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Periodontal Disease as a Risk Factor for Bisphosphonate-Related Osteonecrosis of the Jaw

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Abstract

Background—Previous case reports and animal studies suggest periodontitis is associated with bisphosphonate-related osteonecrosis of the jaw (BRONJ). We conducted a case-control study to evaluate the association between clinical and radiographic measures of periodontal disease and BRONJ.

Methods—25 BRONJ patients were matched with 48 controls. Trained examiners measured probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) on all teeth except third molars, and gingival and plaque indices on six index teeth. Alveolar bone height was measured from orthopantomograms. Most BRONJ cases were using antibiotics (48%) or a chlorhexidine mouthrinse (84%) at enrollment. Adjusted comparisons of cases vs. controls used multiple linear regression.

Results—The average number of BP infusions was significantly higher in BRONJ cases compared to controls (38.4 vs 18.8, $p=0.0001$). In unadjusted analyses, BRONJ cases had more missing teeth (7.8 vs 3.1, $p=0.002$) and high average CAL (2.18 vs 1.56 mm, $p=0.047$) and percent of sites with CAL ≥ 3 mm (39.0 vs 23.3, $p=0.039$) than controls. Also, BRONJ cases had lower average bone height (as a fraction of tooth length, 0.59 vs 0.62, $p=0.004$) and more teeth with bone height under half of tooth length (20% vs 6%, $p=0.001$). These differences remained significant after adjusting for age, sex, smoking, and number of bisphosphonate infusions.

Conclusions—BRONJ patients have fewer teeth, greater CAL, and less alveolar bone support compared to controls after adjusting for number of bisphosphonate infusions. Group differences in antibiotics and chlorhexidine rinse usage may have masked differences in the other clinical measures.

Keywords

Bisphosphonates; Periodontitis; Periodontal Disease; Alveolar Bone Loss; Osteonecrosis; Bisphosphonate-related osteonecrosis of the jaw

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Case reports suggest that periodontitis may predispose patients to developing bisphosphonate-related osteonecrosis of the jaw (BRONJ).¹⁻² In a seminal paper, Marx et al. noted that 84% of BRONJ patients had periodontal disease, including 29% with advanced disease.¹ Similarly a large chart review study by Hoff et al. noted a high prevalence (41%) of periodontitis in BRONJ patients.³ Ficarra et al. reported a series of nine patients with severe periodontal disease in whom BRONJ was noted following extraction of periodontally “hopeless” teeth.⁴

Periodontal pathogens also have been isolated from BRONJ lesions. In a retrospective study, Badros et al. identified *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Peptostreptococcus*, *Streptococcus sp.*, and *Eikenella* species in 9 of 17 BRONJ patients.² Lesions in the remaining 8 patients contained *Actinomyces* species. Likewise, Sedghizadeh et al. showed that bone sections from BRONJ sites contained microbial biofilms comprised predominantly of *Fusobacterium*, *Actinomyces*, *Staphylococcus*, *Streptococcus*, *Selenomonas* and *Treponemes* species.⁵ The contribution of these organisms to BRONJ development is unknown and it is important to determine whether specific bacteria contribute to BRONJ development or merely colonize previously exposed bone.

Researchers also have studied the role of periodontal disease in BRONJ development using animal models.^{6,7} Aghaloo et al. noted that 47% of zoledronate-treated rats showed histological and radiological evidence of osteonecrosis and 21% showed evidence of exposed bone in the presence of ligature-induced periodontitis, while none in the control group showed evidence of exposed bone.⁶ Similarly, Aguirre et al. noted that high doses of zoledronate exacerbated the inflammatory response and periodontal tissue damage, and induced BRONJ-like lesions in rats.⁷

Although observations in both humans and animals suggest that periodontal disease may affect risk for BRONJ development,^{2,8-10} there are few epidemiologic studies evaluating the association between periodontal disease and BRONJ in humans. Therefore, we conducted a case-control study to evaluate the association between clinical and radiographic measures of periodontal disease and BRONJ development.

MATERIALS AND METHODS

Study Population

The University of Minnesota and Park Nicollet Institutional Review Boards approved this study and written informed consent was obtained from all participants. Cancer patients above 30 years of age who had received intravenous bisphosphonate (BP) therapy for cancer management were eligible for the study. Patients with a history of either radiation therapy to the head and neck region or neoplasms (including metastasis) involving the head and neck region were excluded. Patients were recruited from oncology centers in Twin Cities area and from the University of Minnesota School of Dentistry from July 2007 through July 2012. Cases met the American Association of Oral and Maxillofacial Surgeon's criteria¹¹ for BRONJ: having “exposed bone in the maxillofacial area occurring in the absence of head and neck irradiation and showing no evidence of healing for at least 8 weeks after identification in patients treated with BP therapy.” The control group consisted of cancer patients who had received at least 10 intravenous BP infusions and had no evidence of BRONJ.

