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ORIGINAL PAPER

Bisphosphonates and Osteonecrosis of the Jaws: A Review of Clinical Features and the Drug Effect on Oral Soft Tissues

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Abstract The beneficial effects of the nitrogen-containing bisphosphonate drugs have been clearly defined, especially for the treatment for osteoporosis, metastatic or primary bone malignancies, and some rare bone diseases. The adverse effects of these drugs on oral hard and soft tissues are significant and recognized with increasing frequency. The clinical, radiographic, and histopathologic features of osteonecrosis of the jaws (ONJ) are well characterized; the effects of bisphosphonates on oral soft tissues are an emerging area of study. This review will provide an overview of ONJ from a clinical perspective and also discuss recent findings related to bisphosphonate-induced soft tissue pathology.

Keywords Bisphosphonate-induced osteonecrosis of the jaw · Oral soft tissue · Oral wound healing · Angiogenesis · Periodontal ligament fibroblast

Introduction

Bisphosphonates are a class of therapeutic agents that have been approved for use in the treatment of patients with some forms of cancer, osteoporosis, and several rare bone diseases [1]. The nitrogen-containing bisphosphonate drugs have been associated with osteonecrosis of the jaws (ONJ), the principle pathology associated with these medications [2]. Various professional organizations and societies have position papers, summary reports, and treatment recommendations regarding the complications associated with the nitrogen-containing bisphosphonates [3–8]. The most significant risk factors for developing ONJ appear to be related to potency of the bisphosphonate and cumulative dose [9]. Many patients with ONJ are cancer patients who typically receive multiple infusions of the more potent intravenously administered bisphosphonates such as pamidronate and zoledronate [6]. The rationale for the use of bisphosphonates in the cancer patient is to stabilize bones affected by metastatic or primary neoplastic disease involving bone and in treating hypercalcemia of malignancy [10]. Additionally, these drugs may have antiangiogenic effects that inhibit tumor growth and direct toxic effects on tumor cells [11–15]. More cases of ONJ associated with the oral bisphosphonates alendronate, risedronate, and ibandronate are being diagnosed and are likely related to cumulative dose effects [9, 16]. ONJ related to zoledronate, a yearly intravenous regimen to treat osteoporosis, has also been reported [17, 18]. The rationale for use of bisphosphonates in patients with osteoporosis is the interruption of osteoclast-mediated bone resorption [1]. Additionally, initial reports of osteonecrosis of the jaw have been reported in association with the non-bisphosphonate medication denosumab. Denosumab is a human monoclonal IgG2 antibody that binds to the receptor activator of nuclear factor- κB ligand (RANK-L), suppressing bone remodeling [19–21]. The clinical presentation, radiographic findings, and histopathology of ONJ in patients exposed to nitrogen-containing bisphosphonate drugs are presented, with an emphasis on practical considerations for the clinicians involved in the medical and dental care of these patients. Moreover, the effects of bisphosphonates on oral soft tissues have

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important implications regarding the initiation and progression of ONJ and are discussed as well.

Clinical Features

Bisphosphonate-associated ONJ is clinically characterized by exposed necrotic bone (Fig. 1). It is now recognized that patients can present with non-specific clinical findings and symptoms prior to developing exposed necrotic bone [6]. These include pain, tenderness, or swelling of the jaws that may simulate tooth-related causes of pain, or perhaps, neuralgias, defined, or atypical. The potential for ONJ needs to be considered in the differential diagnosis of the patient treated with either oral or intravenous bisphosphonates presenting with jaw pain. In most cases, elimination of a dental cause for the pain can be made based on results of clinical tests and failure to identify classic radiographic features of dental pathosis. However, eliminating or establishing a specific cause can sometimes be problematic, resulting in frustration on the part of the patient and clinician. Swelling of the soft tissues overlying or adjacent to the jaw broadens the clinical differential to include inflammatory or neoplastic processes. If indeed ONJ is present, the overlying mucosa will eventually ulcerate resulting in exposed bone. Attributing ONJ to bisphosphonates can prove difficult, as spontaneous sequestration, incidental trauma to alveolar mucosa, or surgical manipulation may result in sequestration of bone in patients who have not been exposed to these drugs. This fact has resulted in difficulty establishing cause and effect in a subset of patients that have had minimal cumulative bisphosphonate exposure or in those patients who develop ONJ after tissue manipulation or a surgical procedure in the area.

