Bisphosphonate-Related Osteonecrosis of the Jaw: Is pH the Missing Part in the Pathogenesis Puzzle?

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Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a side effect of bisphosphonate therapy, primarily diagnosed in patients with cancer and metastatic bone disease and receiving intravenous administrations of nitrogen-containing bisphosphonates. If diagnosis or treatment is delayed, BRONJ can develop to a severe and devastating disease. Numerous studies have focused on BRONJ, with possible pathomechanisms identified to be oversuppression of bone turnover, ischemia due to antiangiogenetic effects, local infections, or soft tissue toxicity. However, the precise pathogenesis largely remains elusive and questions of paramount importance await to be answered, namely 1) Why is only the jaw bone affected? 2) Why and how do the derivatives differ in their potency to induce a BRONJ? and 3) Why and when is BRONJ manifested? The present perspective reflects on existing theories and introduces the hypothesis that local tissue acidosis in the jaw bone offers a conclusive pathogenesis model and may prove to be the missing link in BRONJ.

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Bisphosphonate-Related Osteonecrosis of the Jaw: The Facts

Since the first descriptions emerged in 2003,1-3 bisphosphonate-related osteonecrosis of the jaw (BRONJ) has become a well-known side effect of increasing clinical importance. Diagnosis is primarily based on a history of bisphosphonate (BP) intake and the presence of exposed necrotic bone in the oral cavity over a period of 8 weeks in the absence of metastases or irradiation of the jaws.4 In addition, soft tissue swelling, ulceration, suppuration, sinus tracts, abscesses, pathologic fractures, and impairment of nerve function can occur.1,4,6 A high cumulative dosage and high bioavailability of BPs are associated with an increased risk for
the manifestation of BRONJ. Indeed, more than 90% of BRONJ cases emerge from patients with cancer and metastatic bone disease receiving BPs intravenously.7,10 Although the bioavailability of oral BP derivatives is approximately 100-fold lower than intravenous applications,11,12 long-term administration of oral BPs is also associated with the risk of BRONJ onset.13,15

BRONJ is primarily associated with nitrogen-containing BPs, most frequently zoledronate (>40% of cases) followed by pamidronate.6,14-16 In contrast, only a few cases of BRONJ are due to non-nitrogen-containing BPs, such as clodronate and etidronate.6 However, the antiresorptive potencies of BP derivatives do not correlate well with the reported number of BRONJ cases. For example, less than 5% of BRONJ cases are linked to ibandronate,6,8,10,15 a BP with an antiresorptive potency a magnitude higher compared with pamidronate,12 which contributes to approximately 25% of reported BRONJ cases.6,15

Several risk factors have been discussed as promoting the onset of BRONJ such as chemotherapy, irradiation of the head and neck region, comorbidities such as diabetes or comedication, for example steroid intake, but also patients’ habits, such as smoking and poor oral hygiene.6,14,17-19 Scientific evidence of other factors remains elusive and should be addressed in future studies. In cases due to oral BPs, the duration of BP intake seems to be an important risk factor, where up to 50% of (mostly osteoporotic) patients do not demonstrate additional risk factors.6,15

In most cases dentoalveolar surgeries (eg, tooth extractions and implant insertions) or infections (eg, apical or marginal periodontitis) precede the manifestation of BRONJ.14-17,20 Trauma and ill-fitted dentures are also thought to trigger the onset of BRONJ.14 However, cases that have occurred spontaneously with no identifiable trigger event have been reported. These cases occurred predominantly in the lingual aspects of the mandible and other areas where the mucosal layer is very thin.6

BRONJ: Current Theories

The exact pathogenesis remains obscure but 4 main theories regarding BRONJ prevail. First, BRONJ is induced by an oversuppression of bone turnover. Due to their high affinity, BPs accumulate in bone and subsequently in cells involved in bone resorption, namely osteoclasts. Osteoclast function is inhibited and consequently bone remodeling is suppressed.21 An oversuppression of bone turnover by a localized toxic BP level may induce an osteonecrosis.22,25 Although the bone turnover in the jaws is higher,24-26 there is no evidence that BPs accumulate at higher concentrations in the jaw (compared with other sites) or that bone remodeling of the jaw bone is affected to a higher degree. A recent study has confirmed that uptake of BP is not increased in the jaw compared with other bones.27

