A model for the pathogenesis of bisphosphonate-associated osteonecrosis of the jaw and teriparatide’s potential role in its resolution

Gayathri Subramanian, PhD, DMD, a Harold V. Cohen, DDS, b and Samuel Y.P. Quek, DMD, MPH, c Newark, NJ NEW JERSEY DENTAL SCHOOL-UMDNJ

Objective. The objective of this study was to present a comprehensive model for the pathogenesis of bisphosphonate-associated osteonecrosis of the jaw (BON).

Study design. Review of PubMed literature relevant to BON, bisphosphonates (BPs), and bone remodeling.

Results. Six case reports of spontaneous resolution of BON lesions following administration of teriparatide (Forteo; Eli Lilly and Co., Indianapolis, IN) were identified. These reports suggest that osteoanabolic therapies may hold promise in BON management. Here we propose that BON pathogenesis is multifactorial and is the combined result of attenuated osteoblastic activity (owing to the patient’s underlying disease, e.g., osteoporosis or multiple myeloma), BP-mediated osteoclast toxicity, and the resultant compromised osteoblast-osteoclast interactions during bone remodeling. Consequently, a vicious cycle of ineffective local remodeling results in the persistence of defective bone, compromised tissue perfusion, and if unresolved, ultimately leads to necrosis.


Much has been written about bisphosphonate-associated osteonecrosis of the jaw (BON). This rare disease entity remains poorly understood, with no established pathogenesis. Currently, there are no established risk assessment guidelines for predicting the susceptibility to developing BON. There are management guidelines for BON with no predictability of cure.1-10

We present a model for the pathogenesis of BON that is based upon current evidence available in the literature. This model takes into consideration the biological basis underlying teriparatide’s potential therapeutic role in BON resolution as has been documented in a recent series of independent case reports.11-16 Our hypothesis for the pathogenesis of BON centers on a defective remodeling process secondary to weakened synergism among the key cell types that interact during bone remodeling: the osteoblasts (OBs), osteoclasts (OCs), osteocytes, and bone-lining cells.

Constant remodeling occurs in healthy adult bone in response to physiological stimuli initiated by bone aging, microdamage, and stress.17-22 All these stimuli ultimately trigger osteocyte death by apoptosis, which then sets into motion the remodeling cascade at the site of damage to replace defective bone.23-28 An optimal balanced interaction among the various cell types during bone remodeling ensures the replacement of defective bone with an equivalent volume of healthy bone. Thus, in the setting of bone homeostasis, injury, or infection, bone mineral density (BMD) and bone strength are preserved. Dam-

aPGY1, General Practice Residency Program, New Jersey Dental School-UMDNJ.
bProfessor, Director, Division of Oral Medicine, New Jersey Dental School-UMDNJ.
cAssociate Professor, Director General Practice, Residency Program, Director Division of Hospital Dentistry, Department of Diagnostic Sciences, New Jersey Dental School-UMDNJ.

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aged or necrotic bone is removed and new healthy bone is laid down at the remodeling or repair site.

Our proposal is that BON occurs subsequent to disruption of the bone-remodeling apparatus at multiple levels, resulting in incompetent/ineffective remodeling that allows for the persistence of defective/necrotic bone. Three major factors may contribute to this disruption in bone remodeling:

1. the patient’s underlying disease status, such as osteoporosis, malignant bone disease or Paget’s disease of the bone
2. the effects of bisphosphonate (BP) medications
3. the modulation of the collective impact of the preceding 2 factors on local bone remodeling at the lesion site

INEFFECTIVE BONE REMODELING IN BON- CUMULATIVE EFFECT OF MULTIPLE FACTORS

1. Role of the underlying disease- suppression of osteoblast function

Bone diseases that warrant clinical management with BPs are all reflective of an underlying imbalance between bone formation and resorption, with a net excess of uncompensated resorption.29,30

Bone homeostasis involves 3 key biological pathways:

- the estrogen endocrine pathway that preserves BMD
- the canonical Wnt/β-catenin signaling pathway, a major signaling pathway that facilitates bone formation
- the receptor activator of NF-κB ligand/receptor activator of NF-κB/osteoprotegerin (RANKL/RANK/OPG) pathway that determines the balance between bone formation and resorption.31-33

Genes belonging to these signaling pathways have been implicated as osteoporosis susceptibility genes. Glucocorticoids are known to disrupt Wnt signaling at multiple steps and suppress bone formation.34 Hence, prolonged treatment with glucocorticoids causes secondary osteoporosis.35,36 Both primary and secondary osteoporosis manifest clinically as reduced BMD and increased susceptibility to fractures.37 However, the diminished bone formation potential does not necessarily affect bone healing.

