

## BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAWS. A SEVERE SIDE EFFECT OF BISPHOSPHONATE THERAPY

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**Summary:** Bisphosphonates (BP) are potent inhibitors of bone resorption used mainly in the treatment of metastatic bone disease and osteoporosis. By inhibiting bone resorption, they prevent complications as pathological fracture, pain, tumor-induced hypercalcemia. Even though patient's benefit of BP therapy is huge, various side effects may develop. Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is among the most serious ones. Oncologic patients receiving high doses of BP intravenously are at high risk of BRONJ development. BPs impair bone turnover leading to compromised bone healing which may result in the exposure of necrotic bone in the oral cavity frequently following tooth extraction or trauma of the oral mucosa. Frank bone exposure may be complicated by secondary infection leading to osteomyelitis development with various symptoms and radiological findings. In the management of BRONJ, conservative therapy aiming to reduce the symptoms plays the main role. In patients with extensive bone involvement resective surgery may lead to complete recovery, provided that the procedure is correctly indicated. Since the treatment of BRONJ is difficult, prevention is the main goal. Therefore in high risk patients dental preventive measures should be taken prior to bisphosphonate administration. This requires adequate communication between the prescribing physician, the patient and the dentist.

**Key words:** Bisphosphonate; Osteonecrosis; Jaw

### Introduction

Bisphosphonates (BP) are synthetic drugs used in the treatment of bone involvement in various osseous diseases as osteoporosis, multiple myeloma, bone metastasis of solid tumors (with or without hypercalcaemia), osteitis deformans ("Paget's disease of bone"), primary and secondary hyperparathyroidism, osteogenesis imperfecta, and other conditions that feature bone fragility (6). By inhibition of bone resorption, they prevent the loss of bone mass, pathologic fractures, pain or hypercalcaemia caused by the underlying disease which significantly improves the quality of life of the affected patients.

### Chemical structure, pharmacological properties and side effects of bisphosphonates

BPs are analogues of inorganic pyrophosphate with characteristic phosphorus – carbon – phosphorus chemical core with two side chains ( $R_1$ ,  $R_2$ ) bound to the carbon atom. According to presence or absence of a nitrogen atom located in the  $R_2$  group, they can be divided into two groups, nitrogen-containing and non-nitrogen-containing bisphosphonates, differing in the mechanism of action on osteoclasts (6, 17). Various BPs exhibit different relative potencies and affinity to the bone. The newer nitrogen-containing BPs as zoledronate are the most potent inhibitors of bone resorption (6, 30). (See Tab. 1.)

**Tab. 1:** Classification of bisphosphonates

Type of BP	Generic name	Trade name
Non-nitrogen-bisphosphonates	Clodronate	Bonefos, Londronat
Aminobisphosphonates	Pamidronate	Aredia, Pamidronate, Pamitor
	Alendronate	Aldrion, Alendrogen, Alendronat, Alenwin, Fosamax, Fosteofos, Gendron, Siranin, Ralenost, Androvance, Fosavance
	Risendronate	Actonel, Juverital, Norsed, Nurrid, Tevanel, Risendronat
	Ibandronate	Bondronat, Bonviva, Bondenza
	Zoledronate	Aclasta, Zometa

BPs may be administered orally or intravenously. Absorption by the gastrointestinal tract is poor. The bioavailability is lower than 1% in most bisphosphonates. Intravenous administration ensures that about 50% of the dose reach the bone (6). The remainder is excreted largely unchanged by the kidneys (31). BPs have a very high affinity for bone matrix and bind rapidly to hydroxyapatite crystals.

The specific mechanism of inhibition of bone resorption is complex and not fully understood. Non-nitrogen containing BPs are taken up by the osteoclasts and trigger intracellular mechanisms leading to apoptosis (25). Nitrogen-containing bisphosphonates have a complex pathway of action resulting in interference with the osteoclastogenesis, in apoptosis and changes in cytoskeletal dynamics (17). Zoledronate has also been known to inhibit human endothelial cell proliferation and to modulate endothelial cell adhesion and migration. BPs also show anti-tumor effect which is thought to be due to induction of tumour cell apoptosis, and inhibition of tumour cell adhesion and invasion. Anti-angiogenic effect of BPs have also been described (6, 17).

Although bisphosphonates have huge clinical benefits, various adverse reactions as renal failure and flu-like symptoms with fever have been reported. Gastrointestinal disorders as dyspepsia and oesophagitis may occur after oral administration. Other adverse reactions as uveitis and scleritis are rare (4). BRONJ is among the most severe side effects of BP therapy.

