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Bisphosphonate-related osteonecrosis of the jaw: a mechanobiology perspective

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ABSTRACT

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a dramatic disintegration of the jaw that affects patients treated with bisphosphonates (BPs) for diseases characterized by bone loss. These diseases are often metastasizing cancers (like multiple myeloma, breast cancer and prostate cancer (Aragon-Ching et al., 2009)) as well as osteoporosis. BRONJ is incompletely understood, although it is believed to arise from a defect in bone remodeling—the intricate process by which sensory osteocytes signal to osteoclasts and osteoblasts to resorb and form bone in response to stimuli. Further, tooth extraction and infection have been overwhelmingly linked to BRONJ (Ikebe, 2013). Because bone cells are highly networked, the importance of multicellular interactions and mechanotransduction during the onset of these risk factors cannot be overstated. As such, this perspective addresses current research on the effects of BPs, mechanical load and inflammation on bone remodeling and on development of BRONJ. Our investigation has led us to conclude that improved in vitro systems capable of adequately recapitulating multicellular communication and incorporating effects of osteocyte mechanosensing on bone resorption and formation are needed to elucidate the mechanism(s) by which BRONJ ensues.

1. Introduction

BRONJ is specifically defined as necrotic bone in the oral cavity that does not heal within eight weeks of onset. Additionally, the affected person must have been exposed to a BP and must not have undergone radiation therapy in the craniofacial region or have suffered previous metastasis to the jaw (Migliorati et al., 2013; Saia et al., 2010; Advisory Task Force on Bisphosphonate-Related Osteoencrosis of the Jaws, 2007; Ruggiero et al., 2014). A position paper published by the American Association of Oral and Maxillofacial Surgeons in 2014 suggests replacing the nomenclature of BRONJ with medication-related osteonecrosis of the jaw (MRONJ) to incorporate cases of osteonecrosis following exposure to other antiresorptive and antiangiogenic treatments. These include the antiresorptive human monoclonal antibody, Denosumab, and antiangiogenic tyrosine kinase inhibitors (Ruggiero et al., 2014). Denosumab prevents osteoclast resorption by inhibiting receptor activator of nuclear factor kappa-B ligand (RANKL), which binds to RANK on the surface of osteoclasts to promote differentiation and activation (Qaisi et al., 2016). Tyrosine kinase inhibitors may exaggerate suppression of bone remodeling by BPs, counteract mucosal healing and increase risk of infection in the jaw. Research shows tyrosine kinase inhibitors, including sunitinib and imatinib, can promote osteonecrosis of the jaw with and without supplementary BP therapy (Ruggiero et al., 2014; Viviano et al., 2017). For the purposes of this review, which explores osteonecrosis associated with only BP therapy, we will continue to use the original terminology.

BPs mitigate bone resorption by osteoclasts and remodeling as a whole. They are used to treat the following conditions characterized by excess bone loss: tumor bone metastasis, osteoporosis, malignancy-associated hypercalcemia and Paget's disease (Feller et al., 2009; Zara et al., 2015; Manzano-Moreno et al., 2015; Heymann, 2010; Landesberg et al., 2011). An increase in BP prescriptions has led to an increased need to interpret the mechanism(s) by which BRONJ develops. From a research standpoint, mechanical trauma (tooth extraction) and inflammation derived from infection have been strongly associated with BRONJ (Ikebe, 2013; Otto et al., 2012; Abu-Id et al., 2008; Aragon-Ching et al., 2009). These two risk factors are closely linked because extraction sockets may become exposed to oral bacteria, causing infection. BPs, mechanical load and inflammation likely contribute to the disease by disturbing normal bone turnover. Limited studies have been performed to discern effects of these risk factors on bone remodeling in isolation, and very little is known about their effects in tandem. Mechanobiology is the study of the coordination of biological mechanisms by mechanical or physical stimuli (Epari et al., 2010). Physical forces

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are translated into biochemical signals that prompt cellular responses by a process called mechanotransduction. In bone, mechanotransduction includes four phases: 1) mechanocoupling (which involves the stretching of bone cells and generation of fluid movement within the bone canaliculae by mechanical loads), 2) biochemical coupling (or the conversion of a mechanical signal into a biochemical reaction by way of cellular pathways), 3) transmission of the signal from the sensor to the effector cell and 4) the effector cell response (Huang and Ogawa, 2010; Duncan and Turner, 1995; Turner and Pavalko, 1998). As current research seeks to elucidate the mechanism(s) by which BRONJ develops, the study of the disease from a mechanobiology perspective will support this resolve. Although we have chosen to present experimental studies on the effects of cofactors on bone cell communication and functional activity, a systematic review of clinical trials, case series and retrospective studies on BRONJ published between 2003 and February 2014 validates our decision to focus on tooth extraction and infection. Fliefel et al. found that, within 3198 cases of BRONJ, 61.7% were caused by tooth extractions, and 5% were associated with periodontal disease (inflammation) (Fliefel et al., 2015).

2. Bisphosphonates

BPs are chemotherapeutical antiresorptive compounds that mediate the morphology and activity of bone cells in several ways; these actions characterize them as risk factors for BRONJ (Zara et al., 2015; Donetti et al., 2014). BPs commonly used in therapy are made up of a central carbon atom attached to a hydroxyl group, which gives BPs the ability to bind to calcium. On either side of the carbon atom is a phosphonate group responsible for the drug's affinity for hydroxyapatite (Fig. 1). As such, BPs are preferentially taken up by bone (Russell, 2011). If a nitrogen or amino group is present, the drug is termed “nitrogen-containing.” Nitrogen-containing BPs (NBPs) are more potent in their antiresorptive capabilities than non-nitrogen-containing BPs by 10 to 10,000 times (Drake et al., 2008). NBPs prevent osteoclast survival and bone-resorbing ability by binding to and hindering enzymes of the intracellular mevalonate pathway. This in turn inhibits prenylation—attachement of isoprenoids for anchorage to cell membranes—of small GTPases. Buildup of unprenylated small GTPases then causes inappropriate activation of signaling pathways (Jobke et al., 2014). The most potent NBP, zoledronic acid (Zafar et al., 2016), is frequently associated with clinical cases of BRONJ.

