Bisphosphonate-related osteonecrosis of the jaw: Current clinical significance and treatment strategy review

Jaewon Kim, DDS, MSD, PhD, **Du-Hyeong Lee**, DDS, MSD, PhD, **Rosemary Dziak**, MS, PhD & **Sebastian Ciancio**, DDS

Abstract: Purpose: This review paper is intended to provide updated information about the significance of bisphosphonate-related osteonecrosis of the jaw (BRONJ) related to dental departments and also to provide treatment information. However, it does not review anti-resorptive related osteonecrosis of the jaw (ARONJ). **Methods:** PubMED was searched for published articles on BRONJ that have particular relevance to clinical aspects in orthodontics, endodontics, periodontics, prosthodontics, oral and maxillofacial surgery, implants and treatment planning. In vitro and animal studies were excluded. **Results:** Bisphosphonate therapy has a significant level of importance within all dental departments, and the treatments for BRONJ are diverse without any documented superiority of one over another. (*Am J Dent* 2020;33:115-128).

Clinical significance: Each dental specialty must be aware of the risk of BRONJ in their patients, especially elderly ones with history of bone-related therapy or tumor. No definite consensus is made for some departments due to lack of evidence and rare cases.

✉: Dr. Sebastian Ciancio, School of Dental Medicine, University at Buffalo, 250 Squire Hall Buffalo, NY 14214, USA. E-✉: ciancio@buffalo.edu

Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is specifically found in patients who admitted the use of bisphosphonates in either intravenous and oral forms. Bisphosphonates were first developed in the 1960s, and following the initial launch of alendronate by Merck & Co in the 1990s, they have gained worldwide popularity for the therapy of fragile and weak bone diseases such as osteoporosis, Paget's disease, bone metastasis, and multiple myeloma. The chemically stable derivative of pyrophosphate, the carbon replacing oxygen mediates both protection and tight bonding to bone by attaching to hydroxyapatite crystals.[1] Once attached to bone, a very long withdrawal half-life of generally 10 years is usual.

The high affinity of bisphosphonates comes from their ability to bind to hydroxyapatite crystals.[2] Early bisphosphonates are the ones without nitrogen, and are called first generation. They are etidronate, clodronate, and tiludronate. Nitrogen-containing R2 sidechains are characteristics of second and third generation bisphosphonates, and they are alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid. In terms of drug potency, zoledronic acid~minodronate > risedronate > ibandronate > incadronate > alendronate > pamidronate is the order.[3] For intake terms, once-weekly (alendronate, risedronate), or once-monthly (ibandronate, risedronate) oral intake is possible.[2] Because of gastrointestinal side effects, intravenous preparations (pamidronate, ibandronate, and zoledronic acid) are available for patients (Table 1).

The current concept is that bisphosphonates are designed to target osteoclasts (Fig. 1). The process of bone resorption includes osteoclastic ingestion of bisphosphonates by endocytosis.[4] The structure of non-nitrogen containing bisphosphonate is similar to inorganic pyrophosphate. By the class II aminoacyl-transfer RNA synthetase, non-nitrogen containing bisphosphonates develop into a part of ATP (adenosine triphosphate) after absorption of minerals from bone to osteoclasts. These nonhydrolyzable ATP analogues mediate osteoclast apoptosis by their cytotoxic effect.

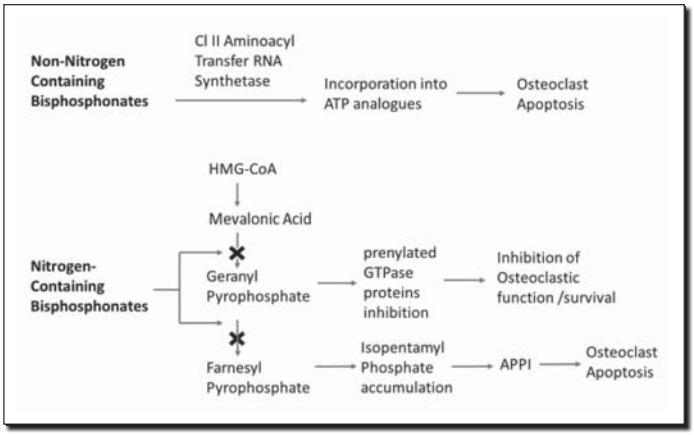

Fig. 1. Mechanisms of action of bisphosphonates on osteoclastic cells: Non-nitrogen containing bisphosphonates are converted to ATP analogues exhibiting apoptotic activity in osteoclasts. Nitrogen containing bisphosphonates inhibits the mevalonic acid pathway, leading to inhibition of osteoclastic function and apoptosis via inhibition of prenylated small GTPase proteins and isopentamyl phosphate accumulation and APPI, an ATP analogue that enhances osteoclstic cell apoptosis. Modified from Russell et al (2006).[4]

For nitrogen containing bisphosphonates, the mode of action is different. The mevalonic acid pathway is essential in formulation of cholesterol and other lipids. Farnesyl pyrophosphate synthase is a key regulatory enzyme in this pathway, and nitrogen-containing bisphosphonate binds to farnesyl pyrophosphate which also has an inhibitory action.[2]

When R1 is an OH group, enhanced bone binding can be seen.[4] The minor change in the R2 side chain can significantly alter the antiresorptive potency of bisphosphonates by inhibiting farnesyl diphosphate synthase, also affecting the binding potency to hydroxyapatite.[3,4]

Rab, Rac, and Rho are guanosine triphosphate binding proteins which have influence on osteoclasts by cellular activities such as survival, stress fiber assembly and membrane ruffling.[4] Post translational modification of these proteins is also inhibited, leading to osteoclast apoptosis.[2] The reason why this only happens in osteoclasts is still unknown. Other in vitro

Table 1. List of bisphosphonates.

	Method of intake	Potency	Mechanism of action
1st Generation (without nitrogen)			Incorporation of intracellular analogues of ATP*
etidronate	PO	1	
clodronate	PO, IV	10	
tiludronate	PO	10	
2nd/3rd Generation (with nitrogen-containing R2 sidechains)			Inhibition of prenylation and function of GTP binding
pamidronate	IV	100	proteins for osteoclast survival*
alendronate	PO	500	
ibandronate	PO, IV	1000	
risedronate	PO	2000	
zoledronate	IV	10,000	

*From Bisphosphonates: From bench to bedside, Russell et al (2006).[4]

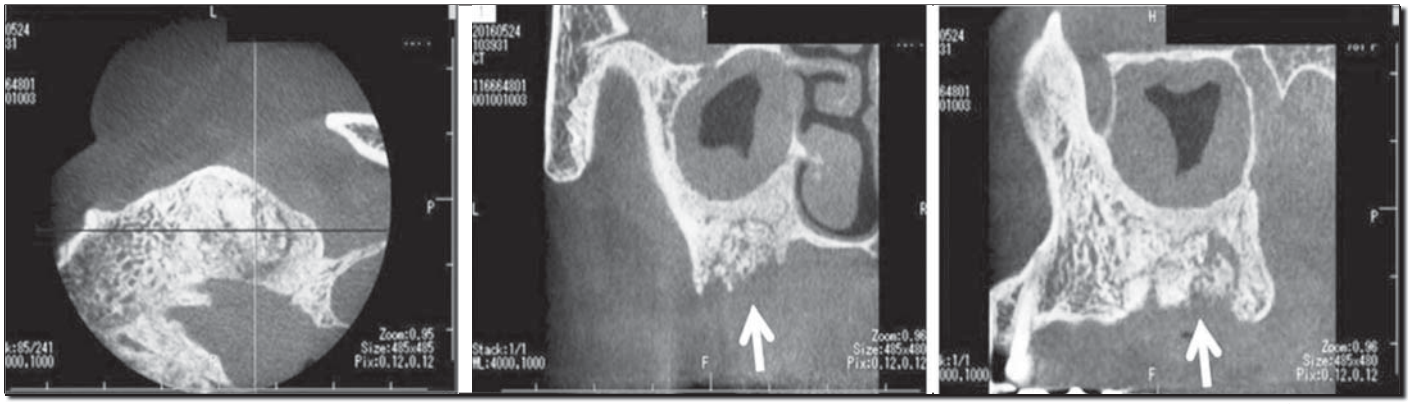

Fig. 2. Dental cone beam computed tomography shows sequestrum (white arrow) in a BRONJ patient. (Reprinted with permission from Taguchi et al[17]).

studies by Luckman et al[5] showed that bisphosphonates inhibit prenylation of Ras, another class of GTP binding protein.

