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PERSPECTIVES

Pathogenesis of Osteonecrosis of the Jaw

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Abstract

Osteonecrosis of the jaw is a condition associated with high-dose bisphosphonate use, usually seen in the context of the management of skeletal metastatic disease. Its etiology is uncertain, and none of the currently proposed models appears adequate to account for all its clinical features. This review considers each of the possible contributory factors and suggests that the combination of an initiating injury, secondary infection, and toxicity to bone and non-bone cells from high local concentrations of these drugs is likely to be responsible for the development of this problem.
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Since the condition now commonly referred to as osteonecrosis of the jaw (ONJ) was first described in oncology patients receiving high dose intravenous bisphosphonate therapy (1), it has been given a variety of names, and individual writers have displayed a variety of diagnostic approaches. Some of the names given to this condition are inappropriate, since they have implied an etiology which is not established (*e.g.*, *avascular* necrosis of the jaw). The diagnostic situation has been clarified somewhat with several recent consensus statements, particularly that from the ASBMR (2), agreeing that the key element in defining this condition is the presence of exposed bone in the mouth for more than six to eight weeks. It is frequently precipitated by a dental extraction or other invasive oral procedure (*e.g.*, dental implants). When reviewing reports of this condition, it is important to be mindful of the fact that some authors have applied the term to virtually any oral pathology occurring in a bisphosphonate-treated patient. The currently agreed definition of exposed bone in the mouth is purely an operational one which has the merit of providing diagnostic clarity but which remains non-specific. There are a large number of other conditions that can also present in this way, including local trauma, infection of soft tissue or bone, bone tumors or metastases, and jaw necrosis following radiotherapy to the region. Therefore, having ascertained that osteonecrosis is present, it is important to determine whether it can be attributed to any of these other causes, before it is assumed to be causally linked to previous or current use of bisphosphonates. When osteonecrosis occurs in bisphosphonate users and it is not attributable to other conditions, it is reasonable to regard this as being 'bisphosphonate-associated osteonecrosis of the jaw'. A number of etiologies for this problem have been hypothesized and these are summarized in Table 1.

Cancer-Related Factors

In 95% of patients developing bisphosphonate associated ONJ, there is an underlying diagnosis of disseminated malignancy. Metastatic cancer itself increases the risk of infection and is associated with impaired tissue healing. Added to that are the complications from the use of cytotoxic, immunosuppressive and glucocorticoid drugs, to which these patients are often exposed. This combination of effects is likely to make cancer patients

• Impaired immunity and healing related to malignancy • Vascular compromise • Low bone turnover • Bisphosphonate toxicity to bone • Bisphosphonate toxicity to soft tissue

Table 1. Possible etiologies of bisphosphonate-associated osteonecrosis of the jaw.

more likely to develop oral osteomyelitis or to have delayed healing and/or infection of dental extraction sites. Available evidence suggests that infection is an important component of ONJ, and a recent histological series showed *Actinomyces* to be present in all eight patients presented (3). However, these features have existed in cancer patients for many decades and do not explain the emergence of ONJ as a new problem in the last few years, though they might contribute to its substantially greater prevalence in oncology practice.

Vascular Compromise

As noted above, some earlier reports made the assumption that compromised vascular supply was a key etiological feature of ONJ. It is not clear how this usage crept into the literature, and it may have been by analogy with the clinically very different problem of avascular necrosis of the hip. The only common features of these conditions are the word 'necrosis' and the fact that both conditions affect bone. What direct evidence there is suggests that reduced vascularity is not a major etiological contributor. Hansen (3) has reported patent vessels in seven of the eight cases studied histologically, as have others (4), and surgeons anecdotally report bleeding from affected bone if surgical resection is attempted. Also, the clinical picture is very different from avascular necrosis of bone at other sites, which usually presents with local pain or increased radiological density, but not with a breakdown of overlying soft tissue. However, there is *in vitro* evidence that bisphosphonates at high concentrations (*e.g.*, zoledronate 10^{-4}M) inhibit the proliferation of endothelial cells (5). Bisphosphonates have also been shown to be associated with reduced revascularization of the prostate gland in castrated rats treated with testosterone (5), though this is not necessarily a specific vascular effect, since it could represent toxicity to the prostate cells themselves. Thus, toxic effects of bisphosphonates on endothelial cells may contribute to the reduced bone and soft tissue healing in ONJ, but this is unlikely to be the principal etiological factor.