All participants underwent a comprehensive oral examination. One of two trained examiners (BSM and VTM) measured probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) at six sites on all teeth except third molars, and measured gingival index (GI) and plaque index (PI) on six index teeth.^{12,13} Alveolar bone height was

measured from digital or conventional orthopantomograms taken within 6 months of enrollment. Film images were scanned and converted into digital format at 600 dpi resolution. All images were analyzed using an imaging software program[§]. Mesial and distal bone heights (measured in pixels) were determined as a proportion of tooth length as described previously.¹⁴ A full-mouth bone-height score was computed for each participant by averaging mesial and distal proportions from all measurable teeth.

Statistical Analysis

Characteristics of cases and controls were compared using Fisher's exact test or Pearson's chi-squared test for categorical variables and using two-sample t-tests for continuous measures. Unadjusted comparisons used two-sample t-tests (checked by Wilcoxon signed-rank tests). Adjusted analyses used multiple linear regression. One set of adjusted analyses ("Adjusted analysis 1") adjusted for sex, age (entered linearly), and smoking (ever vs. never). A second set of adjusted analyses ("Adjusted analysis 2") also adjusted for number of bisphosphonate infusions, and also included the interaction of group with number of BP infusions, which allowed cases and controls to differ in the rate of change of the outcome with number of BP infusions. Controls had 43 or fewer infusions while cases had as many as 96, so the six cases with the most infusions (at least 60) were excluded from this second set of adjusted analysis, leaving only 19 cases with 48 or fewer infusions. Omitting these six cases reduced but did not eliminate the difference between cases and controls in average number of infusions.

Three BRONJ cases were edentulous and thus provided no data for clinical periodontal measures or bone loss, though they did provide data for number of missing teeth. A variant analysis of the clinical periodontal and bone-loss outcomes included these three participants by assigning them the worst possible score for each outcome and analyzing the ranks of outcomes.¹⁵ For all outcomes, the analyses excluding and including the edentulous participants gave qualitatively identical results, so we present only results from analyses excluding the edentulous participants. For each case with recent extractions, we "added back" teeth that were extracted just before developing BRONJ. No controls reported extractions shortly before study enrollment.

Finally, an analysis was done with case/control status as the outcome, using as potential predictors the number of intravenous BP infusions and some oral health measures; this was done using logistic regression with likelihood ratio tests.

RESULTS

Patient Characteristics

Clinical and radiographic data from 25 BRONJ cases and 48 controls were included in this study, though some data were missing because of edentulism or missing radiographs. Table 1 compares the groups according to patient characteristics. Cases and controls did not differ significantly in age, sex, race or smoking status. Also, the groups did not differ significantly in terms of diabetes mellitus prevalence ($p=0.66$) or corticosteroid use ($p=0.45$). All participants had received or were receiving intravenous zoledronate, pamidronate, or both. The average number of BP infusions was significantly higher in BRONJ cases compared to controls ($p=0.0001$). BRONJ cases also received BP therapy for a longer period, although the difference was not statistically significant ($p=0.23$). Most patients had received BP therapy for metastatic breast cancer management.

[§]Adobe Photoshop CS3 version 10, Adobe Systems Inc., San Jose, CA

At the time of sampling, BRONJ cases had discontinued BP therapy for an average of 11.4 months (range 2 to 30 months) following BRONJ diagnosis, while controls continued to receive intravenous BP therapy for cancer management.

BRONJ Characteristics

Table 2 lists salient characteristics of BRONJ participants. BRONJ was noted more frequently in the mandible (80%) than the maxilla (28%), although some participants exhibited lesions in both jaws. The posterior mandible was the most frequently affected site (56%). Tooth extraction was the most frequent precipitating factor for BRONJ development (64%). A few patients developed BRONJ following implant placement, root canal therapy, or restorative dental care, while others (24%) developed lesions spontaneously, i.e., in the absence of a preceding dental procedure. As part of BRONJ management, most cases were taking an antibiotic (penicillin, clindamycin, amoxicillin/clavulanate, or cephalexin) or using a 0.12% chlorhexidine mouth rinse at the time of enrollment.

Clinical Periodontal Measures

Table 3 summarizes the clinical periodontal findings in BRONJ cases and controls. In unadjusted analyses, BRONJ cases and controls did not differ significantly in terms of average PD, BOP, GI, PI, or percent of sites with probing depth 4–6 mm. However, the groups differed significantly for average CAL ($p=0.047$), percent of sites with PD >6 mm ($p=0.018$), and percent of sites with CAL ≥ 3 mm ($p=0.039$). Clinically, the difference in percent of sites with PD >6 mm was minimal (0.49 [SD 1.27] vs 0.03 [SD 0.24]).