BRONJ is characterized as bone in the maxillofacial area with necrosis recurring for more than 8 weeks in bisphosphonate-treated patients and with no history of radiation therapy.[1] The jaw is most predisposed to BRONJ because the alveolar bone turnover rate is very rapid and teeth and gums are an easy entrance for bacterial infection.[6] The intravenous route has more risk for BRONJ than the oral route.[7] Bisphosphonates with higher potency, more constant dosing, a higher incremental dose and a longer duration of treatment are all primary risk factors of BRO 2009NJ.[8]

In the 2007 position paper of the American Association of Oral and Maxillofacial Surgeons,[7] BRONJ was classified into three stages: stage 1, which shows only a bone denudation without infectious signs; stage 2, which includes pain and swelling which suggests bacterial infection in addition to stage 1; and stage 3 is the infection beyond alveolar bone level, in which bone necrosis can extend to the lower outline of the mandible. In 2009, from the same position paper, stage 0 was added, with the no evidence of necrotic bone, but with indefinite clinical findings and symptoms.

Methods are still under development for the definite diagnosis of BRONJ. One study[9] showed that the overall positive predictive value (PPV) for recognition of BRONJ was very low, suggesting low efficacy of the current algorithm and potential misinterpretation of BRONJ occurrence. In the Kim et al[10] study, serum TRACP 5b and the RANKL/OPG ratio have been considered as possible biomarkers. On the other hand, a prognosticator for a BRONJ risk was suggested using a C-terminal crosslinking telopeptide (CTX) level lower than 150 pg/ml.[11] In this prospective study with over 950 patients with 2,461 extractions, it was concluded that a CTX level lower than 150 pg/ml indicated a three-fold greater possibility of BRONJ, and the total risk was 0.2%. In a systematic review, capacity of the morning fasting serum CTX test for expecting the occurrence of BRONJ was evaluated.[12] However, the conclusion was that there is no predictive value to the test. This is in accordance with the study of Fleisher et al,[13] that suggests that radiographic PDL widening may be a more sensitive marker than CTX testing. For histopathological diagnosis, empty lacunae without osteocytes as well as hemorrhagic and chronic inflammatory cells infiltrate could be also seen.[14] In a recent study by Kim et al,[15] machine learning to predict BRONJ related to dental extraction was explored. Using an area under receiver operating characteristic curve, machine learning method was superior when matched to general statistical methods with drug break and serum CTX levels.

Despite recent advancement on the predictive method of BRONJ, traditional diagnostic methods such as radiographs can still aid in the confirmation process. On the radiographic image, visibility of the lamina dura, sclerotic bone areas appearing like a honeycomb, non-visible periodontal space, widening of the periodontal space in late stages, sclerotic changes, and alveolar sockets without evidence of healing can be identified.[16] In addition, a panoramic image combined with CT scans would be appropriate to detect trabecular and cortical bone changes, and in case of soft tissue changes, MRI would be sufficient[17] (Fig. 2).

Bisphosphonate is not only the drug which causes osteonecrosis in the jaw. Denosumab (Dmab; a RANKL-inhibitor) is also used as antiresorptive therapy and, Dmab-related ONJ is referred to as antiresorptive agent-related ONJ (ARONJ).

Table 2. Risk factors of BRONJ.

Systemic risk factors	Local risk factors
Advanced age	Poor oral hygiene
Systemic disease	Maxilla lesion
Rheumatoid arthritis	Multiple tooth extraction
Hypocalcemia	Excessive biting force
Hypoparathyroidism	Ill-fitting denture
Osteomalacia	Periodontal disease
Vitamin D deficiency	Gingival abscess
Renal dialysis	Inflammatory disease;
Anemia	apical periodontitis
Paget's disease	Tori
Glucocorticoids	
Obesity	
Smoking	
Drinking	

Tyrosine kinase inhibitors, such as Sunitinib (Sutent), Imatinib (Gleevec), Sorafenib (Nexavar), Regorafenib (Stivarga), Axitinib (Inlyta), Pazopanib (Votrient), Cabozantanib (Cometriq), Dasatinib (Sprycel) can induce osteonecrosis. Also, monoclonal antibodies such as Bevacizumab (Avastin), Rituximab (Rituxan), Adalimumab (Humira), Infliximab (Remicade), Romosozumab (Evenity) are possible candidates. Fusion proteins, such as Afliberept (Zaltrap) and mTOR inhibitors, which are Everolimus (Afinitor), Temsirolimus (Torisel), radiopharmaceuticals such as Radium 223 (Xofigo), selective estrogen receptor modulators (SERM), Raloxifene (Evista), and immunosuppresants such as Methotrexate are other examples. Corticosteroids can be involved in the jaw necrosis as well.[18] Anti-angiogenic drugs such as Bevacizumab, Sunitib, Cabozantinib affect and inhibit vascular endothelial growth factors (VEGF), and have been also known to cause osteonecrosis of the jaw and therefore the term: ”medication-related osteonecrosis of the jaw” (MRONJ) has been more recently adopted[8] to include ONJ that is associated with all types of medication including bisphosphonates.

For the local and systemic risk factors of BRONJ, various studies have reported many reasons, suggesting that there is no single factor for the prevalence (Table 2). The risk factors for BRONJ have been reported to be: elderly age, occurrence in maxilla, diabetes mellitus, tooth extraction, in particular multi extractions.[19] Taguchi et al[17] also stated that main oral health-care plays a role in the risk of ONJ separate from antiresorptive medications. Ill-adapting dentures, extreme bite pressure, pathologic periodontal condition, gingival abscess, apical periodontitis which is an example of an inflammatory disease can also be the triggering factors. Systemic diseases include anemia, hypocalcaemia, hypoparathyroidism, osteomalacia, rheumatoid arthritis (RA), vitamin D deficiency, renal dialysis, and Paget disease of bone.[17] Glucocorticoids can also be risk agents due to suppressed activities of inflammatory cells and immune cells.[20] If inflammatory dental disease is present in cancer patients exposed to IV bisphosphonates, the risk of initiation of BRONJ will increase 2.7- to 7-fold.[21] Also, lifestyle factors such as smoking, drinking and obesity could be the factors increasing risk of ONJ.[17] With respect to the location of the condition, the lingual side of the mandible is susceptible due to injury in oral mucosa, and bony protuberances such as maxillary torus, mandibular lingual tori and mylohyoid ridge can be possible candidates, with lesions more commonly found in the mandible.[7,17,20] In the Wat et al[8] study, 65% of cases were present in the mandible, 28.4% in maxilla, 6.5% in both mandible and maxilla, and 0.1% in other locations.

Table 3. Association of BRONJ for each dental disciplines.

Discipline	Association
Orthodontics	Influencing rate of tooth movement; poor space closure; poor root parallelism; longer treatment time; no reports on orthodontic tooth movement causing BRONJ.
Endodontics	BRONJ can mimic periapical lesion; caution needed when using rubber dam clamp; avoid overfilling; may be associated with external cervical resorption.
Periodontics	Periodontitis is associated with BRONJ; no reports on periodontal surgery causing BRONJ; Bisphosphonate may play a role as host modulator therapy, however, histologic evidence is lacking.
Prosthodontics	Avoid soft tissue trauma by removable and fixed partial denture component; use soft liners.
Oral Surgery	Torus injury is common; extraction still highest risk factor; no reports of BRONJ after other surgical procedures.
Implants	BRONJ associated with either intraoral and intravenous form; contrasting conclusions between case reports and systematic reviews.