Low Bone Turnover

Many authors have assumed that reduced bone turnover is important in the development of ONJ. Certainly, reduction in bone turnover is the principal pharmaceutical action of bisphosphonates, and there has been concern since these drugs first came into clinical use that reduced turnover would interfere with normal repair mechanisms in bone and result in increased skeletal fragility. This remains a hypothesis for which there is little clinical evidence. Moreover, ONJ presents as a failure of soft tissue healing following invasive dental procedures, which is difficult to link causally to a hypothesized increase in skeletal fragility. In fact, the bone in ONJ lesions is not 'frozen' and Hansen (3) has reported active osteoclastic resorption in more than half of ONJ patients (Fig. 1), as have Bartl and Mast (4). It is likely that local infection is a potent stimulus to osteoclastogenesis via stimulation of local cytokine production.

In most other conditions associated with low bone turnover, such as hypoparathyroidism, ONJ-type lesions have not been reported. However, osteomyelitis and osteonecrosis complicating extractions have been reported in osteopetrosis (6). In some cases this appears to be ischemic as a result of obliteration of the marrow by the sclerotic bone (7;8), and in others osteophyte

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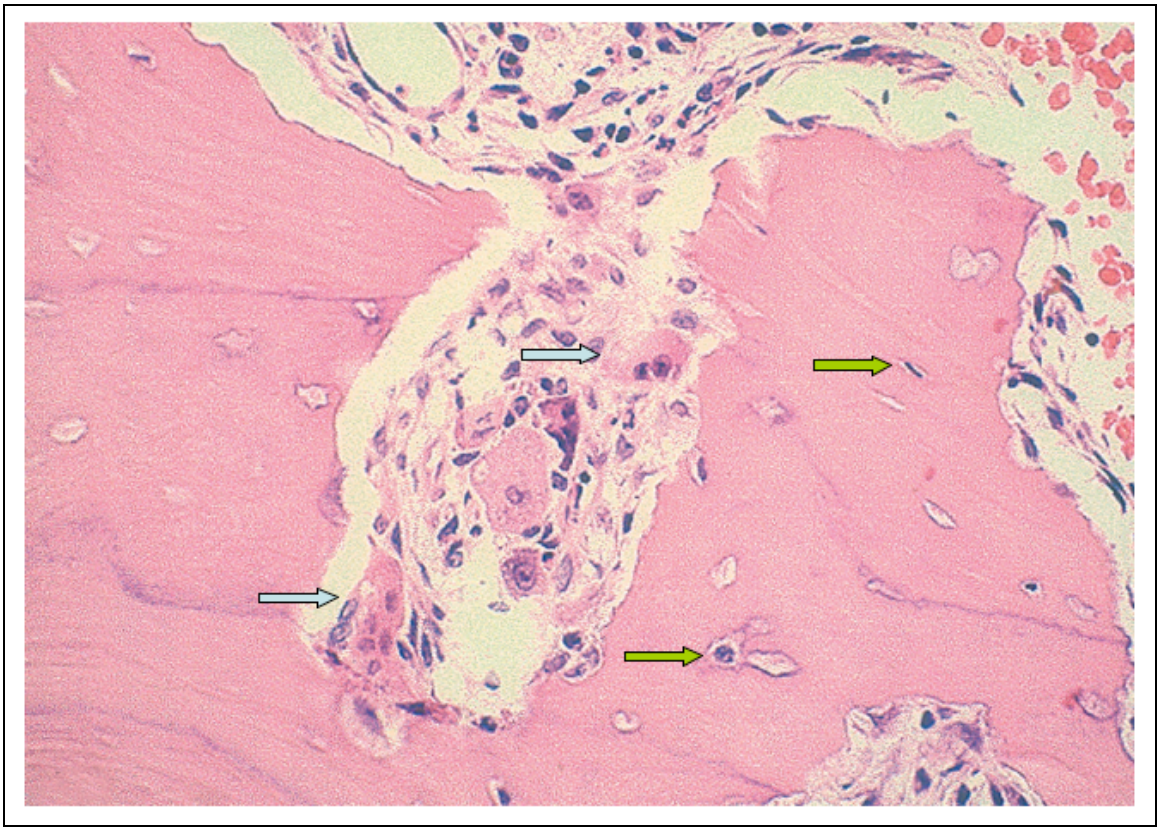