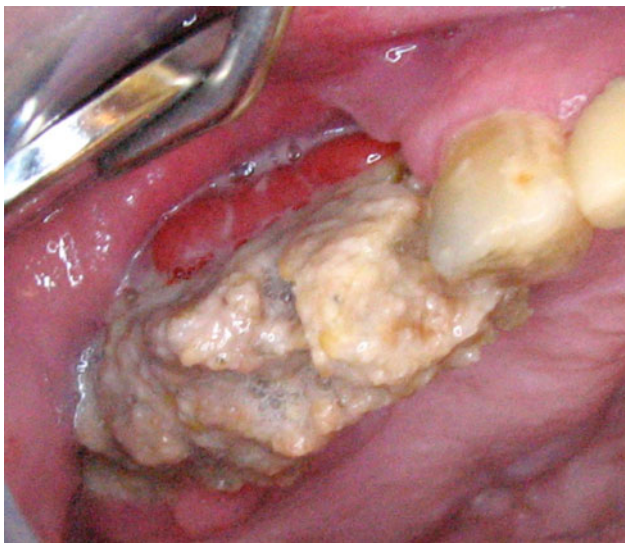

Fig. 1 Mucosal ulceration and necrotic bone of the right maxilla in a patient receiving monthly zolendronate therapy for lung carcinoma metastatic to bone

Some ONJ patients have exposed bone that is somewhat asymptomatic with no significant signs of inflammation or infection. This has been termed Stage 1 disease. The area of exposed bone may represent a small area measuring as little as a millimeter to a large area measuring several centimeters. The mandible is more commonly involved than the maxilla. Exposure sites may be unifocal or multifocal; synchronous or metachronous involvement of both maxilla and mandible can occur. Progression of Stage 1 ONJ or de novo presentation with symptoms of pain, erythema, and possible purulence in the area of exposed bone is classified as Stage 2 disease. Stage 3 disease is defined as exposed necrotic bone with pain, infection, and one of the following: involvement characterized by osteolysis, extending beyond the alveolar bone, the inferior border or ascending ramus of the mandible, involvement of the maxillary sinus or zygoma that may result in pathologic fracture, oral cutaneous, oral antral, or oral nasal fistula formation [6]. Clinically advanced stage disease is often associated with a fetid odor as the exposed necrotic bone allows for microbial adherence. Plaque and calculus consisting of mineralized microbial colonies form on this exposed bone, similar to microbial adherence to teeth. Deep fistulous tracts often develop with or without purulence [22]. When purulence is present, pain is typically noted. Maintaining good oral hygiene can be a challenge due to pain, and the exposed bone itself deters patients from manipulating the involved ONJ area and adjacent regions. Tooth mobility and even spontaneous exfoliation of teeth can occur and may represent the initial clinical manifestations of ONJ. Another manifestation of ONJ frequently encountered is the "dry socket" [22]. This represents failure of bone to form in an area of recent extraction as necessary granulation tissue and blood clot for new bone formation does not form on the now evident necrotic bone. Routine restorative, periodontal, endodontic, and surgical dentistry become a challenge in patients with defined ONJ and too in those individuals treated with bisphosphonates and the potential to develop ONJ. This problem is exacerbated by the fact that ONJ is not a reversible phenomenon and infrequently easily treatable. Often exposed bone sequestrates spontaneously or with a surgical assist. Healing of mucosa overlying the area of sequestration is common in oral bisphosphonate ONJ cases, especially those patients with a lower cumulative dose or those that have discontinued use. However, the greater the cumulative dose or exposure to the more potent bisphosphonates frequently results in persistent or progressive disease [23, 24]. Patients with periodontal disease and non-restorable teeth seem to be at particular risk of developing ONJ [5]. The potential for ONJ is also of

