorption of phosphorus and/or oxides (now recognized to include pyrophosphate) in affected tissue, but the mechanisms were not identified. At the time, the prevailing theory was that phosphorus entered the bloodstream, affecting the skeleton and jaw bones, resulting in weak bones and pain. When infection was already present, a more

devastating condition resulted. The similarities to bisphosphonate-associated osteonecrosis are remarkable and include enhanced susceptibility based on dose, as well as a history of oral infections.

Other conditions that may provide clues to why jaw bones/teeth are more susceptible to bisphosphonates versus other mineralized tissues of the body may be gleaned from pathologies associated with lingual mandibular sequestration, osteoradionecrosis, viral and fungal infections, and osteomyelitis (2;12). Lingual mandibular sequestration appears at the gross level as a mild form of bisphosphonate-associated osteonecrosis, i.e., slivers of bone are sequestered in the region of the mylohyoid ridge with spontaneous resolution, in an otherwise healthy individual. The suggested explanation for this situation is that minor trauma to the thin mucosa and underlying periosteum results in bone necrosis. Woo *et al.* propose that patients on bisphosphonate therapy, with associated hypodynamic bone, may exhibit a more profound osteonecrosis when subject to local trauma; therefore, a logical reason why the jaw bones, with thin mucosa protection, may be a target for osteonecrosis (2).

Osteonecrosis is a well-known complication of head and neck irradiation. Irradiation, especially at high doses (usually more than 6000 cGy), may result in irreversible damage to bone and vasculature in the local region. Predictions of risk for patients undergoing treatment are not precise, but risk is clearly related to radiation dose and the amount of bone exposed to irradiation. The mandible is at higher risk than the maxilla for osteonecrosis. Osteonecrosis is reported more frequently in dentulous patients and even more so if teeth within the treatment field are removed after therapy. Spontaneous exposure of bone is often delayed and risk for osteonecrosis continues indefinitely post-radiation therapy (13). Some studies suggest that the hypoxic, hypoxic and hypovascular environment associated with irradiation osteonecrosis can be treated with hyperbaric oxygen, but it is not clear if this is of any value for

bisphosphonate-associated osteonecrosis (14). In fact, it is still not clear whether or not the vasculature is substantially compromised and/or if the effects on vasculature are comparable between patients receiving bisphosphonates or irradiation treatments. Similarities to bisphosphonate osteonecrosis with regard to susceptibility include dose, aggressiveness, site-preference to mandible versus maxilla (although Migliorati *et al.* (1) suggest that bisphosphonate-associated osteonecrosis has a greater predilection for the maxilla, support for this statement is lacking), and the presence of teeth. A difference is that suppuration and associated bacterial infection are not as common with irradiation osteonecrosis as with bisphosphonate-associated osteonecrosis. Furthermore, at the histological level, bisphosphonate-induced necrotic bone exhibits a paucity of Howship's lacunae with decreased reversal lines, while Howship's lacunae and reversal lines appear normal in bone from patients with a history of osteoradionecrosis.

Acute and chronic osteomyelitis are the most common types of osteomyelitis and the types most frequently caused by infection of bone/bone marrow of the mandible/maxilla as a consequence of a periapical abscess or physical injury (e.g., fracture/surgery). Manifestations include pain, purulent exudate, lymphadenopathy, pyrexia, leukocytosis, and other signs and symptoms of dental infection. Bone necrosis may occur. Chronic cases are also associated with infection, and clinical presentation and course are dependent on the virulence of microorganisms involved and on the patient's resistance. Other factors include anatomical location, with the molars being the most frequent site in the mandible; immunologic status; nutritional status; age; and the presence of other systemic factors (e.g., Paget's disease, history of irradiation at sites, sickle cell disease, medications (steroids)). Therefore, common features of bisphosphonate-associated osteonecrosis, osteomyelitis, and oral complications of osteopetrosis include location, with the more frequent site being the mandible versus maxilla, and suggest that the anatomical

aspects of bone factor prominently in these conditions.

Between Health and Osteonecrosis: Spectrum of Oral Manifestations

The increasing awareness of oral-systemic links related to development, maintenance, disease-pathologies, and repair/regeneration of oral versus other tissues has resulted in improved interactions between oral and other healthcare providers. Bisphosphonate-associated osteonecrosis of the jaw is one more example of such links and highlights the need for even better communication and data gathering between healthcare providers and between healthcare providers and patients. Interesting and relevant to the discussion of bisphosphonate-associated oral disease is the known sensitivity of oral tissues to alterations in phosphate (Pi) and pyrophosphate (PPi) levels and to changes in the Pi/PPi ratio. For example, some individuals having mutations in the gene for tissue non-specific alkaline phosphatase (TNSALP) exhibit severe periodontal disease due to high PPi levels at sites of tooth root formation (cementum formation) resulting in no root formation (i.e., no cementum), and thus no periodontal ligament attachment to anchor the tooth to bone, severe periodontal disease, and exfoliated teeth (15;16). In contrast, individuals with mutations in ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1, also known as PC-1) and the ankylosis gene (*ank*) exhibit craniometaphyseal dysplasia, but the specific oral phenotype has not been detailed (17;18). Patients with kidney disease having altered phosphate levels (i.e., hyperphosphatemia), exhibit radiographic changes in oral bones. These are just a few examples of diseases and pathologies with oral manifestations, and emphasize the need to monitor the oral health of individuals and especially the quality of oral bones in patients reporting a history of bone disorders and/or taking medications or vitamins linked with bone regulation.

One interesting possibility for the apparent

sensitivity of oral hard tissues to Pi/PPi concentrations may relate to the levels of the factors controlling Pi/PPi within oral tissues versus other tissues, as suggested by recent investigations of hypophosphatasia (16;19). Although evidence to date does not suggest any alterations in alkaline phosphatase levels in patients taking bisphosphonates, it is possible that high concentrations of bisphosphonates may regulate genes and proteins such as *ank*, TNSALP, and PC-1, which control local levels of Pi/PPi, resulting in a further inhibition of bone-turnover, remodeling, and consequently enhanced necrotic bone (e.g., TNSALP as a substrate is turned-off by high levels of bisphosphonates and thus Pi levels decline).

Future Directions, Issues, Opportunities, and Alternative Medications

There are many unanswered questions: Is the uptake of bisphosphonates different in oral versus other skeletal sites? Are there adequate animal models of bisphosphonate-associated osteonecrosis? What are the risk factors, and do they include genetic aspects, in addition to the suspected clinical factors? What are the most beneficial treatment approaches for the management of bisphosphonate-associated osteonecrosis? Better knowledge of the cellular and molecular basis of the disease state would help to inform our decisions. For example, if the issue is bisphosphonate-associated compromise in vascularity, agents to promote angiogenesis could be considered. If the lack of osteoclasts is a key factor, then agents that increase osteoclasts, such as PTH, could be administered in select instances during a window of time. The timing of bisphosphonate administration and its withdrawal during selected phases of healing after trauma or surgery need to be investigated. Several institutes at the NIH have expressed interest in supporting studies focused on bisphosphonate-associated osteonecrosis. Along these lines, the NIDCR-funded practice-based network projects (3 grants) (20) have selected a case-control study of bisphosphonate-associated osteonecrosis of the jaw. Routine data that will be collected, assessed and

compared include medical and dental history, as well as exposure history to various medications, doses of bisphosphonates, age, sex, and pre-existing medical conditions. With continued research impacting clinical outcomes, the consequences of bisphosphonate-associated osteonecrosis will be minimized.

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