A similar imbalance between bone formation and resorption is also encountered in malignant bone diseases, such as multiple myeloma, in which myeloma cells selectively attenuate bone formation signaling pathways.38-42 Antagonism of the Wnt signaling pathway has been documented in Paget’s disease.43,44

Thus, as a population, the disease subsets of patients have an underlying compromised osteoblast function, which, we believe, renders them susceptible to developing BON.

2. Role of treatment with BPs- suppression of osteoclast function

Following intravenous or oral administration, a small fraction of the BPs bind avidly to hydroxyapatite crystals exposed in actively remodeling bone matrix. The remaining circulating BPs are rapidly removed from circulation by the kidneys. The matrix-bound fraction of BPs has a half-life of nearly 11 years. The bound BPs are toxic to osteoclastic function and survival. The cytotoxic effect of BPs on OCs occurs during bone remodeling when OCs endocytose BPs bound to the bone matrix.35,46 This is reflected by a significant reduction in the serum levels of collagen-I C terminal cross-linked telopeptide (CTX).47

Thus treatment of patients with osteoporosis or malignant bone disease with BPs reverses the uncompensated resorption and retards bone loss. Patients with osteoporosis demonstrate an improvement in BMD and reduced fracture incidence, whereas those with malignant bone diseases demonstrate a delay in skeletal-related events (SREs), such as osteolytic lesions and pathologic fractures upon treatment with BPs.46,48,49

We believe that BON only occurs in patients with preexisting suboptimal osteoblastic function. In contrast, in patients with an intact resilient bone-remodeling apparatus, the inhibition of OC function by itself does not result in pathology. For instance, treatment of healthy fracture patients with BPs results in the formation of an exuberant callus that persists, resists resorption and so, delays, but does not impair fracture healing.50 Similarly, implants coated with BPs require increased pull-out strength.51

It appears that it is the combined reduction in bone formation and bone resorption secondary to an underlying disease process and BP treatment, respectively, that significantly attenuates bone remodeling in BON patients, hence compromising the bone-remodeling response to physiological stimuli, such as bone aging, microdamage, and mechanical stress.19,22 Again, this attenuation in bone remodeling does not lead to the development of BON in most patients receiving BPs. Only a small fraction of these patients ultimately develop BON. We believe that this is primarily because the final determinant of BON development is the modulation of local bone remodeling.

3. Factors that influence local bone remodeling to maintain bone homeostasis and response to injury

Physiological bone remodeling involves multiple complex interactions between osteocytes, OBs, OCs, and bone-lining cells.19-22,52 Osteocytes, embedded in the bone matrix, are programmed to undergo apoptosis or cell suicide in response to aging, microdamage, and mechani-
1. Incoming OCs are exposed to toxic concentrations involving a combination of the following local events: motion a vicious cycle of ineffective remodeling in-demand upon local remodeling resources, setting into paired. This defective remodeling process places a high would have otherwise been promptly resorbed and re-
aging bone create a zone of apoptotic osteocytes that from ineffective remodeling of microdamage and/or remodeling process (Fig. 1A). Persistent bone defects treatment with teriparatide.
reports of resolution of BON incidentally noted upon 

2. Osteoblastic function is dependent on reciprocal 

3. The zone of apoptotic osteocytes widens either be-
cause of the accumulation of unrepaird microcracks, 
or because of the persistence of aging/damaged bone.

4. BPs are known to impair targeted remodeling, al-
lowing microdamage to persist for longer periods compared with untreated bone. This persistent but attenuated attempt at healing without adequate re-
repair often results in local bony sclerosis that fails to strengthen the bone.

5. Additionally, renewal of local vasculature is com-
promised because of ineffective bone remodeling. The antiangiogenic effect of BPs may further comp-
ound the situation.

This cascade of events ultimately results in a widen-
ing central zone of brittle, adynamic, poorly vascular-
ized bone that eventually necroses but persists unre-
sorbed amidst the relative lack of inflammation and 
pain, the hallmark of BON. This central zone of necro-
sis is surrounded by a zone of attempted remodeling and repair. BON is thus an evolving lesion resulting from incompetent but persistent remodeling.

Exposure of this necrotic bone to the oral cavity eventually results in infection, suppuration, and devel-
oment of fistulous tracts, and the patient becomes symptomatic. The presence of infection results in the spread of necrosis, resulting in higher morbidity.

In summary, the development of BON is contingent on the underlying disease status of the patient, treat-
ment with BPs, and the outcome of local remodeling. The combined effect of these factors tip healthy remodel-
ing toward the development of BON.