concern in cases where dental implants are placed in the jaws of patients exposed to the nitrogen-containing bisphosphonates. Again, risk here seems to be related to potency and cumulative exposure to this class of medications. Animal models are invaluable to further define drug mechanisms [25] and may form a basis to further evaluate the drug potency and cumulative dose issue [26]. Inappropriate bone fill of a prior extraction socket, as noted in a dental radiograph, should raise concerns about potential for ONJ should dental implant placement be contemplated. The utility of bone turnover markers in guiding oral surgical treatment decisions is controversial as mean and median measurements noted in large study groups may not extrapolate to an individual case [9, 27, 28]. Although not a definitive predictor of ONJ development, these markers may have a role in risk assessment before oral or other surgical procedures involving bone [29, 30].

Radiographic Features

Radiographic findings of jaw bones affected by bisphosphonate-related ONJ are variable, ranging from subtle to obvious changes [31, 32]. However, none of the findings are pathognomonic for ONJ and can simulate inflammatory periapical pathology, osteomyelitis, primary neoplasia, metastatic disease, or various metabolic bone diseases and dysplasias. The radiographic changes are more likely to be identified in individuals with exposure to high-potency bisphosphonates over a prolonged period or the lower-potency oral bisphosphonates with high cumulative dose. Most cases of ONJ are initially evaluated with plain radiographs using a periapical, occlusal, or panoramic view [31]. It has been described that bone sclerosis characterized by an increased radiodensity at the involved site may be observable. This finding is expected given the prime pharmacologic effect of the medication, the altered bone formation and resorption dynamic. Prominent lamina dura, the portion of alveolar bone peripheral to the periodontal ligament that surrounds the tooth root, is frequently identified and is an additional indication of overall bone sclerosis. Necrotic alveolar jaw bone can result in a periosteal reaction, and new bone formation that can best be recognized with an occlusal film, an image taken perpendicular to the occlusal plane of the dentition, or in some panoramic radiographic formats. Periosteal new bone formation is not a common finding in early stage ONJ. Failure of postsurgical remodeling such as absence of bone fill in the expected time frame and post-tooth extraction is another radiographic finding that should alert the clinician to ONJ in the bisphosphonate exposed patient [6, 9]. Overtime, increasing areas of osteolysis, characterized by radiolucent

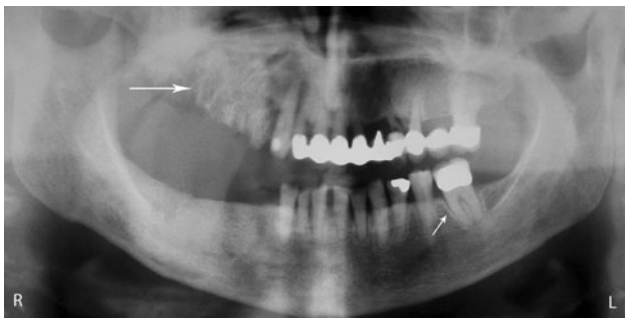

Fig. 2 Panoramic radiograph of patient receiving zolendronate therapy, referenced in Fig. 1. A large sequestrum is noted in the right maxilla (*long arrow*). The sclerotic lamina dura of recently extracted teeth is present in the right maxilla, and this feature is also noted in the remaining dentition, most prominent in the left mandible (*short arrow*)

regions surrounding sequestra, are noted within more radiodense osteosclerotic areas (Fig. 2).

These findings described earlier are also identified with other imaging techniques including computerized tomography (CT) scans that can offer accurate three-dimensional information that assists the clinician, especially if surgical debridement of ONJ bone is planned [32]. Magnetic resonance imaging (MRI) findings have been reported to demonstrate early changes characterized by loss of normal T1 hyperintensity of fatty marrow in the maxilla and mandible [33]. Positron emission tomography (PET) using both F-18 fluoride and F-18 fluorodeoxyglucose (FDG) tracers demonstrated increased tracer enhancement in the regions of bisphosphonate-related ONJ. PET appears to be a sensitive method but not specific for bisphosphonate ONJ [34]. PET differentiation of jaw pathologies such as bisphosphonate-related ONJ, osteomyelitis, osteoradionecrosis, and diffuse sclerosing osteomyelitis may be possible by the differentiation of inflammation and infection from bone remodeling [35]. O'Ryan and colleagues retrospectively studied Technetium 99 scintigrams of patients being evaluated for oncologic care and correlated findings with the temporal development of ONJ [36]. Bone scintigraphy showed positive tracer uptake before the development of ONJ in approximately 66% of patients who had scintigrams before clinical evidence of ONJ. The ONJ that eventually developed corresponded to areas of tracer uptake. Thus, CT, MRI, PET, and scintigraphy are ancillary techniques that may be used but are not required currently to establish a diagnosis of ONJ.