2.1. Effects of bisphosphonates on osteoclasts

BPs act on osteoclasts to inhibit bone resorption. They prevent osteoclast formation, alter phenotype, prohibit function and promote apoptosis (Sharma et al., 2013; Gong et al., 2011; Bagan et al., 2013). They form chelates with calcium ions and bind to hydroxyapatite on the exterior of bone, prompting release of a soluble factor that prevents precursor cells from fusing to form osteoclasts (Zara et al., 2015). Osteoclasts are multicellular and contain the following: 1) ruffled borders (to which proteins and acids are localized for the degradation of bone (Stenbeck, 2002)), 2) intracytoplasmic vesicles (by which the products of bone degradation are transported intracellularly (Galvão et al., 2011)) and 3) sealing zones (ring shaped actin-rich structures that encircle the sites at which the plasma membranes adhere to the bone (Teti et al., 1991; Matsumoto et al., 2013)). BPs cause an increase in size and number of nuclei, disrupt the cells' ruffled borders, prevent formation of intracytoplasmic vesicles and promote detachment of sealing zones (Jobke et al., 2014). Further, NBPs obstruct the mevalonate pathway of cholesterol synthesis which restricts the enzyme, farnesyl diphosphate synthase. As described above, small GTPases cannot be prenylated (Manzano-Moreno et al., 2015), and osteoclasts are unable to break down bone.

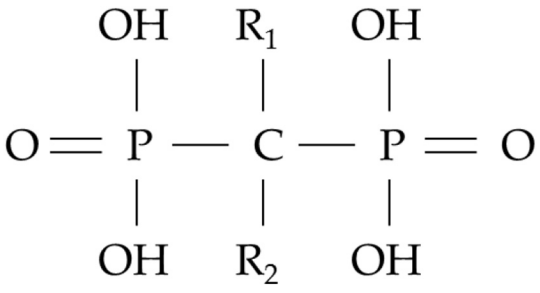

Fig. 1. Chemical structure of a BP. If a nitrogen or amino group is present, the drug is termed “nitrogen-containing.”

2.2. Effects of bisphosphonates on osteoblasts and osteocytes

While the effects of BPs on osteoblasts and osteocytes are much less studied, there is evidence that both contribute to the onset of BRONJ—the osteoblasts through altered mineralization and the osteocytes through mechanotransduction. BPs administered at high doses ($\geq 10^{-5}$ M) have been shown to arrest the osteoblast cell cycle and induce apoptosis, thereby reducing proliferation of the osteoblast lineage. Low doses ($\sim 10^{-9}$–10^{-6} M) have been reported to exert positive effects on osteoblasts (Zara et al., 2015; Manzano-Moreno et al., 2015). Importantly, BPs promote connexin 43 (Cx43)-required osteocyte survival (Plotkin et al., 2008). However, it is likely that osteocyte survival is also BP dose-dependent with cell death occurring at high concentrations (Pazianas et al., 2014). Evidence infers that BPs gain access to osteocytes by way of the canalicular network. Fluorescent BP analogues have been shown to target osteocyte lacunae, specifically lacunar walls that neighbor osteocytes recently embedded near the surface of bone. However, it is unknown whether this process is BP type-dependent (Roelofs et al., 2010).

2.3. Effects of bisphosphonates on tissue properties of bone

In addition to acting on individual cells, BPs can significantly alter the tissue properties of bone. For example, BP therapy has been shown to decrease apatite crystal size and perfection that can lead to compromised mechanical characteristics, like elastic modulus and contact hardness (Bala et al., 2012). Several studies on the properties of the jawbone following BP treatment, including cortical porosity, bone mineral density (BMD) and crack surface density (Cr. S. Dn), have been carried out in beagle dog models. One study indicated that exposure to BP treatment impacted jaws but not tissue mineralization. After three months of exposure, average tissue mineralization was unchanged but jaws displayed significantly decreased cortical porosity and significantly increased areal BMD when compared to controls. However, other studies reported significantly higher Cr. S. Dn. in the basal alveolar regions of experimental samples treated with high-dose BP for one year as well as matrix necrosis occurring between one and three years of high-dose therapy (Allen, 2011).

Kim et al. investigated the role of microdamage in conjunction with BP on BRONJ development. Rats were administered injections of BP or saline for six weeks. Tooth extractions were performed, and treatments were sustained for eight weeks before sacrifice. The number and length of microcracks in the BP group were greater than those in the control group; 68.4% of the rats that were injected with BP were sorted into a BRONJ group. BRONJ faction samples showed significantly greater crack density (Cr. Dn.) as well as Cr. S. Dn when compared to samples from the non-BRONJ group. The authors conclude there is a significant relationship between the aggregation of unrepaired microcracks and the onset of BRONJ. This aggregation represents a plastically yielded and mechanically compromised environment. In addition to affecting bone cell morphology and activity, high-dose/long-term BP treatment likely decreases bone's mechanical integrity and propagates microcrack formation, supporting BRONJ development (Kim et al., 2016).