### Incidence of BRONJ and risk factors

The association of long-term application of BPs and exposed necrotic bone has been first described by Marx in 2003 (30). Since then, about 5000 cases of BRONJ have been documented (8, 10, 11, 26, 37, 38, 44). Various definitions make it difficult to make conclusions about the incidence which has been reported to be less than 10% by various studies (15, 31, 42). It is likely, however, that mild cases remain unidentified (24). Most incidences of BRONJ have been reported as a result of intravenous administration of high doses of aminobisphosphonates (4, 31). Association of BRONJ and non-nitrogen BP is very rare (9). High risk patients for BRONJ development are those with malignant disease receiving intravenous BP therapy in high doses and/or with a history of chemotherapy, or concomitant medications of systemic corticosteroids or anti-angiogenic agents. A history of diabetes mellitus seems to mildly increase the risk (21). The length of bisphosphonate therapy is also an ascertained risk factor (7). Patients receiving BPs orally, mainly for the treatment of postmenopausal osteoporosis, are at low risk of developing BRONJ (1, 25, 27).

### Pathogenesis and clinical presentation

BRONJ can be defined as a pathological condition characterised by the presence of an area of exposed necrotic bone

in the maxillofacial region lasting for more than 8 weeks in a patient who was receiving bisphosphonate and had not received radiation therapy to craniofacial region (42). This definition doesn't include so called 'non-exposed' variant of BRONJ, where no denuded necrotic bone is exposed, but bone pain, swelling, sinus tract or radiographic abnormality is present (31). In BRONJ, frank bone exposure is often complicated by secondary infection of the denuded bone leading to development of osteomyelitis, presenting by abscess or fistula formation or even pathologic fractures, which have a severe impact on the quality of life of the affected patients (see Fig. 1).



**Fig. 1:** Exposed necrotic bone of the alveolar process bilaterally in the mandible

The pathogenesis of BRONJ has not been completely understood so far, but following factors are thought to play a role in pathogenesis: inhibition of osteoclasts leads to impaired natural remodelling process being critical for bone healing. The bone becomes over-aged and self-healing capacity is decreased. Besides, inhibition of angiogenesis additionally disables the healing of the bone and the soft tissues (31). Tooth extractions, other minor dentoalveolar surgeries, trauma and bruises from poorly fitting dentures are then common triggering factors of bone exposure (3, 25, 30, 42). Spontaneous occurrence has also been observed (23). This may be caused by underlying odontogenic infection leading to disruption of the continuity of oral epithelium (18). Very likely, genetic variations among individuals confer susceptibility or resistance to BRONJ development, since BRONJ occurs only in a certain percentage of BP users (20).

The American Association of Oral and Maxillofacial Surgeons suggested a staging system based on four stages of BRONJ (31, 34, 42).

- Stage zero is represented by the non-exposed variant, where other symptoms and signs as pain, sinus tracts or radiologic markers are present (14).

- First stage includes asymptomatic bone exposure.
- Second and third stage include patients with exposed bone of various extent with other concomitant symptoms and signs which are mainly a result of secondary infection of the necrotic bone. (See Tab. 2.) The symptoms may include increased tooth mobility, formation of sinus tracts, suppuration and traumatic ulceration of oral mucosa adjacent to exposed bone, mandibular fracture or cervical lymphadenopathy (36).

**Tab. 2:** Staging of BRONJ (according to AAOMS)

Stage	Bone exposure	Recommended treatment
0	No bone exposed, but presence of symptoms and signs as bone pain, sinus tracts, radiologic evidence of bone changes	
I	Exposed bone, no symptoms and signs of infection	Antibacterial mouth rinses
II	Exposed bone, pain, signs of infection	Antibacterial mouth rinses Systemic antibiotics Analgesics
III	Exposed bone beyond the dento-alveolar process, cutaneous fistulae, oro-antral or oro-nasal fistulae, pathologic fracture	Antibacterial mouth rinses Systemic antibiotics Analgesics Surgical therapy (optional)

For identifying BRONJ, panoramic radiographs, dental cone beam computed tomography or spiral computed tomography are useful (18). Radiologic markers, caused either by direct effect of BPs or by secondary infection of the necrotic bone include osteosclerosis, osteolysis, thickening of lamina dura, widening of periodontal space, thickening of periosteum, subperiosteal bone formation,



**Fig. 2:** Radiologic changes of the alveolar bone in a patient with BRONJ

sequestra, fracture and radiologic evidence of sinusitis (29) (see Fig. 2). Bone scintigraphy, PET scans or MRI may help in identifying early areas of bone involvement, where clinically no exposed bone is present (18, 35). However, specificity of these radiological methods is low and similar findings may be caused by odontogenic infections or bone involvement in multiple myeloma.