Histopathology

Light microscopy examination of pathology specimens associated with bisphosphonate-related ONJ typically

consist of bone sequestra; bone that lacks osteocytes and is detached from viable bone. Bacterial organisms are noted on the surface of the necrotic bone. Osteoclasts are not readily identifiable (personal observation), presumably due to bisphosphonate-induced apoptosis; also, recognizing necrotic bone and bacterial debris would not be conducive to osteoclast survival. However, Lesclous and colleagues demonstrated an abundance of mononuclear multinucleated cells in tissue peripheral to necrotic bone [37]. Soft tissue is often noted in association with these bone sequestra and consists of granulation tissue that may be lined in part by epithelium. The necrotic bone has a coral-like quality with a thickened trabecular pattern (Fig. 3). This phenotype is likely due to disruption of the physiologic remodeling process as the bisphosphonates interfere with the bone formation and resorption dynamic. High-resolution micro-CT scans of ONJ specimens have demonstrated variability in bone density [38]. In resection specimens, the interface of necrotic bone and viable bone demonstrates an inflammatory infiltrate. The histopathology of ONJ is similar for both the more potent intravenous bisphosphonates and oral bisphosphonates, with some exceptions (vide infra). In the ONJ cancer patient treated with bisphosphonates, concomitant metastatic deposits (e.g., breast or prostate carcinoma) and primary bone neoplasia (e.g., myeloma) need to be excluded. The identification of malignancy in areas of bisphosphonate-related ONJ is exceedingly rare in our experience.

The bacterial aggregates that form on the surface and extend into the labyrinthine spaces of these bone sequestra are composed of an admixture of filamentous, rod, and coccal forms. Sometimes these bacterial aggregates may resemble *Actinomyces* species. Cultures taken from exposed necrotic bone are most often composed of commensal organisms. An *Actinomyces* sp may be the sole organism, as several *Actinomyces* spp are part of the normal oral microbiome. However, culture confirmation is mandatory to specifically diagnosing actinomycosis, as it is our opinion that a diagnosis based solely on hematoxylin and eosin–stained decalcified bone sections is not possible. While identification of *Actinomyces* species by conventional phenotypic microbiology methods is difficult and unreliable [39], molecular methods have helped in this regard, but are not routinely employed. Identification of the specific organism may direct antibiotic use.

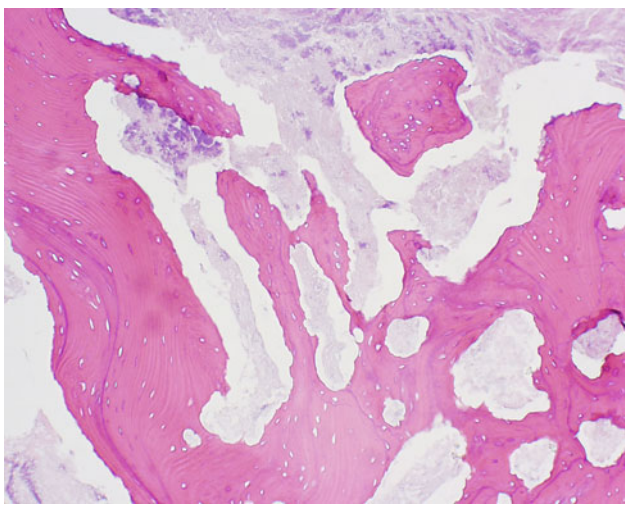

Fig. 3 Hematoxylin and eosin–stained decalcified section demonstrating necrotic bone with empty lacunae with associated bacterial aggregates characterized by a *pale blue* amorphous appearance (original magnification 40×)