Whether or not BON develops may be determined by the relative qualitative/quantitative balance and reciprocal interactions between osteoblastic and osteoclastic function (Fig. 1B), as discussed previously. This implies that mea-
suring the levels of serum markers for bone formation and resorption simultaneously may reflect the relative balance between these 2 processes and help predict the risk of developing BON. A recent retrospective study reported correlation between relative reduction in bone formation, as reflected by serum levels of the marker serum osteocalcin (s-OC), and the development of BON.

The integrity of osteoblastic function determines the outcome of compromised bone remodeling. Robust active osteoblastic function could sustain the remodeling cycle despite compromised osteoclastic function and subvert the development of BON. Conversely, inadequate osteoblastic function feeds into the vicious cycle by failing to appropriately stimulate OCs to remove defective bone. Modulating the relative balance between OB and OC function by boosting osteoblastic activity could potentially augment the crosstalk with OCs required to break the vicious cycle of ineffective bone remodeling and restore bone health. It is in this capacity to facilitate local remodel-
ing that teriparatide has generated much interest as a potential tool for the management of BON lesions.
Fig. 1. (A) Model for ineffective remodeling and the pathogenesis of BON. (B) Osteoblastic function as a determinant of BON development. Image is available in color at www.ooooe.net.
TERIPARATIDE AND THE RESOLUTION OF BON LESIONS

Recently, 6 independent case reports have documented the ability of a drug called teriparatide to affect clinical resolution of BON lesions (summarized in Table I).\textsuperscript{11-16} The initial reports were coincidental observations made in patients whose osteoporosis medications were switched from BPs to teriparatide because of BON resulting from BP therapy. Among these patients, one was on intravenous BPs before developing BON,\textsuperscript{13} whereas the remainder were originally on oral BPs. Within a few weeks, clinical resolution of the BON lesions was noted. The most recent study reported the resolution of BON when treatment with teriparatide was instituted specifically to study its effect on BON.\textsuperscript{11}

We believe that teriparatide holds promise in the management of BON because it actively promotes bone remodeling. Teriparatide is a synthetic peptide that corresponds to the N-terminal\textsuperscript{1-34} residues of human parathyroid hormone (PTH). It is the only osteoanabolic drug currently approved by the Food and Drug Administration, for the management of osteoporosis.\textsuperscript{21,57-59} Teriparatide is administered as a once-daily low-dose subcutaneous injection for up to 24 months. This regimen promotes anabolic bone deposition. During this period, increased bone formation is evidenced by increased markers of bone formation in serum (markers, such as procollagen I-N terminal polypeptide and bone alkaline phosphatase),\textsuperscript{60-62} without a corresponding change in markers of bone resorption (Fig. 2).\textsuperscript{59}

Because teriparatide maintains the N-terminal region of the intact peptide (PTH), it recognizes the same receptor (parathyroid hormone receptor)\textsuperscript{65} expressed on the surface of OBs,\textsuperscript{64} and has an anabolic window, similar to PTH, when administered at low intermittent doses.\textsuperscript{65}

Teriparatide’s osteoanabolic effects are mediated directly and indirectly. Teriparatide enhances osteoblastic function by inhibiting the apoptosis of OBs and promoting the differentiation of osteoblast progenitors, the preosteoblasts.\textsuperscript{57,58} It also stimulates the proliferation of preosteoblasts, thus expanding the pool of OB precursors that actively engage in crosstalk with pre-OCs and OCs and eventually differentiate to constitute mature OBs. Teriparatide reduces expression of sclerostin, a Wnt antagonist that is primarily secreted by osteocytes, and thus disinhibits Wnt signaling (reviewed in Canalis et al.\textsuperscript{57}). In addition, it increases the expression of insulinlike growth factor (IGF)-1, a growth factor that potentiates bone formation.\textsuperscript{66}

Treatment with teriparatide also promotes the expression of RANKL in preosteoblasts.\textsuperscript{67,68} This enhances the activation of OCs by OBs, augmenting the crosstalk between the 2 cell types. OCs are derived from circulating blood precursors and, thus, are constantly renewed, in contrast to cells of osteoblastic origin, which are locally derived. It is our proposition that the augmentation of osteoblastic function would result in an increased recruitment and activation of osteoclastic cells from the circulation. This increase in OC recruitment and activation will ultimately overcome the local attrition of OCs attributable to BP toxicity. This is why teriparatide’s osteoanabolic effects could hypothetically help overcome BP-induced toxicity of OCs and hence augment bone remodeling in BON.