It is still unclear whether the bacteria are the cause of the onset of the BRONJ. In one study,[1] *Actinomyces* were considered the causative factor. BRONJ also has similar characteristics to *Actinomyces* osteomyelitis. This is in accordance with the Kos et al[22] study, where *Actinomyces* was significantly detected in necrotic bones. However, Wang et al[19] indicated MRONJ had low association with *Actinomyces* infection, while finding α-hemolytic streptococci, *Neisseria*, *Prevotella intermedia*, coagulase negative staphylococci, and corynebacterium. Lesclous et al[23] studied 30 patients with nitrogen-containing bisphosphonates therapy and reported that the clinical feature of ONJ was statistically connected to the inflammatory cell count. The data suggested that bone necrosis is ahead of clinical outbreak and is an inflammatory process. Bisphosphonates also have a demonstrated ability to interfere with normal angiogenesis.[14] This would be fatal due to the dynamic turnover rate of alveolar bone.

In a review paper,[24] which divided the management of BRONJ to various dental disciplines: general dentistry, management of periodontal disease, implant placement and maintenance, oral and maxillofacial surgery, endodontics, restorative dentistry, prosthodontics, and orthodontics. However, more updated and in-depth analysis of BRONJ relative to each dental discipline is now needed. To analyze the effects of bisphosphonate therapy on dental patients in a more practical way, we divided the dental specialties/disciplines into orthodontics, endodontics, periodontics, prosthodontics, oral and maxillofacial surgery, and implants. Practitioners in these divisions deal extensively with bone in the jaw, and the use of bisphosphonates by patients can have great clinical significance. For each such department we present herewith human case reports, clinical trials and systematic reviews on BRONJ. In vitro studies and animal experiments were excluded. Ultimately, the goal of this review paper was to review the current concept of BRONJ, and delineate its clinical significance in the departments of orthodontics, endodontics, periodontics, prosthodontics, and oral and maxillofacial surgery with emphasis on evidence-based treatment plans (Table 3).

Orthodontics

The life span of humans is increasing due to medical developments, and as a result, their esthetic requirements have soared. Esthetics is not just sought out by the young population, but also by elderly patients.

The influence of bisphosphonates on orthodontics is diverse; studies are discussed here in order of hierarchy of evidence. In one case report by Morita et al,[25] a 55-year-old woman with past medical history of irradiation and bisphosphonate treatment underwent a cord blood transplantation for treatment of extranodal natural killer T cell lymphoma. To avoid extraction, her residual root was treated by orthodontic tooth extrusion. The tooth was restored without complication at the end. This case shows that orthodontic force may be useful in treatment of teeth which require extraction in bisphosphonate treated patients. Krieger et al[16] reported on the outcome of a 66-year-old woman who had extensive dental therapy. Even when oral alendronate was taken for 7 months during orthodontic treatment, it was successfully completed after 13 months of tooth movement. However, the recommendation was that treatment should be done with very light forces combined with monitoring. On the other hand, another case report by Rinchuse et al[26] presented two patients who were treated by orthodontics combined with bisphosphonate therapy. One case was a 35-year-old woman under alendronate sodium treatment for 16 months. In this patient, approximating the extraction space and paralleling root was very challenging, combined with radiopaque regions and sclerotic lines (denser bone and enlarged periodontal ligament space) were seen in a panoramic radiograph. Eventually the treatment was completed but not with the optimal result. The other case was a 77-year-old male who was treated with IV bisphosphonate for 11 months, later diagnosed with multiple myeloma. After extraction of the lower lateral incisor, the space was attempted to be closed with stainless steel wire, but this became very difficult and was discontinued after 13 months, when the patient also exhibited small osteonecrosis of the mandible. The tooth movement showed only tipping, not bodily movement.

In a retrospective cohort study, which reviewed women over age 50 who were treated during 2002 to 2008, Lotwala et al[27] noticed that bisphosphonate use was correlated with longer orthodontic treatment times in extraction patients, higher possibility of inadequate space closure and poor root parallelism. In addition, no BRONJ was reported. In a systematic review[28] of the influence of bisphosphonates on treatments of orthodontics, it was reported that topical or systemic application of bisphosphonates reduced orthodontic tooth movement and decreased orthodontic tooth movement and skeletal relapse after procedures such as expanding maxillary arch or mandibular distraction. Another systematic review[16] concluded that low-risk patients (low dose and short period of intake) who are taking bisphosphonates can safely undergo orthodontic treatment. However, the treatment outcome is still erratic, especially in high-risk patients. It was noted that in extraction cases or space closure, lengthened treatment time, decelerated tooth movement, and side issues should be anticipated. Several recommendations were subsequently proposed by Zahrowski[29] and it was noted that if the patient had a high risk/high level of osteoclastic inhibition with IV bisphosphonates treatment, orthodontic treatment should be avoided because of possible strong inhibition of tooth movement, and also increased possibility of osseous repair that might overwhelm compromised alveolar bone capacity. Also, it was proposed that retainers should be made to only cover the tooth, to avoid any pressure on the tissues. Another paper[30] by the same author, showed that decreased bone function due to bisphosphonate therapy will result in gradual movement and excessive mobility. Radiographic indicators will include sclerosis around teeth, indefinite PDL, or large PDL space. If these signs are present, one should consider careful monitoring, stopping the drug or delaying or stopping orthodontic treatment. In another review paper,[31] it was stated that the most important consideration for bisphosphonate treatment in patients who require orthodontic treatment is that even if initial tooth movement appears normal, subsequent tooth movement can be inhibited. In an article by Abela et al,[32] it was advised to inform the possibility of ONJ to the bisphosphonate taking patients, although in the literature there is no single reported case in which orthodontic treatment has ever caused ONJ. Complex orthodontic treatment should ideally commence only after testing the response of the tooth to orthodontic forces. In another review,[33] it was concluded that bisphosphonates reduce bone turnover, increasing the orthodontic treatment time and also the need to promote enhanced retention pharmaceutically. It also stated that the evidence based on animal or in vitro studies is not enough to have any clinical implications.

In conclusion, there is a limited number of studies involving the effect of bisphosphonates on orthodontic tooth movement in humans. Currently there is no report of BRONJ inflicted by orthodontic tooth movement. However, bisphosphonates seem to have influenced factors such as tooth resorption and rate of movement due to their effects on osteoclasts and fibroblasts.

Endodontics

The incidence of secondary caries and restorative failure increases with elderly age, and to save the tooth, endodontic treatments are required. Endodontists have to frequently deal with periapical lesions inside the jawbone.

One case report by Mosaferi et al[34] highlighted a 52 year-old Caucasian woman treated for a left upper lateral incisor and canine lesion. The lesion did not heal after conventional root canal therapy, periapical surgery, and extraction. Later it was diagnosed as BRONJ mimicking periapical radiolucent lesion. The dentist was unaware that the patient had been taking 4 mg/5 mL intravenous Zometa for the past 4 years, so this case emphasizes the importance of careful medical history taking. Two case reports by Sarathy et al[35] indicated an association between endodontic treatment and BRONJ. One case was a 72 year-old male who, 10 months after zoledronate therapy, developed lingual recession and exposed bone on the lower left second permanent molar. Endodontic treatment was performed but there was no progress. Moreover, furcation involvement on the lower left first permanent molar, which was treated with previous root canal therapy, was initiated. Ultimately, conservative debridement and antibiotic therapy was performed but the patient refused further therapy. The other case was a 74 year-old male, who was treated with 14 months of intravenous pamidronate and 27 months of intravenous zoledronate. The maxillary left econd molar (#15), which had the previous

history of root canal treatment, showed exposure of buccal and lingual bone, and later was extracted with partial maxillectomy. In a case report by Katz,[36] a 60 year-old female patient who was on pamidronate therapy for 1 year, followed by 1 year of zoledronate was presented. She had a history of multiple myeloma treated with chemotherapy. Pain was reported only during mastication or exposure to cold. Palatal bone was already exposed on the maxillary second molar (#2), and root canal therapy was done. The patient became comfortable after 2 days.