Fig. 1. Tissue specimen from a patient with ONJ, demonstrating a bone resorption lacuna containing large, multinucleated osteoclasts (blue arrows). Note is also made of viable osteocytes (green arrows) in some areas of the bone. From Hansen *et al*. (3), *J Oral Pathol Med*. 2006 Mar;35(3):155–60, used with permission.

formation may act as a focus for local trauma (6). There are now a number of non-bisphosphonate pharmaceuticals that substantially reduce bone turnover, including denosumab and cathepsin K inhibitors. To date, ONJ has not been reported with these agents, though they have not yet been used outside the context of clinical trials. The presence or absence of ONJ with further use of these pharmaceuticals will provide critical information regarding its possible etiology.

Bisphosphonate Toxicity to Bone

A hypothesis related to bisphosphonate-induced low turnover is that ONJ is a manifestation of direct bisphosphonate toxicity to bone. Histological studies of ONJ-affected tissue do show some empty osteocytic lacunae (3) or necrotic osteocytes (4), but they also show some lacunae containing apparently healthy osteocytes (3) (Fig. 1). The development of ONJ is related to bisphosphonate potency and to total dose, which would be consistent with the hypothesis of toxicity. ONJ incidence might also be related to the route of bisphosphonate administration (higher incidence after intravenous administration) (9) which is itself associated with higher tissue doses and is used for more potent agents. However, it would be expected that this toxicity would be apparent at other sites, since bone death often becomes clinically apparent, either as pain or as mechanical failure (as in avascular necrosis of the hip or knee). Also, if there were generalized bone toxicity from the use of bisphosphonates, inhibition of fracture healing would be expected. Despite isolated case reports (10), reduced fracture healing has not been convincingly demonstrated despite being carefully studied in the context of several randomized controlled trials (11-13).

Bisphosphonate Toxicity to Soft Tissue

More recently, we have hypothesized that bisphosphonates accumulate in the bone of the alveolar ridges of either the mandible or maxilla, and result in toxicity to the overlying soft tissue (14). This hypothesis, which does not necessarily exclude any of the others outlined above, potentially addresses many of the shortcomings of the other explanations. While the anti-resorptive effects of bisphosphonates depend upon the precise targeting of these drugs to bone mineral and thence to the osteoclast, it is now clear that micromolar concentrations of bisphosphonates impact on the functions of a number of other cell types. The acute phase reaction, which commonly occurs with intravenous amino-bisphosphonate administration, results from inhibition of farnesyl pyrophosphate (FPP) synthase in monocytes, leading to activation of γ,δ T cells (15). Similar effects have been demonstrated in a wide variety of cell types, including macrophages, endothelial cells, a variety of tumor cells, osteoblasts, and epithelial cells (16). These effects are related to the duration of exposure of the cells to bisphosphonate, and to bisphosphonate potency, implying that there is a gradual accumulation of bisphosphonate within cells over time. Correia (17) has demonstrated this elegantly with studies of the proliferation of periodontal ligament fibroblasts in the presence of alendronate (Fig. 2).