The granulation tissue that frequently accompanies ONJ specimens consists of myofibroblasts, fibroblasts, and endothelial-lined channels with an inflammatory infiltrate of neutrophils, plasma cells, and lymphocytes. Epithelium originating from surface oral mucosa or the gingival sulcus may proliferate along the edge of the granulation tissue. The appearance of osteoclasts juxtaposed to areas of bone resorption may question the diagnosis of bisphosphonate-related osteonecrosis. It has been our experience that when osteoclasts are readily identified in a specimen, the clinical history submitted with a bone sequestrum often does not confirm an exposure to bisphosphonate medication, or the exposure may be to an oral bisphosphonate and a low cumulative dose (e.g., a few months). Thus, there can be interpretive problems at the light microscopic level in definitively diagnosing bisphosphonate-related ONJ, in the absence of the potentially relevant history. A recent retrospective study of alveolar bone samples obtained during osteotomy for implant placement taken from bisphosphonate-naive patients indicates regions of necrotic bone and subclinical osteomyelitis, findings that may indicate a potential risk of ONJ [40].

The clinical data that accompany ONJ specimens typically draw attention to the bisphosphonate exposure, the type of bisphosphonate and clinical indication for bisphosphonate use but rarely the cumulative bisphosphonate dose or exposure to multiple bisphosphonates. The pathologist, if suspicious for ONJ and in the absence of a complete clinical history, may elect to contact the submitting clinician or note the possibility that the observed necrosis may be related to bisphosphonate exposure, thus necessitating clinical correlation. These deficiencies in clinical correlation result in a subset of ONJ cases that go unconfirmed as being bisphosphonate related.

Effects of Bisphosphonates on Oral Soft Tissues

Although studies describing the effects of nitrogen-containing bisphosphonates on alveolar bone are numerous [1, 2, 6, 41, 42], the effects of this drug class on the oral

soft tissues are less well studied. Accordingly, the role of these drugs in oral wound healing and oral fibroblast and epithelial cell function specifically is poorly understood. In addition, the effects of bisphosphonates on angiogenesis in the oral cavity are not well characterized and are crucial to understanding oral wound healing. Finally, while studies examining signaling pathways and cytokine secretion in oral cells are underway, further research will be invaluable in delineating the adverse effects of these drugs on oral cavity soft tissues. Thus, modulation of oral soft tissues by bisphosphonate treatment is an emerging area of study and will likely lead to further understanding of the origin and progression of ONJ, as defects in soft tissue may influence the development of osseous pathology. A brief summary of the effects of bisphosphonates on oral soft tissues is provided below.

Bisphosphonates, in Conjunction with Oral Bacteria, Modulate Cell Signaling and Cytokine Production

While studies involving cell signaling and cytokine secretion in response to bisphosphonates are limited, a careful search of the literature reveals that inflammatory cytokines and chemokines are upregulated in human gingival fibroblasts following treatment with alendronate and lipid A, a bacterial component that binds toll-like receptor (TLR) 4. Specifically, interleukin-6 (IL-6) and IL-8 secretion is enhanced in gingival fibroblasts [43]. Moreover, the signaling molecule Smad3 is required for alendronate-induced IL-6 and IL-8 production by gingival fibroblasts, and the transcription factor NFκB is also increased in these cells upon stimulation with lipid A and alendronate. Such findings are corroborated by studies in a murine macrophage cell line infected with the periodontal pathogens *Porphymonas gingivalis* or *Tannerella forsythia*, which demonstrate increased IL-1β secretion following pretreatment of these cells with alendronate. This effect was also seen with TLR ligands Pam_3CSK_4 (TLR1/2) and lipid A and correlates with enhanced caspase 1 activity [44]. These data suggest a mechanism whereby gingival fibroblasts and macrophages respond to alendronate directly in conjunction with bacterial stimuli to produce inflammatory mediators, indicating that bisphosphonate treatment may contribute to inflammation within the oral cavity in patients receiving these medications.