However, in some cases, rather than a treatment itself, the equipment related to endodontic therapy might cause problems related to BRONJ. In a case report by Gallego et al,[37] BRONJ was developed after successful endodontic therapy. The lingual bone was exposed on the lower second molar area, suggesting influence of a rubber dam clamp adversely affecting periodontal and mucosal tissue.

Bisphosphonates can be also associated with external cervical resorption. In one study, possible predisposing causes for external cervical resorption were systemic disease and medication, including bisphosphonates, and the frequency of appearance was 2.4%.[38] In a case series by Patel et al,[39] it was stated that alendronatic acid treatment can have pro-inflammatory effects that can start acute-phase response, which has been shown to be associated with the discharge of TNF alpha, IL-1, IL-6 which can trigger osteoclastogenesis and bone resorption. In his report of three cases, the teeth had no causable factor but a systemic condition, which was induced by bisphosphonates therapy.

In a retrospective study by Hsiao et al,[40] 34 teeth from patients on bisphosphonate therapy, and 38 control teeth were compared for the outcome of root canal therapy. The healing rate was 73.5% in the treated patients and 81.6% in the controls with no statistically significant difference. On the other hand, the retrospective study of Dereci et al[41] on 24 patients was different from previous studies, in that it evaluated the success of endodontic therapy based on the duration of IV zoledronate medication. The conclusion was that more non-healed and incompletely healed teeth were found in patients receiving the zoledronate therapy for longer than 1 year. A systematic review[42] of 145 articles comparing the association between systemic disease and endodontic outcome has been conducted, but regarding bisphosphonates treatment, only one paper by Hsiao et al[40] was included. It was concluded in this review that the quality of evidence was moderate, and more research was needed.

Various papers have proposed endodontic treatment recommendations for BRONJ treatment. In a paper by Katz,[36] it was recommended that nonsurgical endodontic treatment should be considered as an alternative treatment instead of extraction, and minimization of trauma to the adjacent tissue (apical and marginal gingival area) must be considered for patients seen after bisphosphonate treatment.

One of the theories why root canal therapy is safe for BRONJ is that endodontic treatment does not cause soft tissue toxicity, and *Actinomyces*, one of the possible factors for BRONJ, is not in the intra-canal flora.[43] In the Moinzadeh et al[44] review, several recommendations were proposed to prevent BRONJ: 1-minute mouthrinse with chlorhexidine prior to the start of the treatment, avoid using the anesthetic agents with vasoconstrictors, work under aseptic conditions, avoid any damage to the gingival tissue, particularly with rubber dam clamp, and to avoid patency and overfilling.

In conclusion, bisphosphonates seem to have significant effects in endodontics by being one of the possible causes of external cervical resorption, also mimicking peri-radicular lesions. Endodontic therapy can be used as an alternative to dental extraction of potential BRONJ patients. However careful instrumentation and avoidance of soft tissue injury must be directed.

Periodontics

The development of periodontitis involves complex interaction between biofilm and host response. Periodontitis exists in 71% to 84% of ONJ cases.[45] The role of bisphosphonates in the field of periodontology seems to have two sides: as a risk factor for BRONJ, and, on the other hand, a helper in prevention of progression of periodontitis as a host modulator.

In the Thumbigere-Math et al[46] case control study, the goal was to determine if occurrence of BRONJ can be caused by periodontal disease as a risk factor. Twenty-five patients with BRONJ were compared with 48 controls. The authors stated that fewer teeth, greater clinical attachment loss with less alveolar bone support are associated with risk for BRONJ. No significant differences in gingival index, plaque index, bleeding on probing, or pocket depth were found but the use of antibiotics and chlorhexidine rinses might have improved the above factors in BRONJ patients. In one cross-sectional study,[45] the history of ONJ was compared with controls to determine if periodontitis is a risk factor. A significant association between periodontitis and ONJ was found in at least one site with a probing depth of 4 mm (P= 0.003). *P. gingivalis* and IL-1 beta levels were significantly related as well. The author suggested that periodontitis and associated bacteria can be possible factors for ONJ pathogenesis. In the Krimmel et al[47] study, relevance of dental and oral health to BRONJ was evaluated. Fifty patients were analyzed, and without periodontal treatment, the occurrence of BRONJ was 15 months earlier compared to patients who had treatment. The periodontal health did not affect the healing outcome of treated BRONJ (P> 0.999).

One case report[48] showed how fatal the outcome of BRONJ can be when implant therapy is combined with periodontitis in a patient who had been taking risedronate orally for 15 years. In this 82 year-old female patient, the teeth in the entire lower dentition were lost, along with pathological fractures on the body and condyle of the mandible. From the radiograph, it was assumed that the implant was placed when periodontal disease was not controlled, however the author concluded the role of active periodontitis in the role of MRONJ is not certain.

Probably the most unique role of bisphosphonate in the field of periodontology is its potential as a therapeutic agent. In many studies, bisphosphonates were tested for treatment of periodontitis. The current concept of periodontitis is now changing, with more emphasis on inflammation as a central role, rather than specific microbiota.[49] Host modulation therapy is a concept to change host responses to pathogens. Along with SDD (sub-antimicrobial doxycycline) and NSAIDS, bisphosphonates are also used experimentally on humans for treatment of periodontitis.

Twenty-two postmenopausal women with moderate to severe chronic periodontitis were studied for a possible host modulating effect of bisphosphonate.[50] In this 12 months study, the regimen was risedronate 5 mg, calcium citrate 250 mg, and Vitamin D 400 IU once daily. The results were an increase in bone density, and no progression of the disease without further bone loss in the experimental group. Scaling and root planing resulted in a significant gain in clinical attachment levels and reduction in pocket depth. In a 12-month randomized controlled study[51] involving 70 patients, bisphosphonate therapy significantly improved clinical attachment level (CAL), probing depth (PD), and bleeding on probing (BOP) after non-surgical periodontal therapy. The dosing regimen was alendronate 10 mg/day or risedronate 5 mg/day plus calcium citrate at 1,000 mg/day and Vitamin D3 at 400 IU per day. In 2007, 335 patients with periodontal disease were included in a ran-domized clinical trial[52] that involved taking alendronate 70 mg once weekly for 2 years. Combined with prophylaxis, the bisphosphonate did not have an effect on bone loss but the low bone mineral density group was significantly reduced. No BRONJ was detected. Sharma et al[53] tested the clinical effectiveness of 1% alendronate gel in adjunct to mechanical treatment for aggressive periodontitis therapy. The study was a randomized controlled clinical trial and showed the significant mean pocket reduction and clinical attachment gain was greater in the group with alendronate gel. A systematic review on the efficacy of bisphosphonates as a supplement to nonsurgical periodontal therapy was done by Akram et al[54] in 2017. Eight studies were included for qualitative synthesis, and the risk of bias was high in seven out of eight papers. The meta-analysis showed bisphosphonates + SRP was favored. The paper concluded that adjunctive bisphosphonate therapy appears to be helpful in treatment of periodontitis in a short term, but the follow-up period was short.

Despite many ongoing experiments with a hope that a bisphosphonate can be a helpful remedy for a cure of periodontitis, there is no clear consensus yet. In the review paper of Chambrone et al,[55] it was recommended that patients with severe periodontitis who take bisphosphonates must be advised of the risk of developing BRONJ following invasive periodontal procedures. In the position paper in the US,[7] local risk factors for BRONJ included periodontal surgery involving osseous surgery. However, the authors could not find a single case report of BRONJ caused by periodontal surgery alone indexed in PubMED. In the position paper of the American Association of Oral and Maxillofacial Surgeons,[7] poor oral hygiene was presented as a risk factor for BRONJ.

