

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

Sven Otto, MD, DDS,\* Sigurd Hafner, MD, DDS,†  
 Gerson Mast, MD, DDS,‡ Thomas Tischer, MD,§  
 Elias Volkmer, MD,|| Matthias Schieker, MD,¶  
 Stephen R. Stürzenbaum, PhD,# Emmo von Tresckow, PhD,\*\*  
 Andreas Kolk, MD, DDS,†† Michael Ehbrenfeld, MD, DDS,‡‡ and  
 Christoph Pautke, MD, DDS,§§

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 antiangiogenic 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.

© 2010 American Association of Oral and Maxillofacial Surgeons

*J Oral Maxillofac Surg* 68:1158-1161, 2010

## Bisphosphonate-Related Osteonecrosis of the Jaw: The Facts

Since the first descriptions emerged in 2003,<sup>1-3</sup> 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.<sup>4</sup> In addition, soft tissue swelling, ulceration, suppuration, sinus tracts, abscesses, pathologic fractures, and impairment of nerve function can occur.<sup>1,4-6</sup> A high cumulative dosage and high bioavailability of BPs are associated with an increased risk for

\*Resident, Department of Oral and Maxillofacial Surgery, Ludwig Maximilians University of Munich, Munich, Germany.

†Consultant, Department of Oral and Maxillofacial Surgery, Ludwig Maximilians University of Munich, Munich, Germany.

‡Senior Consultant, Department of Oral and Maxillofacial Surgery, Ludwig Maximilians University of Munich, Munich, Germany.

§Consultant, Department of Orthopaedic Surgery, Technische Universität München, Munich, Germany.

||Resident, Experimental Surgery and Regenerative Medicine, Department of Surgery, Ludwig Maximilians University of Munich, Munich, Germany.

¶Senior Consultant, Experimental Surgery and Regenerative Medicine, Department of Surgery, Ludwig Maximilians University of Munich, Munich, Germany.

#Senior Lecturer, Pharmaceutical Science Division, King's College London, London, United Kingdom.

\*\*Roche Pharma AG, Grenzach-Wyhlen, Germany.

††Senior Consultant, Department of Oral and Cranio-Maxillofacial Surgery, Technische Universität München, Munich, Germany.

‡‡Professor and Head of Department, Department of Oral and Maxillofacial Surgery, Ludwig Maximilians University of Munich, Munich, Germany.

§§Senior Consultant, Department of Oral and Maxillofacial Surgery, Ludwig Maximilians University of Munich, Munich, Germany.

Address correspondence and reprint requests to Dr Otto: Department of Oral and Maxillofacial Surgery, Ludwig-Maximilians-University, Lindwurmstr 2a, Munich 80337, Germany; e-mail: [Sven.Otto@med.uni-muenchen.de](mailto:Sven.Otto@med.uni-muenchen.de)

© 2010 American Association of Oral and Maxillofacial Surgeons

0278-2391/10/6805-0032\$36.00/0

doi:10.1016/j.joms.2009.07.079

the manifestation of BRONJ. Indeed, more than 90% of BRONJ cases emerge from patients with cancer and metastatic bone disease receiving BPs intravenously.<sup>7-10</sup> Although the bioavailability of oral BP derivatives is approximately 100-fold lower than intravenous applications,<sup>11,12</sup> long-term administration of oral BPs is also associated with the risk of BRONJ onset.<sup>13</sup>

BRONJ is primarily associated with nitrogen-containing BPs, most frequently zoledronate (>40% of cases) followed by pamidronate.<sup>6,14-16</sup> In contrast, only a few cases of BRONJ are due to non-nitrogen-containing BPs, such as clodronate and etidronate.<sup>6</sup> 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,<sup>6,8,10,15</sup> a BP with an antiresorptive potency a magnitude higher compared with pamidronate,<sup>12</sup> which contributes to approximately 25% of reported BRONJ cases.<sup>6,15</sup>

