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## Normal serum bone markers in bisphosphonate-induced osteonecrosis of the jaws

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We obtained serum bone markers and other relevant endocrine assays on 5 patients with osteonecrosis of the jaw (ONJ). The assays were C-telopeptide, N-telopeptide, bone-specific alkaline phosphatase, osteocalcin, intact parathyroid hormone, T3, T4, TSH, and Vitamin D 25 hydroxy. Diagnostic criteria for ONJ were those formulated by the American Association of Oral and Maxillofacial Surgeons. Four of our patients were women. Two had metastatic breast cancer and had been treated with zoledronic acid; one had also received pamidronate. Two others had osteoporosis and had been treated with daily alendronate. One man had metastatic prostate cancer treated with zoledronic acid. All patients had been withdrawn from bisphosphonate for at least 6 months. None were taking or had taken corticosteroids. None of the lesions had shown any significant healing and all were still causing the patients considerable distress. Yet the bone markers were within the normal range as measured in our laboratory, except for intact parathyroid hormone, which was slightly elevated in one case of metastatic breast cancer (177 pg/mL). Because the jaws have a greater blood supply than other bones, and a high bone turnover rate, bisphosphonates are highly concentrated in the jaws. This anatomic concentration of bisphosphonates might cause bisphosphonate-osteonecrosis to be manifested exclusively in the jaws and is consistent with our finding of normal serum bone markers in ONJ patients. (**Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;106:389-91**)

Wilkinson et al.<sup>1</sup> have reported that users of intravenous bisphosphonates had an increased risk of inflammatory conditions, osteomyelitis, and surgical procedures of the jaw and facial bones. The increased risk may reflect an increased risk for osteonecrosis of the jaws (ONJ). Indeed, the estimated ONJ incidence among patients receiving zoledronic acid is 10% and the mean time to the onset of osteonecrosis among patients is 18 months.<sup>2</sup> This risk may increase for patients taking corticosteroids.<sup>3,4</sup>

The mechanism for bisphosphonate-induced ONJ is unclear. Migliorati et al.<sup>5</sup> have hypothesized that ONJ may be attributable to marked inhibition of bone remodeling that occurs with high doses of bisphosphonates, predisposing patients to osteonecrosis when there are additional demands on the bone that require remodeling or growth to maintain vitality.

The oral cavity is never aseptic and, hence, the necrosis observed in these patients may also involve the effects of host-bacterial interactions, including infection.

Coleman et al.<sup>6</sup> have studied patients with metastatic disease being treated with the intravenous bisphosphonate zoledronic acid. They showed that those patients with high and moderate N-telopeptide levels had 2-fold increases in their risk of skeletal complications and disease progression compared with patients with low N-telopeptide levels. Levels of N-telopeptide correlate with the rate of bone resorption. Bone resorption exceeding bone formation results in a net loss of bone and ultimately osteopenia or osteoporosis.

We wondered whether in bisphosphonate-treated patients with ONJ we might detect some derangement of N-telopeptide or other bone markers. If so, the ONJ might be due to a generalized change in bone metabolism that manifests itself in the oral cavity because of the acute stresses on bone there.

Bone markers detect products of bone resorption and formation. They are signs of the bone turnover process and may be used as an aid to bone mineral density testing when determining whether or not a patient might have a bone disease. Although one or more bone marker assays may be ordered to help identify patients with increased bone resorption and/or formation rates;

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**Table I.** Bone markers and other relevant endocrine assays for 5 patients with osteonecrosis of the jaw in this study

Assay	Normal
Calcitonin	
<2	pg/mL 0.0-5.0
TSH	
1.48 ± 1.01	μIU/mL 0.35-5.5
T4	
7.28 ± 1.89	μg/dL 4.5-10.9
T3	
94.00 ± 34.20	ng% 79-149
N-Telopeptide	
16.26 ± 3.59	PMOL/L 8.2-34.0
C-Telopeptide	
402.53 ± 241.34	pg/mL 32-580
Vitamin D 25 hydroxy	
35.60 ± 21.73	ng/mL 9.5-52.0
Alkaline phosphatase bone specific	
10.38 ± 4.18	μg/L 0.0-21.3
Osteocalcin	
7.30 ± 3.71	ng/mL 9.4-47.4
Intact parathyroid hormone	
66.00 ± 69.40	pg/mL 16.0-87.0

their routine role in clinical practice with bisphosphonate usage is unproven.

After Mount Sinai Institutional Review Board approval of our proposed study, we obtained bone markers and other relevant endocrine assays on 5 patients with ONJ. The markers and assays are those generally recommended for evaluation of osteopenia.<sup>7</sup> Diagnostic criteria for ONJ were those formulated by the American Association of Oral and Maxillofacial Surgeons.<sup>8</sup> Four of our patients were women. Two had metastatic breast cancer and had been treated with zoledronic acid; one had also received pamidronate. Two others had osteoporosis and had been treated with daily alendronate. One man had metastatic prostate cancer treated with zoledronic acid. Assay results are shown in Table I. All patients had been withdrawn from bisphosphonate for at least 6 months. None were taking or had taken corticosteroids. None of the lesions had shown any significant healing and all were still causing the patients considerable distress. Yet the bone markers were within the normal range as measured in our laboratory, except for intact parathyroid hormone, which was slightly elevated in one case of metastatic breast cancer (177 pg/mL).

Marx et al.<sup>4</sup> have proposed the following mechanism for ONJ. Because the jaws have a greater blood supply than other bones, and a high bone turnover rate related both to their daily activity and the presence of teeth (which mandates daily bone remodeling around the periodontal ligament), bisphosphonates are highly con-

centrated in the jaws. Coupled with chronic invasive dental diseases and treatments and the thin mucosa over bone, this anatomic concentration of bisphosphonates might cause osteonecrosis to be manifested exclusively in the jaws; that is, the exposed bone in the jaws is the direct result of the action of bisphosphonates on the daily remodeling and replenishment of bone. Our finding of normal serum bone markers in ONJ patients is consistent with the mechanism of Marx et al.<sup>4</sup>

A weakness in this mechanism is that it does not explain why bisphosphonates have a predilection for causing ONJ, while corticosteroids by themselves predispose to osteonecrosis of the femoral head but not ONJ.<sup>9,10</sup> Migliorati et al.<sup>5</sup> posited that there might be genetic differences that produce a unique response to bisphosphonates in susceptible individuals, and that genetic polymorphisms might account for an increased risk of bisphosphonate-associated ONJ. Perhaps these genetic differences and polymorphisms, occurring in osteocytes in the jaws, underlie the pathophysiology of bisphosphonate-induced ONJ. Also, it would be worthwhile to measure serum calcium levels, since Ardine et al.<sup>11</sup> have postulated that long-term persistence of low serum calcium levels and high serum parathyroid hormone levels during bisphosphonate treatment predispose metastatic breast cancer patients to undergo ONJ.<sup>11</sup>

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