In conclusion, trauma to the bone itself is a necessary procedure for periodontal surgery, especially when it involves extensive osseous recontouring or curettage of granulation tissue. However, the evidence that this can initiate BRONJ is not clear. Nevertheless, the basics of periodontal therapy, which is maintaining good oral hygiene, should be emphasized. Despite the clinical evidence that bisphosphonates can be helpful as a host modulator therapy by stopping alveolar bone loss, one must be careful about interpreting the results because various in vitro and animal studies of periodontal disease have shown signs of BRONJ in histologic sections.[56-58]

Prosthodontics

Prosthodontic treatments are common in dentistry. Reports of BRONJ in the prosthodontic field are described.

One clinical survey[59] from 128 patients showed that dental prostheses, such as removable dentures or fixed partial dentures, are a possible risk factor for MRONJ in patients treated with bisphosphonates or denosumab. Five patients developed BRONJ under a pontic of fixed partial denture, including a case of a 67 year-old Japanese female who was treated with zoledronic acid hydrate for breast cancer. In the Di Fede et al[60] review article, poorly fitting removable dentures were one of the oral risk factors, along with dental/periodontal infection and peri-implantitis. Also, it was recommended to conduct a 4-month check-up period and to advise patients not to wear any denture for 8-12 hours per day. For the fixed prosthesis, paying attention to not breaching biologic width was recommended as well as not to damage the junctional epithelium, preferably at the supragingival margin. A single case report of an 84 year-old woman addressed left upper jaw pain. Her medical history reported 9 months history of prednisolone and risedronate to prevent osteoporosis caused by steroids. The clinical presentation was that characteristic MRONJ and chronic irritation from the denture flange could have been the cause. The treatment consisted of denture adjustment, antibiotics, debridement. Eventually the patient healed, but this case warns clinicians that even a mucosal trauma, from a denture, can trigger BRONJ.[61] The Pichardo & van Meresteyn[62] study in 2013 explored if BRONJ can be spontaneous. From 44 cases, 97.8% were found to be of a dental origin with triggering factors. The cases that were related to prosthodontics were pre-prosthetic surgery, pressure sore, mylohyoid ridge, and knife-edge ridge, which shows the significance of mucosal trauma. In the Ficarra & Beninati[63] review paper, management guidelines for patients treated with bisphosphonates were explained. One of the recommendations was the use of soft liners in dentures.

In one case report,[64] a 77 year-old woman developed BRONJ on the lower right mandible after IV pamidronate treatment. After resection of necrotic bone, the woman lost significant volume of the alveolar ridge but was successfully restored with telescopic primer crowns, removable dental prosthesis with resilient liner combined with an acrylic base. This case indicates that even after losing a large amount of supporting bone, prosthodontic treatment is possible, without the need of dental implants, if there is an adequate number of teeth left for partial dentures.

Generally, the placement of implants in the same area where BRONJ occurred previously is not recommended because of the high risk of failure.[65] However, there is no scientific evidence behind this theory. Nevertheless, considering patients who already went through multiple surgeries, a denture treatment option could be a realistic treatment modality. The role of prosthodontic knowledge on the severely resorbed ridge could be beneficial.

In conclusion, BRONJ can occur even after trauma from the denture, and also from a pontic. However, there is a lack of evidence from systematic reviews or cohort studies. Trauma to the mucosal tissue seems to be the initial triggering factor, and to prevent this, supragingival prosthesis and well-fitting dentures are important. Periodic follow-up is recommended for

the patients with a high risk of BRONJ. Even after the treatment of BRONJ, the patient is most likely to have severely atrophic ridge after resection surgery, and proper prosthodontic treatment will be the only treatment of choice for rehabilitation.

Oral and maxillofacial surgery

First reports of BRONJ appear to have been from oral and maxillofacial surgeons.[7] The common procedures performed in this specialty are tori removal and extraction. Regarding the torus, a number of case reports have been reported in the literature, suggesting that trauma to the soft tissue can be an etiologic factor for BRONJ.

The first case report of BRONJ on palatal tori was published by Goldman et al[66] in 2006. A 58 year-old woman with metastatic breast cancer developed exposed bone on the palatal torus after receiving intravenous zoledronic acid for 16 months. The histological analysis showed filamentous bacteria, most likely of the *Actinomyces* species. The case report of McLeod et al[67] was of a 77 year-old female patient who had been taking alendronate sodium for 10 years. An asymptomatic bone exposure was seen on her palatal torus, and the entire torus was surgically removed. A stent was used to keep the pressure against the wound, which did heal. In the pathology report, *Actinomyces* species were noted to be present. Another case[68] reported that a woman who was treated with oral bisphosphonate for 9 years developed exposed bone on her palatal torus, 6 months after burning her palate with food. A CT scan showed areas of necrotic bone inside the torus palatinus. The CTX level was in the moderate risk zone, and the lesion was spontaneously healed after discontinuation of the bisphosphonate treatment. Godinho et al[69] also reported osteonecrosis of a palatal torus related to bisphosphonate. The patient was a 67 year-old female, with 6 years of treatment with alendronate, 70 mg/week for osteoporosis. Even though there was no bone exposure, the depression of mucosal tissue was evident along with necrotic bone in the histopathological examination. The CT showed destruction of cortical bone on the torus area. In a case report by Kaneko et al,[70] a 72 year-old woman with osteoporosis developed BRONJ after receiving oral 35 mg alendronate sodium hydrate for 6 years. The lesion disappeared after discontinuing medication and systemic antibiotics combined with antibacterial rinse after 10 weeks.

Overall, the above-mentioned cases have something in common: elderly age, long history of bisphosphonate therapy, and trauma of the soft tissue exposing the bone, leading to BRONJ. Treatment seems to have a good prognosis, not spreading to the adjacent bone. The association between BRONJ and *Actinomyces* species is still unclear.

Currently there is only one case report[71] of previous titanium miniplate causing BRONJ. A 70 year-old female showed cutaneous fistula of the left chin. The dentist placed a titanium miniplate after removal of the cyst at the lower border of the mandible to prevent pathologic fracture in 1990. However, in 2012, she noticed mandibular swelling which showed signs of osteonecrosis. She was taking risedronate sodium orally since 2009. The miniplate and sequestra was removed after drug suspension and antibiotic therapy, and healing was favorable. This case report was not clear whether the lesion was inside the oral cavity as well. The significance of this report shows, even after the treatment, a titanium miniplate can be another risk factor for BRONJ.

Extraction in dental practice is a very common procedure. In the position paper of American Oral and Maxillofacial Surgery,[7] extraction is listed as the number one risk factor for BRONJ. In another clinical report,[72] a 75 year-old woman was noted to have developed BRONJ 4 months after tooth extraction. She had been taking 10 mg of oral sodium alendronate for 5 years, but it was discontinued 3 months before the extraction. This shows that even after suspension of their use, bisphosphonates can still cause BRONJ. Another prospective study by Scoletta et al[73] included 64 patients. Five patients developed BRONJ with the mandible appearing to be at a greater risk. An interesting aspect of this study was that the extraction procedure was preceded by antibiotic therapy with amoxicillin/clavulanate potassium or erythromycin. For the flap opening, a partial thickness flap was used, and for osteoplasty, a piezo surgical device was used, followed by autologous plasma rich in growth factors. This study shows that even with the meticulous procedure to minimize exposure and trauma to the bone, BRONJ can still occur. In a retrospective study by Otto et al,[74] 72 subjects with 216 extractions were reviewed for BRONJ. Three patients progressed to BRONJ, and potential risk factors were duration, route of administration, oral hygiene and steroid intake. In a cohort study by Yamazaki et al,[75] 126 patients had bisphosphonate administration, and five patients developed ONJ, which was associated with tooth extraction. The incidence of BRONJ was not correlated with DMF index, while significantly associated with the type of BP (P= 0.007), and bone loss score. The study also proposed periodontal inflammation with severe alveolar bone loss might be a possible factor.

In conclusion, extensive clinical data in oral and maxillofacial surgery indicate the prevalence of BRONJ, which mainly involves tori and extraction. Previous titanium plate can be another source of BRONJ, but currently there is only one case report.[71] Interestingly, the authors could not find a single case report related to other surgical procedures such as orthognathic surgery, tumor or tori removal, or open reduction/internal fixation of the jaw fracture causing BRONJ. Even after the extraction, the incidence shows very few from the majority of the group, but it does seem that the highest risk of BRONJ is still associated with the dental specialty that causes the most trauma to the jawbone itself.