Bisphosphonates Affect Oral Fibroblast and Epithelial Cell Viability and Function

To determine whether bisphosphonate treatment has deleterious effects on the oral soft tissues directly, numerous studies have examined the effects of such treatment on fibroblasts, epithelial cells, and endothelium [11–13, 15, 45–50]. Notably, experiments in human gingival fibroblasts reveal zoledronate and pamidronate treatments reduce collagen expression [48, 50]. Moreover, in studies using oral epithelial cell lines and fibroblasts, zoledronate significantly decreases proliferation and migration. Apoptosis in oral fibroblasts is enhanced following bisphosphonate treatment [48], and further studies in human gingival fibroblast and keratinocyte cell lines confirm these effects of zoledronate on proliferation and apoptosis. In addition, gene expression analysis reveals that multiple genes implicated in apoptosis are differentially regulated by bisphosphonate treatment [49].

Moreover, studies using periodontal ligament fibroblasts demonstrate that alendronate inhibits the viability of these cells as well [46]. Interestingly, studies using gingival and periodontal ligament fibroblasts show that free zoledronate induces apoptosis and necrosis in these cells. However, no effect is observed when these cells are treated with calcium phosphate incubated previously with zoledronate. Thus, studies using free forms of bisphosphonates must be interpreted with caution, as the bound form of the drug is likely to be the most abundant one to be encountered by fibroblasts within the physiological context of the oral cavity [45, 51]. While it is important to determine the significance of these findings, free bisphosphonates clearly mediate proliferation, migration, and apoptosis in oral epithelium and fibroblasts directly.

Although the aforementioned studies play an important role in our further understanding of the effects of these drugs on oral soft tissues, it is not clear whether the dosages of bisphosphonates used in these in vitro experiments reflect those encountered by gingival cells in individuals with significant bisphosphonate exposure. To address this concern, studies were conducted in dogs given high doses of zolendronic acid equivalent to those given to cancer patients [52]. While no differences are observed in cellular proliferation between control and experimental animals, matrix metalloproteinase 9 (MMP-9) expression is increased in the control animals. MMP-9 plays an important role in wound healing, and differences in expression may explain the delay in wound healing observed in some studies (vide infra). In addition, caspase-3 is elevated in the dogs receiving bisphosphonate therapy, suggesting that these cells may be undergoing enhanced apoptosis, although an additional assay to validate this result failed to show significant differences between the groups. Thus, this study highlights the importance of examining bisphosphonate effects on soft tissues in a physiological setting, as significant differences may emerge between in vitro and in vivo studies.

Angiogenesis is Inhibited by Bisphosphonate Administration

Many studies have shown inhibitory effects of bisphosphonates on angiogenesis, and such findings are confirmed both in vitro and in vivo. Studies using human umbilical vein endothelial cells (HUVECs) demonstrate that selected bisphosphonates inhibit endothelial cell migration, viability, and angiogenesis. Moreover, apoptosis of these cells is enhanced following bisphosphonate treatment [15]. These findings are strengthened by studies in multiple myeloma patients undergoing zoledronate therapy. In these patients, circulating endothelial cells are reduced in number and more apoptotic events are observed when compared with healthy controls. Furthermore, a correlation is seen between apoptotic cells and duration of bisphosphonate treatment [11]. Moreover, cancer patients demonstrate decreased levels of circulating vascular endothelial growth factor (VEGF) following zoledronate treatment, suggesting an inhibitory effect on angiogenesis [53]. However, this effect seems to be restricted to individuals receiving multiple doses of bisphosphonate, as no inhibition of angiogenesis is seen in a single-dose zoledronate model in rats mimicking once yearly injections administered for osteoporosis treatment [54]. Therefore, although the effect is likely dose- and time-dependent, bisphosphonates clearly inhibit VEGF and angiogenesis.

Effects of Bisphosphonate Therapy on Oral Wound Healing are Controversial

To elucidate the effects of bisphosphonate therapy on wound healing, several groups have used animal models to recapitulate surgical procedures performed by dental professionals. A recent publication shows that zoledronate therapy inhibits normal reparative processes in alveolar bone in rats, but does not affect the oral soft tissues. Accordingly, rats treated with zoledronate with surgically induced palatal soft tissue defects showed apparently normal healing of the overlying soft tissue, although the underlying osseous tissue was necrotic. Thus, the authors conclude that bisphosphonates selectively target bone and have no detectable effects on soft tissue wound healing [55]. Additional studies in rats using an extraction model reveal that alendronate administered over a 70-day period decreases woven bone formation and blood vessel area and number 10 days postextraction, although at day 70, there was no difference between control and experimental animals [56], indicating that this effect is not sustained long term.