Physiological remodeling is initiated when the physical communication between local OBs and the underlying osteocytes is interrupted as a result of osteocyte apoptosis. Apoptosis of osteocytes is a physiological response to aging, microdamage, and strain. The accumulation of cyclic adenosine monophosphate (cAMP) in the osteoblastic cells overlying this defective bone, is believed to then initiate the remodeling cycle.\textsuperscript{69} Because teriparatide increases cAMP levels in OBs, it may enhance the crosstalk between osteocytes and OBs, sensitizing them to respond to the underlying unresorbed bone in BON.

Therefore, treatment with teriparatide may revitalize bone remodeling in BON by

1. directly stimulating OBs, bypassing their dependence on local OCs for optimal reciprocal stimulation
2. augmenting Wnt signaling and bone formation
3. increasing the recruitment and activation of OCs from the circulation to effectively remove the necrotic bone

Teriparatide may thus aid in the resolution of BON lesions, by augmenting effective bone remodeling under osteoanabolic conditions (Fig. 1B). In addition, the use of teriparatide has therapeutic value in osteoporosis. Treatment with teriparatide addresses the pathophysiological mechanisms of impaired bone formation in osteoporosis, especially chronic glucocorticoid treatment–induced osteoporosis by alleviating the underlying disease phenotype.

THE STRENGTHS AND WEAKNESSES OF OUR MODEL FOR BON’S MULTIFACTORIAL PATHOGENESIS

Our model for BON pathogenesis is consistent with existing evidence on BON. We regard BON as a dynamic lesion, with ongoing but ineffective remodeling, in an attempt to eliminate and repair defective bone. There is increasing evidence for active bone remodeling in BON lesions, contradictory to the theory that BON is the direct result of low bone turnover following treatment with BPs. The earliest evidence for active
## Table I. Summary of case reports that documented clinical resolution of BON with teriparatide

<table>
<thead>
<tr>
<th>Publication</th>
<th>Age/sex</th>
<th>Medical condition</th>
<th>Drug/duration of treatment with BP/steroid</th>
<th>Spontaneous vs postextraction BON</th>
<th>Stage of BON</th>
<th>Location of BON</th>
<th>Duration of treatment with teriparatide for clinical resolution</th>
<th>Imaging</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harper and Fung</td>
<td>75/F</td>
<td>Osteoporosis</td>
<td>Alendronate (70 mg daily) × 1 y</td>
<td>Postextraction</td>
<td>Stage II</td>
<td>L, R maxilla</td>
<td>3 mo</td>
<td>10 mo panoramic X-ray</td>
<td>Coincidental observation</td>
</tr>
<tr>
<td>Lau and Adachi</td>
<td>56/F</td>
<td>Fibromyalgia, glucocorticoid-induced osteoporosis, osteoarthritis, hiatus hernia, irritable bowel syndrome</td>
<td>Prednisone 18 mo (other medications, refer to(13)) (Sequentially) Etidronate, calcitonin, clodronate, pamidronate, zoledronate × 3 y</td>
<td>Postextraction</td>
<td>Stage III (soft tissue in right pyriform area of floor of nose)</td>
<td>Not mentioned: 10 mo for radiographic evidence of healing</td>
<td>10 mo panoramic X-ray</td>
<td>Multiple surgical interventions before teriparatide switch unsuccessful</td>
<td></td>
</tr>
<tr>
<td>Narongroeknawin et al.</td>
<td>63/M</td>
<td>Osteoporosis</td>
<td>Alendronate × 5 y</td>
<td>Postimplant</td>
<td>Stage I</td>
<td>L, R maxilla</td>
<td>4 mo for clinical/radiographic resolution</td>
<td>4 mo periapical X-ray</td>
<td>Allografts were placed upon removal of implant Alveoloplasty, debridement and sequestrectomy prior to teriparatide switch</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>78/F</td>
<td>Osteoporosis</td>
<td>Alendronate 70 mg/wk PO × 5 y</td>
<td>Postextraction</td>
<td>Stage II</td>
<td>R mandible</td>
<td>4 wk</td>
<td>Bone regeneration seen as early as 5 wk, 6 mo later (panoramic X-ray)</td>
<td>Off-label use of teriparatide for BON</td>
</tr>
<tr>
<td>Tsai et al.</td>
<td>72/F</td>
<td>Not elaborated</td>
<td>Weekly alendronate × 4 y</td>
<td>Postimplant</td>
<td>Stage III (extraoral fistula)</td>
<td>R mandible</td>
<td>5 mo for bone regeneration</td>
<td>5 mo panoramic X-ray</td>
<td></td>
</tr>
<tr>
<td>Cheung et al.</td>
<td>88/F</td>
<td>Osteoporosis</td>
<td>Alendronate 70 mg/wk × 10 y (previously, 20 y of prednisolone 5 mg/d)</td>
<td>Postextraction</td>
<td>Stage II/III (CT scan demonstrates extension to beyond the alveolus)</td>
<td>L mandible</td>
<td>8 wk for clinical resolution/radiographic healing</td>
<td>CT scan at 8 wks</td>
<td>Off-label use of teriparatide for BON</td>
</tr>
</tbody>
</table>