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 comedications, for example steroid intake, but also patients' habits, such as smoking and poor oral hygiene.<sup>6,14,17-19</sup> 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.<sup>6,13</sup>

In most cases dentoalveolar surgeries (eg, tooth extractions and implant insertions) or infections (eg, apical or marginal periodontitis) precede the manifestation of BRONJ.<sup>7,14,17,20</sup> Trauma and ill-fitted dentures are also thought to trigger the onset of BRONJ.<sup>14</sup> 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.<sup>6</sup>

## 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.<sup>21</sup> An oversuppression of bone turnover by a localized toxic BP level may induce an osteonecrosis.<sup>22,23</sup> Although the bone turnover in the jaws is higher,<sup>24-26</sup> 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.<sup>27</sup>

Second, BRONJ could be a response to infection. BPs are known to modulate the immune response of different cell types.<sup>28,29</sup> 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.<sup>30,31</sup>

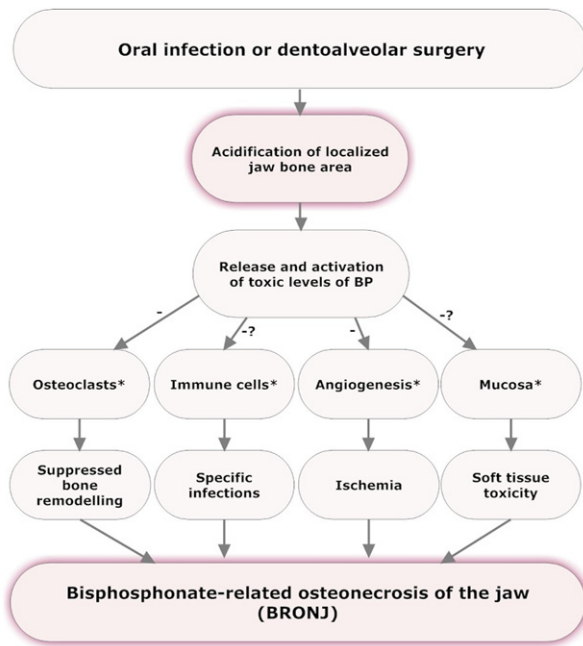
Third, BRONJ is a possible result of ischemia due to the antiangiogenic effects of BPs. Although the description of BRONJ as avascular necrosis and the antiangiogenic effect in BPs in tumor tissues suggest a role in the pathogenesis of BRONJ,<sup>30,32</sup> the angiogenesis during bone formation seems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

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.<sup>35-37</sup> 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,<sup>38,39</sup> 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,<sup>21</sup> 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 lacunas during bone resorption, where acid pH increases the dissociation between BP and hydroxyapatite.<sup>40</sup> 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 al<sup>41</sup> demonstrated in rats that bone-bound alendronate is released at acidic pH. In humans, acidic milieus are common in infections and



**FIGURE 1.** Schematic diagram of the potential pathogenesis of BRONJ with decreased pH value as a crucial activator depicts inhibition of the listed processes or tissues (-), identify cursorily investigated pathogenesis theories (?), and identify the points at which risk factors (smoking, diabetes, steroids, chemotherapy, poor oral hygiene, comorbidity) might aggravate the BRONJ pathogenesis (\*).

Otto et al. *Pathogenesis of Bisphosphonate Necrosis. J Oral Maxillofac Surg* 2010.

wound healing after surgical procedures. Indeed, pH values in the range of 6.2 are not uncommon during infections.<sup>42-44</sup> 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,  $\text{NH}_2$  to  $\text{NH}_3^+$ ), thereby increasing the transformation of respective derivatives to potentially toxic levels.<sup>40,45,46</sup> 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 derivatives (such as etidronate or clodronate) have been reported.<sup>6</sup>

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.<sup>7,14,19</sup>

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.

#### Acknowledgments

The authors thank Rainer Bartl, MD, and Inga Drosse, DVM, for the inspiring discussions and helpful advice.