Implants

Dealing with implant patients who are receiving a bisphosphonate is more than just drilling and placing the titanium inside the patient's jaw. The unique property of implant placement could be the drilling procedure itself, which also means another trauma to the existing bone, both with heat and mechanical force. Also, even after the implant procedure, its upper component (abutment and crown) is still exposed to the microbes of the oral environment, unlike the fixation with screws in fracture/orthognathic surgery. Since the association between BRONJ and implants seems distinct from other procedures, the authors provided this separate section.

The Al-Sabbagh et al[76] study gathered data from patient interviews of 203 patients who received 515 implants. Oral

bisphosphonate was used on one male and 19 females. None of the patients reported BRONJ among them. In the prospective observational study by Tallarico et al,[77] 32 patients with 98 implants were observed. Alendronate treatment was stopped 6 months prior to flapless or mini-flap surgical approach with antibiotics. The results of these approaches showed only one implant failure.

Despite the above findings, there are many reports on BRONJ occurring after implant placement. The Kim et al[65] case report described a BRONJ occurrence in the same region as where the implant treatment was conducted. A 73 year-old patient was diagnosed with BRONJ and sequestrectomy including the implant was performed twice. The medication (alendronate) was stopped, and after 18 months three implants were placed at the same site, this time to the basal bone. This study indicates that even though the previous bone was under the influence of BRONJ, with stopping the medication, subsequent implant placement is still possible. One case report[78] was done on a 62 year-old woman who received maxillary implants 2 years prior to the therapy with zoledronic acid. The patient had a previous history of breast cancer, which showed bone metastasis, and led to the prescription of bisphosphonate. BRONJ was developed after 1 year of zoledronic acid therapy and was treated with maxillectomy. This case is unique as it shows even implants prior to the bisphosphonate therapy can still be affected. Another case report was published by Favia et al,[79] with a 66 year-old female patient who received 4 mg IV zoledronate for breast cancer. MRONJ was developed around the implant area, which was placed more than 6 months before bisphosphonate therapy was started, and uniquely, immunohistochemical examinations showed that breast cancer cell deposits were within the necrotic bone. The author proposed that a chronic inflammatory state can cause stimulation of tumor cells to be entrapped around the jawbone. The lesion healed with partial mandibular resection. A 67 year-old Japanese woman with 7 years of bisphosphonate treatment had a dental implant removed and developed BRONJ after 3 months.[80] The treatment of choice was sequestrectomy under general anesthesia. The reason for dental implant removal in the first place was not BRONJ, but because of shoulder and right upper arm pain. This study shows that implant removal can also cause the trauma triggering BRONJ. A case report of a 79 year-old woman was published in 2015.[81] The patient was taking 5 mg of zoledronic acid intravenously once a year to treat osteoporosis. After the implant surgery, no osseointegration was attained and a decision to do peripheral ostectomy and removal of necrotic bone was made. This report is interesting as the interval between the medication taking period was long, yet still enough to cause BRONJ. Storelli et al[82] reported on a 77 year-old patient with eight implants placed in 2009. She had taken oral alendronic acid since 2006. The patient reported acute pain, tissues with purulent secretions, and sinusitis. Eventually she had all necrotic bones and implant removed. A 75 year-old woman's case was reported by Doh et al.[83] She had been taking alendronate for 2.5 years. After implant placement, pain and pus discharge was evident for 10 months. Bisphosphonate was suspended, and replaced with teriparatide. Even though the implants were lost, healing was favorable with some bone formation. Another case report[84] demonstrated the effect of teriparatide by removing the implant, which was involved in severe BRONJ. A 66 year-old woman had a 5-month treatment of teriparatide after the diagnosis of BRONJ, and sequestrectomy was performed. CT showed improved bone defect in the mandible. The Lopez-Cedrun et al[85] case series was comprised of nine patients who developed BRONJ after implant placement. Patients were taking alendronate (n=6), ibandronate (n=2) and risedronate (n=1) orally. The average period of development of BRONJ after implant placement was 60 months. Clinical features and the results of treatment were similar to BRONJ without implant involvement. This case series warns that the development of BRONJ is possible even after up to 96 months following placement of implants. The Pogrel et al[86] case series also reported 11 patients who had previously placed implants without any complications, then developed BRONJ after therapy with bisphosphonates or denosumab. The characteristic of this implant failure was that it happened to the previously successful osseointegration between implant and bone. The authors of the paper proposed masticatory force, that is high enough to cause localized bone necrosis, could be the contributing reason. A 15 case series was reported[87] on the patients with bisphosphonate treatment, along with the block bone graft and simultaneous implant placement. Three cases showed implant failure, and two cases showed bone exposure. The medications were PO Ibandronat (Boniva), IV Clodronate (Bonefos), and PO Alendronate. This case series is unique because it showed BRONJ can occur regardless of bone graft. Matsuo et al[88] did a retrospective review on six patients who developed one BRONJ at the implant site. No significant differences were found in the age, BP treatment duration, residual tooth count, oral hygiene level and implant placement. The case on BRONJ development was a 61-year-old woman who received the placed implant 2 years before the administration of zolendronic acid was initiated. After stopping bisphosphonate 1 year later, complete marginal resection of the affected site was performed. After the surgery, the wound was completely closed but she significantly lost the structure of the mandible.

When the study is more advanced towards a case-control or retrospective study that involves more patients, association between implant and BRONJ seems to be obvious. Holzinger et al[89] divided 13 patients with 47 implants into three groups: implant placement before BP treatment, implant placement during BP treatment, implant placement after BP treatment. From the Kaplan-Meier curve and Wilcoxon's rank sum test, the results showed during and after BP treatment there was more rapid development of BRONJ. The authors concluded that BPs could have potential effects of peri-implantitis and implant loss. Lazarovici et al[90] reviewed BRONJ associated with implant placement in 27 patients. Among them, 16 patients had the implants removed. The time of the development of BRONJ was different among the different bisphosphonate treatments, 68 months for alendronate, 16.4 months for zoledronic acid, and 50.2 months for pamidronate, suggesting the need for long term follow up on implant patients with various different types of bisphosphonate therapy. In one retrospective study,[91] 16 implant failures associated with BRONJ were reported in 589 patients with oral bisphosphonate therapy. All were women, and alendronate was prescribed

Table 4. Treatment strategy for BRONJ.

Treatment varies between stages	
Discontinuation of the drug is the 1st choice	
May consider systemic antibiotic therapy	
Non-surgical therapy: Chlorhexidine gluconate/hydrogen peroxide mouth rinses, removal of necrotic bone	
Surgical therapy: Surgical debridement, tension free closure, partial resection	
Reported treatment methods	
Switching to etidronate/clodronate	Endo et al.(2017)[116]
Teriparatide	Mizohata et al.(2018)[117]
Sitafloxacin (STFX)	Ikeda et al.(2015)[118]
Simplified extraction protocol	Malden et al.(2009)[101]
Preventive reconstructive plate	Pedrazzoli et al.(2016)[119]
Resection/microvascular reconstruction	Neto et al.(2016)[120]
Ultrasonic bone surgery (piezosurgery)	Blus et al.(2013)[121]
Bone marrow stromal cells (BMSCs)	He et al.(2017)[122]
Platelet rich fibrin (PRF)	Kilic et al.(2018),[123] Soyan et al.(2014)[124]
Plasma rich in growth factors (PRGF-Endoret)	Anitua et al.(2013)[125]
Nd:YAG laser	Vescovi et al.(2012)[126]
Doxycycline fluorescence-guided Er:YAG laser ablation with Nd:YAG /diode laser biostimulation	Porcaro et al.(2015)[127]
Visually enhanced lesion scope	Assaf et al.(2014)[128]
Ozone therapy	Agrillo et al.(2012),[129] Kaptan et al.(2013)[130]