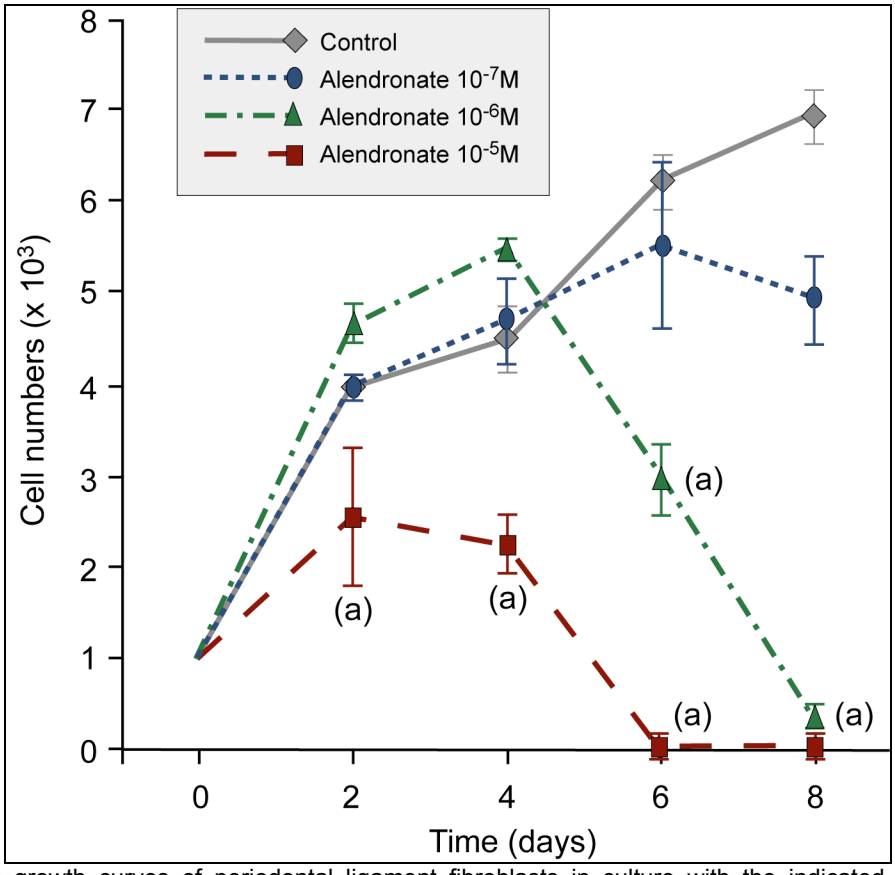

Fig. 2. Cell growth curves of periodontal ligament fibroblasts in culture with the indicated alendronate concentrations. Significant differences from control are indicted by "(a)". From Correia *et al*. (17), *Dent Traumatol*. 2006 Dec;22(6):312–7, used with permission.

At alendronate concentrations of 10^{-7}M, inhibition is not seen until eight days of culture, whereas at concentrations of 10^{-5}M, inhibition is present at two days. In macrophages, bisphosphonate entry is mediated by fluid-phase endocytosis (18), a unidirectional process that leads to progressive intracellular accumulation of

bisphosphonate in the absence of any mechanism for its re-release or metabolism. Bisphosphonate uptake from bone by non-resorbing cells, and the resultant inhibition of cell growth, can be increased when these cells are cultured in the presence of resorbing osteoclasts, possibly as a result of bisphosphonate being passed to the adjacent cells by transcytosis (19). The active bone resorption of the ONJ lesion creates exactly this scenario.

The epithelial toxicity of the bisphosphonates has been studied in some detail because of the propensity of these drugs to cause gastrointestinal inflammation and ulceration. Numerous case reports have been published documenting this phenomenon, which probably represents a local contact toxicity, similar to the oral ulceration which results from the sucking of bisphosphonate tablets (20). The *in vitro* correlate of this is a dose-related inhibition of proliferation of human keratinocytes (Fig. 3) that is also likely to be mediated by inhibition of FPP synthase, since it is reversible when downstream metabolites in the mevalonate pathway are added to the culture media (21).