#### References

- Marx RE: Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *J Oral Maxillofac Surg* 61:1115, 2003
- Migliorati CA: Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 21:4253, 2003
- Wang J, Goodger NM, Pogrel MA: Osteonecrosis of the jaws associated with cancer chemotherapy. *J Oral Maxillofac Surg* 61:1104, 2003
- American Association of Oral and Maxillofacial Surgeons: Position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 65:369, 2007
- Khosla S, Burr D, Cauley J, et al: Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 22:1479, 2007
- Abu-Id MH, Warnke PH, Gottschalk J, et al: "Bis-phossy jaws"—High and low-risk factors for bisphosphonate-induced osteonecrosis of the jaw. *J Craniomaxillofac Surg* 36:95, 2008
- Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS: Factors associated with osteonecrosis of the jaw among bisphosphonate users. *Am J Med* 121:475, 2008
- Yarom N, Yahalom R, Shoshani Y, et al: Osteonecrosis of the jaw induced by orally administered bisphosphonates: Incidence, clinical features, predisposing factors and treatment outcome. *Osteoporos Int* 18:1363, 2007
- King AE, Umland EM: Osteonecrosis of the jaw in patients receiving intravenous or oral bisphosphonates. *Pharmacotherapy* 28:667, 2008
- Rizzoli R, Burllet N, Cahall D, et al: Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. *Bone* 42:841, 2008
- Gertz BJ, Holland SD, Kline WF, et al: Studies of the oral bioavailability of alendronate. *Clin Pharmacol Ther* 58:288, 1995
- Berenson JR, Hillner BE, Kyle RA, et al: American Society of Clinical Oncology clinical practice guidelines: The role of bisphosphonates in multiple myeloma. *J Clin Oncol* 20:3719, 2002