daily. Eleven patients were never smokers, three former, and two current. There were more late (1> year after placement) failures than early failure (1≤ year after placement), with higher percentage of failure in the mandible. Another retrospective study[92] investigated the relationship between MRONJ and peri-implantitis. Among 34 patients, peri-implant MRONJ occurred in 15 patients (44%). Signs of peri-implantitis, which was indicated if peri-implant bone loss was more than 2.5 mm or 25% of implant length (39%) were suggested to be related with peri-implant MRONJ. This study is unique as the percentage of MRONJ is as high as 44% among reviewed patients. The retrospective study of Zahid et al[93] in 2011 included 26 BP patients who received 51 dental implants. Only three implants failed, and it was concluded that a significant association was found only between implant tread exposure and bisphosphonates, and no relationship with implant failure. In the Famili & Zavoral[94] case-control study on 30 patients with osteoporosis/osteopenia, three patients were treated with Fosamax, Fortical and Forteo prior to implant surgery. Contrary to the previous studies, there was no effect of these treatments on the success of the implants. The Giovannacci et al[95] study was done on 15 patients with peri-implant bone necrosis. Patients were divided into two groups, one group with necrosis immediately after the implant placement (2-10 months), and the other group with MRONJ 1-15 years after implant treatment. Six patients were in the first group while the other nine patients were in second group.

Many systematic reviews were done by researchers with regards to the implant and BRONJ. A systematic review by Guazzo et al[96] was conducted on 10 papers. Seven were retrospective studies, two were cross sectional studies, and one was a prospective study. The risk of bias and heterogeneity was high, however, the conclusion was that bisphosphonates should be considered as risk factors in implant surgery. Another systematic review was done by de-Freitas et al[97] related to bisphosphonate treatment and dental implants. Fifteen studies were included, and the studies with short follow up suggested that bisphosphonate therapy does not affect the success of the implant. However, BRONJ patients with implant placement had systematic problems such as malignant disease and osteoarthritis, suggesting evaluation of general health status is important. Gelazius et al[98] also did a systematic review on bisphosphonate treated patients who underwent implant therapy. Patients with intraoral bisphosphonate therapy had a higher chance of success in implant treatment (five implants failed out of 423). In contrast, the intravenous group had six implants failed from 68. A systematic review by Schmitt et al[99] evaluated 18 studies in patients with BP or antiresorptive therapy. The implant survival rate was 92.86% to 100% in patients, and osteonecrosis occurred more frequently in patients with malignant disease. An overview[100] of the systematic review evidence was conducted on seven papers, published between 2009 and 2017. The evidence suggested that bisphosphonate use does not increase the risk of BRONJ in implant treated patients. Also, there was no valid method to predict the risk of BRONJ before surgery. However, none of these reviews fulfilled the quality assessment (AMSTAR).

In conclusion, contrary to many case reports and case-control studies, systematic reviews do not support an association between BRONJ and implant placement. Case reports have shown that bisphosphonates can affect the previously placed implant, and the form of bone loss can occur around bone-implant interface with thread exposure, or the bone firmly attached to the implant. BRONJ can occur even after implant extraction. Implants can still be placed at the same site where BRONJ has occurred, but subsequent case reports of the reconstruction of the site with bone graft to restore the volume is lacking. Oral and intravenous forms of bisphosphonates both seem to be related to BRONJ associated with implant placement.

Treatment strategy for BRONJ

Treatment strategy can be divided into preventive, non-surgical, and surgical therapy (Table 4).

Malden et al[101] suggested risk factor reduction by: cessation of smoking, improvement of oral hygiene and periodontal health, discontinuation of bisphosphonate/corticosteroid therapy. Kalra et al[102] suggested the importance of prevention in the review article, by removing hopeless teeth, subgingival scaling, and adjusting poorly fitting dentures before bisphosphonate therapy. Karna et al[103] did a systematic review and meta-analysis on the effectiveness of dental interventions in preventing or reducing MRONJ in cancer patients. The preventive measures declined MRONJ incidence by 77.3% in six studies. However,

because of risk of bias, the papers' quality of evidence was low. Scoletta et al[104] did a prospective study on 37 patients. If the clinical diagnosis of BRONJ was made, the patient underwent a treatment with daily therapy of 0.12% chlorhexidine mouth rinse, and if radiological diagnosis was made, an antibiotic protocol was initiated. In the case of unresponsive patients, surgery was proposed and evaluation of symptoms and signs were done every 2 months. After 2 years, 20 patients (54.1%) showed wound healing of soft tissue coverage over bone. Yoshiga et al[105] found prognosis factors for the conservative treatment of BRONJ. The remission rate was only 57.5%, and anticancer drugs, periodontal disease, the level of bone exposure and dosage of IV bisphosphonates represent specific risk factors for BRONJ. The paper also suggested that urinary cross-linked N-terminal telopeptide of type 1 collagen (NTX) levels can be a prognostic factor.

One treatment strategy is use of systemic antibiotics. It does have its own evidence, as BRONJ deals with bone infection, along with the microorganisms. Fifty-nine patients with BRONJ were compared with respect to prognosis of oral and intravenous bisphosphonates.[106] Conservative treatments were done such as oral and IV antibiotics (PCN, cephems, macrolides, and clindamycin). Also for the disease with further progression, sequestrectomy was performed, and in the presence of pathological fracture, segmental mandibular resection was done. However, 50% of the patients with IV bisphosphonates did not show any improvement. In the Moozzati et al[107] study, a total of 1,480 extractions were reviewed on patients with bisphosphonates: one group used the flap and primary closure method after extraction, while the other group used extraction without primary closure, with socket filled with absorbable gelatin sponge. All patients were treated with antibiotics, amoxicillin and clavulanic acid, starting from the evening before the surgery, one tablet every 12 hours for a total of 6 days. Neither technique showed any sign of BRONJ. In a preventive protocol proposed by Lodi et al,[108] 38 extractions healed without any signs of BRONJ. The protocol was 0.2% chlorhexidine once a day rinse with oral hygiene treatment 2-3 weeks before extraction. Three days before the procedure, the patient took 1 g of amoxicillin every 8 hours for 17 days. During the surgery, full thickness flap was raised and primary closure was done. 1% chlorhexidine gel was applied on the surgical wound three times a day until the second visit. Scoletta et al[109] proposed a refined protocol for the treatment of patients with potential bisphosphonate therapy. Two weeks before the tooth extraction, the patient underwent oral prophylaxis. Amoxicillin/clavulanate potassium was prescribed every 8 hours for 6 days, including the evening before the surgery. After the extraction, platelet rich growth factor (PRGF) was filled into the socket and covered with autologous fibrin, secured with a suture. A total of 202 tooth extractions were performed without BRONJ development.

The most important prevention strategy could be the discontinuation of the medication. The position paper of The American Association of Oral and Maxillofacial Surgeons[7] has recommended drug 'holiday' for 3 months before and after dental surgical interventions. However, it should be dictated by the individual condition of the patient.[110] The above mentioned 'holiday' is supported by the observational study by Hasegawa et al,[111] that from 434 extractions, patients were divided into two groups; one with a 3-month holiday, the other one with continuous treatment with bisphosphonates. No BRONJ were found in the drug holiday group.

For the management of established ONJ, the treatment varies between stages:[112]

Stage I: Topical chlorhexidine gluconate or hydrogen peroxide mouthrinses.

Stage II: Topical antiseptic mouthrinses + antibiotic therapy.

Stage III: Topical antiseptic mouthrinses + antibiotic therapy, surgical debridement where appropriate.