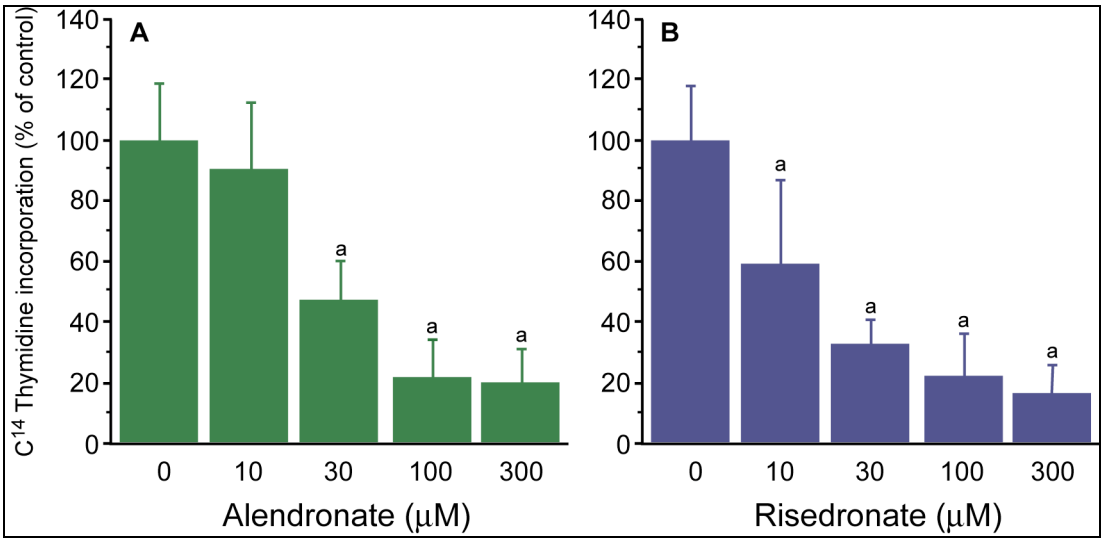

Fig. 3. Effects of alendronate and risedronate on the growth of normal human epidermal keratinocytes in culture. "a" denotes significant differences from control, P<0.0001. From Reszka *et al*. (21), *Mol Pharmacol*. 2001 Feb;59(2):193–202, used with permission.

While *in vitro* studies have clearly established toxic effects of bisphosphonates on a wide variety of cell types, it remains debatable as to whether adequate concentrations are reached *in vivo* for this toxicity to be clinically apparent. Approximately half of an intravenous dose of bisphosphonate is taken up by the skeleton, where it is retained indefinitely (22;23). Human (24) and rat (25) studies show that skeletal uptake of bisphosphonate is sustained with long-term administration. The cortical bone of the mandible has much higher turnover than appendicular sites (26) and this is particularly true for the alveolar bone (27). Therefore, bisphosphonates will be selectively concentrated into the jaw, and we have previously estimated that four years use of zoledronate at a dose of 4 mg/month would result in an average skeletal content of 70 nmol/g of bone (14), and probably two to three times this level in alveolar bone. Since epithelial toxicity is apparent when cells are exposed to zoledronate concentrations of 1 nmol/mL, it is entirely plausible that local concentrations at an extraction site will indeed be high enough to exert clinically important effects on non-skeletal cells.

An Integrated Model

It is important to remember that most cases of ONJ are precipitated by some form of local trauma, such as the placing of dental implants, a tooth extraction, or epithelial

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damage caused by poorly fitting dentures. This results in bisphosphonate being released from damaged bone into an environment where epithelial cells are actively proliferating in order to heal the break in the oral mucosa. As noted above, super-added infection is very common, which is a potent stimulus to local bone resorption and, thus, further bisphosphonate release. Bisphosphonate effects on T cells and other immune cells (28) may contribute to the persistence of local infection, and inhibition of endothelial cell proliferation and reductions in the production of growth factors such as vascular endothelial growth factor and platelet-derived growth factor (29;30) may also be important contributory factors. Thus, there is the potential for establishing a self-perpetuating cycle in which a lesion initiated by mucosal trauma is sustained by infection, leading to more bisphosphonate release, and to bisphosphonate inhibition of immune function and the capacity of soft tissues to heal the mucosal breach. This scenario is presented diagrammatically in Figure 4.