## Prevention

In about 60% of the patients, osteonecrosis is a result of tooth extraction, less often it may develop spontaneously or as a result of chronic trauma to oral mucosa, often caused by ill-fitting dentures (43). Therefore BRONJ seems to be a preventable complication to a certain degree (40). Prior to the bisphosphonate administration, high risk patients should be informed about the possible side effects of bisphosphonate therapy and should be referred to the dentist to have all dental diseases treated (1, 37). Endodontic and periodontal therapy as well as tooth extractions and other oral surgical procedures should be performed before the onset of bisphosphonate therapy (4, 31, 42). The design of removable dentures should be checked to minimize the chance of trauma to the oral mucosa (4). These preventive measures will minimize the risk of BRONJ. After the BP therapy has been initiated, surgical procedures in oral cavity should be avoided. Endodontic treatment is a preferred alternative to tooth extraction. However, if an extraction must be performed, prophylactic systemic antibiotic therapy combined with antibacterial mouth rinses and soft tissue primary closure of the socket following an atraumatic extraction would decrease the risk of BRONJ development.

## Management

Therapy of BRONJ is generally difficult and should be adjusted to individual patient's needs based on the general medical status, the stage of BRONJ and life expectancy (42). With conservative therapeutical approach, complete resolution is rarely achieved. The main goal of BRONJ management is prevention of infection of the necrotic bone and reduction of symptoms (34). In the first stage, where no signs of inflammation are present, antimicrobial mouth rinses (chlorhexidin) are used to reduce the risk of bone infection. In the second and third stage where symptoms and signs of infection are present, systemic antibiotics and analgesics are indicated in addition to antimicrobial mouth rinses (32). Various antibiotic regimens have been tested in several studies; penicillin, doxycycline, quinolones, metronidazole, clindamycin (19, 31, 34). None of the studies suggested the most effective one. In addition to medical therapy, minor surgical procedures are often performed. These include sequestrotomy of mobile bone fragments, equalisation of prominent bony edges and minor debridement with soft tissue closure (2, 16, 31). Aggressive surgical treatment approach with wide bone resection is controversial (34).



Since BPs affect the whole jaw, surgical trauma to the bone could lead to progression of osteonecrosis. Moreover, visualisation of vital bone margins during the surgery is difficult (32). Therefore the results are not easily predictable. Several reports on radical surgical therapy of BRONJ with positive results have been published so far (1). These suggest that carefully planned segmental bone resection with pre- and postoperatively administered antibiotics could result in complete resolution (41, 46). Reconstruction of the bony defect have been performed with either titanium plates, or vascularised bone grafts and local soft tissue flaps (5, 45). Yet, resective surgery should be indicated carefully following accurate diagnostic procedure and preoperative assessment with respect of patients morbidity and life expectancy. Other therapeutical modalities of BRONJ have been presented in the literature. These include human recombinant parathyroid hormone peptide, teriparatide, an anabolic agent that stimulates bone remodelling and counteracts the effects of BP. A few cases of BRONJ resolution after teriparatide administration for the treatment of osteoporosis have been reported. In these patients, BPs were switched to teriparatide due to BRONJ development. A small recent study documented resolution of BRONJ, when teriparatide treatment was instituted specifically to study its effect on BRONJ (33). Pentoxifylline and  $\alpha$ -tocopherol may improve the effect of antibiotic therapy which has been suggested by a single small uncontrolled study (12). Hyperbaric oxygen therapy and ozon have been used in BRONJ management, however with little evidence of positive effect (13, 39). Platelet-rich plasma and Nd:YAG laser have been attempted to improve outcome of surgical therapy (22, 28). So far there is little evidence of efficacy of these procedures. Withdrawal of BPs has not shown significantly positive outcomes (42). This is most probably caused by very long half-life of BPs (ranging among 1 to 10 years in various species), therefore discontinuation of the therapy for a short period is not likely to decrease the effect of BPs on the bone metabolism (4).

## Conclusion

BRONJ as a side-effect of BP therapy is a relatively rare complication but may have a huge impact on the quality of life of the affected patients. Patients receiving high doses of BP intravenously are at high risk of BRONJ development. Oral administration on the other hand causes significantly lower risk of BRONJ. Nevertheless, no ideal treatment strategy has been suggested so far. Most authors agree on conservative treatment approach. In certain cases, surgical therapy may be the option, provided the procedure is planned and indicated carefully, with respect of patients general health status and life expectancy. The subset of patients in whom complete resolution of BRONJ is achieved is low. Reduction of symptoms and infectious complications is the aim of BRONJ management. Nevertheless, primary goal is prevention to avoid this serious complications

of BP therapy. Side effects and possible risks should be explained and clarified to the patient by the prescribing physician before the therapy onset as well as dental preventive measures should be taken. Patients in whom intravenous administration of high doses of BP is planned are at high risk of BRONJ development. Therefore dental examination and treatment of all dental diseases is highly recommended prior to BP administration. This requires close cooperation between the patient, the dentist and the physician. Lack of communication could increase the risk of BRONJ.

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