Surgical/Nonsurgical therapy

In the Lu et al[113] study, a retrospective review of the 27 cases of surgically/nonsurgically treated jaws of BRONJ was evaluated. In this paper, treatment strategies were: nonsurgical treatment using antimicrobial rinses, elimination of necrotic bone followed by placement of tetracycline impregnated Gelfoam, guided bone regeneration with allograft bone material plus tetracycline, and radical resection of all necrotic bone and immediate reconstruction. There were only two failures with intravenous bisphosphonate users. The systematic review of Ramaglia et al[110] included 13 studies that were not case controlled or randomized. While a conservative treatment method showed favorable results in early stages, heterogeneity of responses existed in advanced stages. Williamson et al[114] did a prospective study on 40 patients, for whom BRONJ did not respond well to conservative therapy. The surgical method included antibiotic therapy, surgical debridement and tension-free closure. During the follow up, there were no complications. Comas-Calonge et al[115] did a systematic review comparing surgical treatment vs conservative treatment. The study concluded that in early stages of BRONJ (stages 0,1), conservative treatment combined with antibiotic approach seemed to be the best approach. However, in the higher degree BRONJ, surgical debridement, sequestrectomy, and bone removal provided successful treatment, with a 58-100% success rate.

Current treatment modalities for BRONJ are diverse, with no one superior over another. More randomized controlled studies are needed for a definitive treatment plan.

Switching medication to etidronate and clodronate

In 2017, Endo et al[116] proposed using non-nitrogen containing bisphosphonates, which are etidronate and clodronate, that can be a potential replacement drug for bisphosphonates. Non-nitrogen containing bisphosphonates have less strong anti bone resorptive effects than nitrogen containing bisphosphonates. Etidronate and clodronate can competitively inhibit the phosphate transportation and reduce or prevent nitrogen containing bisphosphonate induced inflammation and necrosis. Another possible benefit of these drugs is an analgesic effect. However, more human clinical trials are needed.

Teriparatide

Teriparatide is an osteoporosis drug that can be injected subcutaneously in a daily or weekly preparation. It can induce bone formation by differentiation of osteoblastic cells. A case report of a 78 year-old woman presenting with palatal torus MRONJ reported a cure with teriparatide treatment.[117]

Sitafloxacin (STFX)

Ikeda et al[118] treated BRONJ patients with STFX. Among 20 cases of BRONJ, 19 cases healed by 2-10 weeks of STFX administration. STFX can kill quinolone-resistant bacteria. The bacteria showed susceptibility to STFX while showing some degree of resistance to commonly used antibiotics.

Simplified extraction protocol

Malden et al[101] reported an extraction protocol to prevent BRONJ. The extraction should be performed with the least traumatic approach, preferably one tooth at a time, and selective grinding of sharp bony edges should be done without lifting the periosteum. Additionally, chlorhexidine mouthwash can be used postoperatively. Signs of BRONJ must be monitored, by patient's pain or fetor oris, and bad taste.

Prevention of mandibular fractures by reconstructive plate

Pedrazzoli et al[119] treated 10 of his patients with a technique which can prevent mandibular fractures of stage 3 patients. This technique applies the reconstructive plate on the outer border of the mandible, just above the platysma with extraoral approach, with curettage of necrotic bone at the intraoral surgical site. The benefit of this technique is not losing a blood supply and preventing a contact between necrotic bone and the plate itself.

Resection and microvascular reconstruction

Neto et al[120] did a literature review of microvascular reconstruction on BRONJ patients and found 10 articles and 40 patients which met the criteria. From the reports in the 10 articles, BRONJ recurred in two cases (5%), and non-union was 5% (2/40). He concluded that the complication rate of microvascular reconstruction was acceptable. This is an important finding since most of the later stage BRONJ will require very extensive reconstruction along with the flap.

Ultrasonic bone surgery (piezosurgery)

Blus et al[121] treated nine cases of BRONJ with piezosurgery and achieved a favorable outcome of soft tissue healing after 1 month. The hypothesis was that application of ultrasonic vibration and powerful cavitation might have washed out the microbial mass around the involved bone. Also, it is a generally accepted concept that the ultrasonic instrument is less traumatic than conventional burs.

Bone marrow stromal cells (BMSCs)

He et al[122] found that BMSCs play a vital role in bone regeneration. That study included the bones acquired from three BRONJ patients, and BMSCs were isolated. BMSCs had influence on BRONJ by decreased proliferative ability, self-renewal capacity, multi-differentiation capacity, and osteoclast-inducing ability. This suggests that BMSCs can be used for the future treatment for BRONJ.

Platelet rich fibrin (PRF)

Kilic et al[123] reviewed various methods to treat BRONJ, and among them was platelet rich fibrin. The case report was tension-free suturing of platelet rich fibrin to the surrounding soft tissue to cover the bone.

Soyan et al[124] also reported total closure of BRONJ with double layer PRF membrane, which acted as a barrier and stimulated healing. The surgery was done on a 75 year-old man with 5 × 10 mm bone exposure.

Plasma rich in growth factors (PRGF-Endoret)

Anitua et al[125] reported a case of a 50 year-old patient with BRONJ, with severe pain and hemimandibular paresthesia. Treatment consisted of resection of necrotic bone and application of PRGF. One year later, the paresthesia disappeared and partial bone regeneration was noted.

Nd:YAG low level laser therapy

Vescovi et al[126] proposed the treatment method in 2013 of using Nd:YAG laser after 587 extractions. The treatment protocol was low level laser therapy with a Nd:YAG laser, five applications of 1 minute each. Five bone exposures were additionally treated with a Er:YAG laser. The authors concluded that this laser therapy was a reliable method.

Doxycycline fluorescence-guided Er:YAG laser ablation with Nd:YAG/diode laser biostimulation

A case report was done by Porcaro et al[127] of one patient, using three cycles of ablation and 23 cycles of biostimulation after 1% chlorhexidine gel, rifamycin, and doxycycline for 10 preoperative and 7 postoperative days. The lesion improved from stage III to stage I.

Visually enhanced lesion scope

This technique uses doxycycline as a fluorescent marker, and with a loss of fluorescence, interpreted as osteonecrotic bone.[128] Using this method, the treatment was carried out on BRONJ patients and 19 out of 20 healed without recurrence.

Ozone therapy

Agrillo et al[129] treated 131 cases with ozone therapy in BRONJ patients over 5 years. The benefit of ozone is that it forms bone sequestrum, and improves vascularization of underlying bone. The success rate was 90%. Kaptan et al[130] also reported success of two cases of BRONJ after application of topical gaseous ozone.

In conclusion, conservative therapy seems to work in lower stages of BRONJ, while higher stages require invasive surgical therapy. Among various treatment modalities based on case series, no one treatment seems to be superior over another, with each of them reporting success. The clinician should follow the treatment plan according to the stage, and discontinuation of the medication must be considered.

Conclusion

Bisphosphonate therapy seems to have a significant influence on patient treatment approaches in all dental disciplines. In orthodontics, it can affect the tooth movement as bisphosphonates have a strong association with cells responsible for bone metabolism. In endodontics, avoiding the soft tissue injury by the clasp seems appropriate, and such endodontic therapy can be a strong alternative to traumatic extractions. In periodontics, while various studies have used bisphosphonate as part of treatment for periodontitis, more studies are needed to clarify that clinically decreasing the bone resorption does support the success of the treatment. In addition, adequate oral hygiene is an important factor. In prosthodontics, avoiding

mucosal injury by any of the fixed or partial denture components must be a priority. In oral surgery, extraction seems to cause the most damage to the bone, with high association with BRONJ. Tori seem to be very easily traumatized, and care must be taken to avoid damage to the epithelial surface. Implant placement is the field where BRONJ seems to be most strongly associated, as the procedure itself is trauma to the bone by drilling, and making another communicatory channel with the microorganisms in the oral cavity. None of the current BRONJ treatments seem to have a higher rate of success over another. However, treating with the correct method at the appropriate stage appears to be necessary for success.

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Dr. Kim is a resident and Dr. Ciancio is a Distinguished Service Professor, Department of Periodontics and Endodontics and Dr. Dziak is Professor, Department of Oral Biology, School of Dental Medicine, University at Buffalo, Buffalo, NY, USA. Dr. Lee is Associate Professor, Department of Prosthodontics, School of Dentistry, Kyungpook National University, Daegu, South Korea.

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