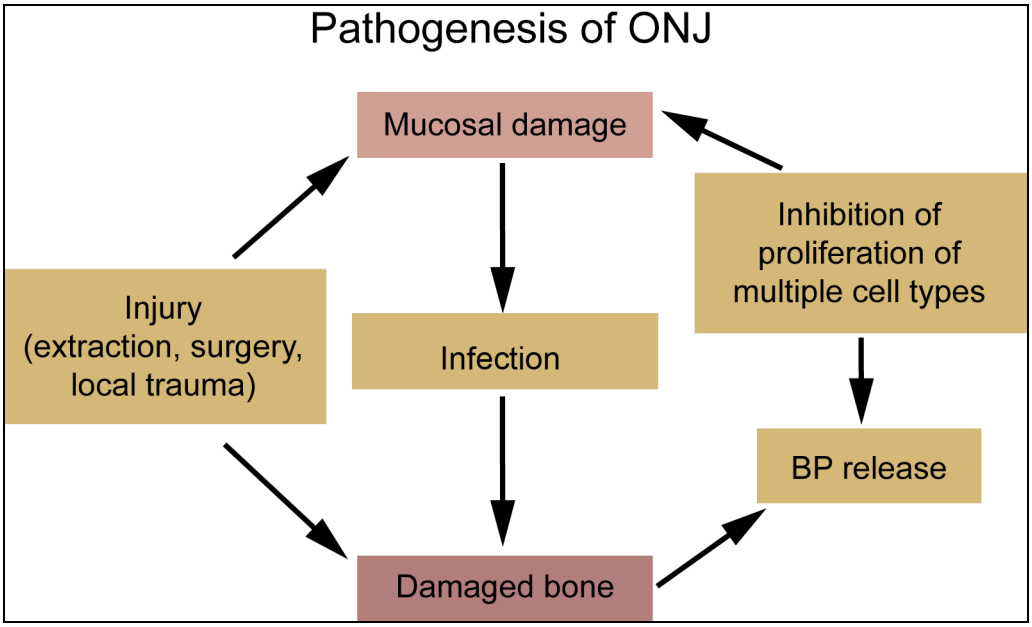

Fig. 4. Possible scenario for the interaction of factors contributing to the development of osteonecrosis of the jaw.

Clinical Implications

The possibility of bisphosphonate toxicity to non-bone cells resolves many of the shortcomings of other explanations for this condition; in particular, it explains how a bone-targeted drug is able to produce what is predominantly a soft tissue lesion. Focusing on the soft tissue lesion as the key aspect of ONJ also explains why further bone resection does not lead to resolution of the problem, and may in fact make it worse by extending the damaged bone surface from which bisphosphonate can be released. Clinical experience to date suggests that the best management of ONJ is aggressive antibiotic therapy if infection is present, and the use of regular mouthwashes. If local release of bisphosphonate is key to sustaining the lesion, then mouthwashes may be valuable simply through diluting and washing away this toxin, thus diminishing its uptake into regenerating epithelial cells. Bisphosphonate toxicity in these cells might also be lessened through the local administration of downstream metabolites of FPP synthase, since these compounds have been shown to reverse bisphosphonate toxicity to epithelial cells *in vitro* (21). This model also suggests discontinuation of bisphosphonate administration as being an important step in managing this clinical problem, since it will remove that component of soft tissue toxicity attributable to circulating bisphosphonate.

Conclusion

The bisphosphonates remain very useful compounds for producing targeted inhibition of osteoclast activity. The low incidence of side-effects associated with their use is related to the specificity of this targeting. ONJ appears to be a manifestation of toxicity to non-bone cells as a result of high intensity therapy over a long period of time. There is clearly much more work to be done assessing the mechanisms by which bisphosphonates enter cells other than osteoclasts, and these studies may give insights into minimizing the side effects of these drugs, as well as to their targeting to non-bone tissues for use as anti-tumor agents.

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