Vol. 112 No. 6 December 2011

Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

ORAL MEDICINE

Editor: Craig S. Miller

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

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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.
Conclusions. Our model for BON pathogenesis advocates for earlier therapeutic intervention in BON. The biological rationale for teriparatide's efficacy in BON justifies further investigation. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:744-753)**

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-

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Received for publication Jan 27, 2011; returned for revision Apr 7, 2011; accepted for publication Apr 17, 2011.
1079-2104/$ - see front matter

doi:10.1016/j.tripleo.2011.04.020

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-κβ ligand/receptor activator of NF-κβ/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 osteoblastic 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.[45,46] This is reflected by a significant reduction in the serum levels of collagen-1 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 callous 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 mechan-