However, contrasting data are reported using a mouse tooth extraction model treated with zoledronate. In this model, blood vessel formation is reduced significantly in the extraction socket, and caspase activity in endothelium and oral epithelial cells is enhanced, suggesting increased apoptosis in these cells. Moreover, a delay in soft tissue closure of the extraction socket is observed, indicating that the migration of oral epithelium is inhibited by zoledronate treatment [57]. In addition, studies using murine oral epithelium reveal inhibition of proliferation when cells are incubated with clinically relevant doses of pamidronate. Furthermore, wound healing is inhibited as determined by an in vitro wound healing assay, although in this study pamidronate did not induce apoptosis of the epithelium [58]. However, in a different model using human gingival fibroblasts and HUVECs, reduced viability is seen following treatment with pamidronate, ibandronate, and zoledronate. Moreover, pamidronate and zoledronate produce significant suppression of migration and proliferation in an in vitro wound healing assay for both cell types [12, 13]. These combined findings suggest that osseous tissue, as well as oral epithelial cells, are affected by bisphosphonate treatment, although the precise role of bisphosphonates in soft tissue wound healing within the oral cavity is not well understood and varies depending on the study model used.

Link Between ONJ and Bisphosphonate-Induced Oral Soft Tissue Pathology

The relationship between oral soft tissue integrity and ONJ is poorly understood, and further research is critical to address the interplay of these tissues in disease development. Notably, bisphosphonates accumulate in alveolar bone over time, and it is postulated that the levels are high enough to lead to soft tissue toxicity, as defects in oral mucosa are frequently observed in conjunction with osteonecrosis [59]. In addition, bisphosphonates inhibit angiogenesis in both bone and soft tissue [15, 60], thereby exacerbating underlying deficits in tissue regeneration and repair. Moreover, mucosal defects can lead to bacterial colonization of the underlying bone, creating a deleterious cycle of poor healing, inflammation, and infection [51, 59].

Furthermore, the cytokine network that regulates interactions between oral soft and hard tissue becomes dysregulated by bisphosphonate administration. Interestingly, oral soft tissues express factors that regulate bone turnover such as RANK-L and osteoprotegrin (OPG) [61, 62]. Several studies demonstrate that bisphosphonates decrease RANK-L and increase OPG levels, both in vitro and in vivo [63–66], suggesting a suppressive effect on bone resorption, although none of these studies examined cells isolated from the oral cavity specifically. In addition, bone morphogenic proteins (BMPs) play an important role in

bone homeostasis [67, 68]. Human periodontal ligament cells express BMP-2 [62], while primary human gingival cells express BMP 2, 4, and 7 [69]. Surprisingly, zoledronate increases bone mineral content, volume, and strength when administered concomitantly with BMP-7 in a rat critical defect model [70]. Moreover, bisphosphonate administration increases proliferation of an osteoblast cell line and enhances the expression of BMP-2 [71]. However, the bisphosphonate incadronate prevents bone maturation in animals containing a BMP-2 implantable device, suggesting that incadronate inhibits the normal bone formation mediated by BMP-2 in this model [72]. Thus, while oral soft tissues secrete cytokines that modulate bone physiology, further studies are needed to delineate these interactions in the oral cavity and to understand their significance in the context of bisphosphonate treatment.

Conclusion

In summary, while nitrogen-containing bisphosphonates play a crucial role in the prevention of osteoporosis in low doses and treatment of primary and metastatic bone neoplasia in high doses, the adverse effects of these medications are an important consideration for clinicians when prescribing these drugs. Detrimental effects are seen in both hard and soft tissues, and future studies must focus on the role of soft tissue in the development of ONJ, as such studies may lead to novel therapeutic approaches in the management of this debilitating complication of bisphosphonate therapy.

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