Second, BRONJ could be a response to infection. BPs are known to modulate the immune response of different cell types.28,29 This may alleviate the immune response toward particular pathogens in biofilms such as Actinomyces species, which were found to be present in most cases of BRONJ.30,31

Third, BRONJ is a possible result of ischemia due to the antiangiogenetic effects of BPs. Although the description of BRONJ as avascular necrosis and the antiangiogenetic effect in BPs in tumor tissues suggest a role in the pathogenesis of BRONJ,30,32 the angiogenesis during bone formation seems to be unaltered by bisphosphonates.33,34

Fourth, soft tissue toxicity may be a mediator of BRONJ by BP’s toxicity toward different cell types, including mucosal tissue. It has been argued that localized accumulation of BPs may, in combination with other cancer therapy medications, lead to mucosal injury followed by exposed bone and BRONJ.35-37 However, exposed bone is not present in all cases of histologically proved necrosis and some clinical symptoms, such as pain, abscess or fistula formation, and even impairment of nerve function, can emerge during the onset of BRONJ.38,39 even when the mucosa is still intact.

Arguably, all theories could play a role in the pathogenesis of BRONJ; however, none of them (in isolation or combination) is able to explain why the jawbone is the exclusive target. A further shortcoming is that current theories do not offer a plausible explanation as to why nitrogen-containing BPs, which do not overly accumulate in the jawbone compared with other bones,21 result in an increased risk of developing BRONJ. It is not the intention of this report to disprove existing hypotheses, but rather present a new pathomechanism proposed to precede and indeed link the other theories (Fig 1).

Effect of pH on BRONJ: The Missing Part in the Pathogenesis Puzzle?

BPs reveal a unique property of selective uptake by their intended target organ. BPs bind to bone at circum neutral pH and are released in an acidic milieu. This physiologic mechanism takes place in the resorption lacunae during bone resorption, where acid pH increases the dissociation between BP and hydroxyapatite.40 To date, this well-known feature has not been linked to the pathogenesis of BRONJ, but may prove to be the missing part in the multifactorial puzzle. Indeed, Sato et al41 demonstrated in rats that bone-bound alendronate is released at acidic pH. In humans, acidic milieus are common in infections and
wound healing after surgical procedures. Indeed, pH values in the range of 6.2 are not uncommon during infections. Likewise, the jawbones are frequently exposed to marginal or apical periodontitis, extended caries with endodontic involvement, and surgical procedures such as tooth extractions or implant insertions. Resultant infections can therefore lead to localized tissue acidification (pH reduction) and subsequent increased BP release. Furthermore, pH reduction results in a protonated activation of nitrogen-containing groups (eg, NH₂ to NH₃⁺), thereby increasing the transformation of respective derivates to potentially toxic levels. It is conceivable that BP-derivative specific toxic levels are exceeded in response to a prolonged or localized acidification, which in turn may trigger the cascade of pathways that cumulate in BRONJ (Fig 1). These processes might also occur after minor disturbances such as microtraumata or pressure sores or even spontaneously depending on the local concentration and type of BP and comorbidities, comedications, and the presence of other risk factors. Non-nitrogen-containing BPs, which in general have a lower antiresorptive activity, are not subjected to this process of activation. This correlates with clinical observations, that only single cases of BRONJ with these BP derivates (such as etidronate or clodronate) have been reported.6

Once confirmed, this hypothesis will offer not only rationalization as to why the jaw bone, in particular, is affected, but also explain why dental infections and invasive procedures and nitrogen-containing amino-BPs act as initiators of BRONJ. Furthermore, it offers an explanation as to why immunosuppression, chemotherapy, irradiation, and systemic disorders (eg, diabetes) may increase the risk for the development of BRONJ. Indeed, these circumstances are known to be associated with an increased risk of disturbances in the processes of wound healing and remodeling after dentoalveolar procedures and predispose patients to infections.7-14,19

In conclusion, this work aims to highlight that a localized change in pH caused by dentoalveolar infections or surgeries is to date a neglected, primary factor that may elicit the onset of BRONJ. This observation is potentially a major stepping-stone toward a comprehensive understanding of the pathogenesis of BRONJ and possible future prevention.

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