13. Marx RE, Cillo JE Jr, Ulloa JJ: Oral bisphosphonate-induced osteonecrosis: Risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg* 65:2397, 2007
14. Bamias A, Kastritis E, Bamia C, et al: Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: Incidence and risk factors. *J Clin Oncol* 23:8580, 2005
15. Dimopoulos MA, Kastritis E, Anagnostopoulos A, et al: Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: Evidence of increased risk after treatment with zoledronic acid. *Haematologica* 91:968, 2006
16. Marx RE, Sawatari Y, Fortin M, Broumand V: Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 63:1567, 2005
17. Hoff AO, Toth BB, Altundag K, et al: Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res* 23:826, 2008
18. Wessel JH, Dodson TB, Zavras AI: Zoledronate, smoking, and obesity are strong risk factors for osteonecrosis of the jaw: A case-control study. *J Oral Maxillofac Surg* 66:625, 2008
19. Dimopoulos MA, Kastritis E, Bamia C, et al: Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. *Ann Oncol* 20:117, 2009
20. Badros A, Terpos E, Katodritou E, et al: Natural history of osteonecrosis of the jaw in patients with multiple myeloma. *J Clin Oncol* 26:5904, 2008
21. McDonald MM, Dulai S, Godfrey C, et al: Bolus or weekly zoledronic acid administration does not delay endochondral fracture repair but weekly dosing enhances delays in hard callus remodeling. *Bone* 43:653, 2008
22. Orriss IR, Key ML, Colston KW, Arnett TR: Inhibition of osteoblast function in vitro by aminobisphosphonates. *J Cell Biochem* 106:109, 2009
23. Walter C, Klein MO, Pabst A, et al: Influence of bisphosphonates on endothelial cells, fibroblasts, and osteogenic cells. *Clin Oral Investig* 14:35, 2010
24. Vignery A, Baron R: Dynamic histomorphometry of alveolar bone remodeling in the adult rat. *Anat Rec* 196:191, 1980
25. Garetto LP, Tricker ND: Remodeling of bone surrounding the implant interface. *In* Garetto LP, Turner CH, Duncan RL, Burr DB (eds): *Bridging the Gap Between Dental and Orthopaedic Implants*. Third Annual Indiana Conference, Indianapolis, IN, 1998, pp 89-100
26. Huja SS, Fernandez SA, Hill KJ, Li Y: Remodeling dynamics in the alveolar process in skeletally mature dogs. *Anat Rec A Discov Mol Cell Evol Biol* 288:1243, 2006
27. Bauss F, Pfister T, Papapoulos S: Ibandronate uptake in the jaw is similar to long bones and vertebrae in the rat. *J Bone Miner Metab* 26:406, 2008
28. Wolf AM, Rumpold H, Tilg H, et al: The effect of zoledronic acid on the function and differentiation of myeloid cells. *Haematologica* 91:1165, 2006
29. Roelofs AJ, Jauhainen M, Monkkonen H, et al: Peripheral blood monocytes are responsible for gammadelta T cell activation induced by zoledronic acid through accumulation of IPP/DMAPP. *Br J Haematol* 144:245, 2009
30. Hansen T, Kunkel M, Weber A, James Kirkpatrick C: Osteonecrosis of the jaws in patients treated with bisphosphonates—Histomorphologic analysis in comparison with infected osteoradionecrosis. *J Oral Pathol Med* 35:155, 2006
31. Sedghizadeh PP, Kumar SK, Gorur A, et al: Identification of microbial biofilms in osteonecrosis of the jaws secondary to bisphosphonate therapy. *J Oral Maxillofac Surg* 66:767, 2008
32. Scavelli C, Di Pietro G, Cirulli T, et al: Zoledronic acid affects over-angiogenic phenotype of endothelial cells in patients with multiple myeloma. *Mol Cancer Ther* 6:3256, 2007
33. Deckers MM, Van Beek ER, Van Der Pluijm G, et al: Dissociation of angiogenesis and osteoclastogenesis during endochondral bone formation in neonatal mice. *J Bone Miner Res* 17:998, 2002
34. Cetinkaya BO, Keles GC, Ayas B, Gurgor P: Effects of risenedronate on alveolar bone loss and angiogenesis: A stereologic study in rats. *J Periodontol* 79:1950, 2008
35. Reid IR, Bolland MJ, Grey AB: Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? *Bone* 41:318, 2007
36. Sonis ST, Elting LS, Keefe D, et al: Perspectives on cancer therapy-induced mucosal injury: Pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 100:1995, 2004
37. Landesberg R, Cozin M, Cremers S, et al: Inhibition of oral mucosal cell wound healing by bisphosphonates. *J Oral Maxillofac Surg* 66:839, 2008
38. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL: Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. *J Oral Maxillofac Surg* 62:527, 2004
39. Otto S, Hafner S, Grötz KA: The role of inferior alveolar nerve involvement in bisphosphonate-related osteonecrosis of the jaw. *J Oral Maxillofac Surg* 67:589, 2009
40. Russell RG, Watts NB, Ebetino FH, Rogers MJ: Mechanisms of action of bisphosphonates: Similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 19:733, 2008
41. Sato M, Grasser W, Endo N, et al: Bisphosphonate action. Alendronate localization in rat bone and effects on osteoclast ultrastructure. *J Clin Invest* 88:2095, 1991
42. Hays RC, Mandell GL: PO<sub>2</sub>, pH, and redox potential of experimental abscesses. *Proc Soc Exp Biol Med* 147:29, 1974
43. Bertram P, Treutner KH, Klosterhalfen B, et al: (Artificial pressure increase in subcutaneous abscess with evidence of general systemic reaction). *Langenbecks Arch Chir* 382:291, 1997
44. Wiese KG: (Electrolyte concentration, real and osmotic pressure in abscesses). *Zentralbl Chir* 119:54, 1994
45. Nancollas GH, Tang R, Phipps RJ, et al: Novel insights into actions of bisphosphonates on bone: Differences in interactions with hydroxyapatite. *Bone* 38:617, 2006
46. Rogers MJ, Gordon S, Benford HL, et al: Cellular and molecular mechanisms of action of bisphosphonates. *Cancer* 88:2961, 2000