BON, bisphosphonate-associated osteonecrosis of the jaw; BP, bisphosphonate; CT, computed tomography; F, female; L, left; M, male; R, right.
remodeling in BON came from histopathological studies of BON lesions that demonstrated the presence of numerous OCs close to vital bone exhibiting signs of bone resorption. The only instance where treatment with BPs appears to ameliorate steroid-induced osteonecrosis is in children subsequent to acute lymphoblastic leukemia therapy. In these patients, the clinical improvement can be directly attributed to reduction in bone pain upon BP medication. However, subsequent deterioration has been noted radiographically, consistent with further attenuation of bone remodeling.

Our model further explains why osteonecrosis is encountered in patients who are treated with denosumab, a monoclonal antibody directed against RANKL and hence, is a potent inhibitor of osteoclast function. This indicates that bisphosphonate toxicity is not the only etiologic agent for BON. Currently, there is no single risk factor that can independently predict susceptibility to develop BON. This is understandable if one views BON as the final outcome of multiple events.

Finally, viewing BON as an active lesion can explain why it is possible for BON lesions to potentially heal, with successful elimination of necrotic bone and replacement with healthy bone tissue. In fact, the earliest opportunity for therapeutic intervention in BON may be at stage 0, before frank necrosis and exposure of bone occurs.

Our model does not directly address the apparent site predilection of BON for the jaws. The only sites that have been associated with BON are the jaws and the external acoustic meatus (EAM), both derivatives of the first pharyngeal arch, in contrast to osteoblastic cells in the rest of the body. The following are possible explanations for BON’s site predilection:

1. A recent report by Stefanik et al. highlighted that all OBs are not the same—there exists a differential susceptibility of OBs from the mandible when compared with those derived from iliac crests, to BPs.
2. A multifold suppression of Msx-1, an osteoproliferative transcription factor expressed constitutively only in adult jaws, overexpression of bone morphogenetic protein-2, and suppression of RANKL have all been described in BON samples. Msx-1 is a direct canonical Wnt signaling target that functions along with Msx-2 to mediate Wnt signaling. Thus, the suppression of Msx-1 in the jaw may predispose the patient to develop BON in the jaw.
• In addition, the soft tissue covering the bone in both the jaws and the EAM is thin, and may have a tendency to erode relatively easily when compared with that covering long bones/axial skeleton.

Our model does not specifically factor in key aspects of immune modulation in the pathogenesis of BON. Osteoimmunology is an important emerging field of study. It is likely that any modulation of bone physiology will modulate the immune response as well.97 In addition, it is known that teriparatide has immune regulatory effects.98,99 This could impact its effects on BON. Although this aspect is not accounted for in our model for BON pathogenesis and potential management, these effects may potentially contribute to, and are consistent with teriparatide’s projected curative role in BON.

Lastly, our model does not specifically address the impact of the effect of biofilms of BPs on mucosal tissue in BON development.100-102 This is primarily because we believe that these events modulate BON subsequent to bone exposure to the oral cavity following mucosal dehiscence, and thus may play a role downstream, in frank, clinically evident BON.

CONCLUSIONS

We present here a model for the pathogenesis of BON. We hypothesize that ineffective remodeling in BON is multifactorial. The combined effects of compromised bone formation that accompanies the primary disease and inhibition of bone resorption by bisphosphonates creates a “perfect storm” setting in a subset of patients who eventually develop BON, when unable to maintain bone homeostasis or repair bone injury. Measuring the relative balance between markers of bone formation and resorption may be useful for risk assessment.

There is sound biological rationale as well as preliminary evidence for teriparatide’s effectiveness in BON. Therefore, well-designed clinical studies are warranted to validate teriparatide’s role in the management of BON. Proof of teriparatide’s effectiveness will indirectly confirm our model of BON pathogenesis.

Based on our model of the pathogenesis of BON, the earliest opportunity for effective management of BON may actually be at stage 0,10 before the development of frank necrosis, exposure of bone, and secondary infection.

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Reprints:
Samuel Y.P. Quek, DMD, MPH
Department of Diagnostic Sciences
New Jersey Dental School-UMDNJ
110, Bergen Street
PO Box 1709
Newark, NJ 07101
queksa@umdnj.edu