Even after adding back teeth extracted from cases just before they developed BRONJ, cases had significantly more missing teeth than controls (mean 7.8 vs 3.1; $p=0.002$). After adjusting for age, sex, smoking, and number of BP infusions, cases and controls differed significantly for number of missing teeth (adjusted averages 8.3 [SE 1.4] vs 3.2 [SE 0.9] $p=0.004$), average CAL (adjusted averages 2.4 [SE 0.3] vs 1.6 [SE 0.2] $p=0.016$), and percent of sites with CAL ≥ 3 mm (adjusted averages 44.7 [SE 6.9] vs 24.8 [SE 3.9] $p=0.015$).

Radiographic Alveolar Bone Height

BRONJ participants had significantly less alveolar bone support than controls (Table 4). The average full-mouth bone score (average bone height as a fraction of tooth length) was slightly lower in cases compared to controls in both the unadjusted (0.59 vs 0.62, $p=0.004$) and adjusted analyses for age, sex, smoking and number of BP infusions (0.58 vs 0.63, $p<0.0001$). An average of 20% of teeth in BRONJ cases had bone scores $\leq 50\%$ compared to 6% in controls ($p=0.001$).

Predicting BRONJ Status Using BP Infusions and Alveolar Bone Height

In a multivariate analysis predicting case/control status and using as predictors the number of BP infusions and three oral health measures, the number of BP infusions ($P < 0.0001$) and average proportional bone height ($P = 0.007$) were significantly associated with BRONJ, while the number of missing teeth ($P = 0.93$) and average CAL ($P = 0.37$) were not. Odds ratios (95% confidence intervals) for a one-standard deviation change in these predictors were 12.9 (2.7 to 61.4) for 19 additional BP infusions and 4.2 (1.3 to 13.8) for a 4.5 percentage point decrease in proportional bone height.

DISCUSSION

Studying only participants who received intravenous BP therapy for cancer management, we found that BRONJ cases had more missing teeth, slightly but significantly greater extent and

severity of CAL, and less alveolar bone support when compared to non-BRONJ controls. We found no significant differences in GI, PI, BOP, or PD between groups, although the widespread use of antibiotics and antimicrobial mouth rinses in our BRONJ cases may have improved GI, PI, BOP and PD in this group. In the absence of mechanical periodontal therapy, antibiotics have been shown to have a greater effect on PD and BOP than CAL in patients with untreated periodontitis.¹⁹ Consistent with this, our cases tended to have more CAL than controls despite having similar PD, BOP, and plaque scores. Alveolar bone height, which is arguably less affected than clinical periodontal measures following antibiotic therapy, was significantly lower in our cases than controls.

Our findings regarding alveolar bone support are consistent with those of Yamazaki et al., who noted a significant association between BRONJ incidence and alveolar bone loss in patients receiving intravenous BP therapy.²⁰ Using radiographic alveolar bone loss measures to evaluate periodontal status, these authors found higher prevalence of severe periodontitis in BRONJ patients (20%) compared to non-BRONJ patients (7.4%). Patients who developed BRONJ had significantly higher median bone loss score compared to non-BRONJ patients. In contrast, Carmagnola et al. found no statistically significant difference between BRONJ cases and non-BRONJ controls in alveolar bone support.²¹ The sample size in the latter study, however, was small and BRONJ cases did tend to have more bone loss than controls.

A large longitudinal study by Vahsevanos et al. found that periodontitis did not increase risk for BRONJ in patients receiving intravenous BP therapy.²² The authors reported no statistically significant differences between BRONJ patients and non-BRONJ patients in supragingival or subgingival calculus deposits or in the frequency of PD 4–5 mm and PD ≥ 6 mm, although a higher fraction of cases than controls had deeper pockets. Similarly, based on radiographic evaluation, Estilo et al. did not find an association between BRONJ and periodontal disease in a subset of 28 BRONJ and 282 non-BRONJ patients.²³ In addition, Lazarovici et al., in a case series of 101 BRONJ patients, noted that only 7 had a history of periodontal disease in the BRONJ affected area.²⁴ However, this study does not report the incidence of periodontal disease in other areas of the oral cavity.

Although several studies, including ours, did not find an association between certain periodontal measures and BRONJ, some evidence suggests that oral infections affect BRONJ risk. Hoff et al estimated that the risk of developing BRONJ is about 7-fold higher in patients with a history of periodontal infection and dental abscesses.³ BRONJ lesions also respond well to antibiotics and antimicrobial mouth rinses,^{25,26} and prophylactic antibiotics may reduce the incidence of BRONJ after dental procedures.²⁷ Numerous histological reports also illustrate that infection is a near-universal finding in BRONJ specimens.^{2,5,28–30} Recently, an animal model evaluated the effects of *Fusobacterium nucleatum*, a prevalent periodontal pathogen, in BRONJ development.³¹ In pamidronate treated rats, tooth extraction followed by oral infection with *F. nucleatum* caused BRONJ-like lesions and delayed epithelial healing, both of which were completely suppressed by a broad-spectrum antibiotic cocktail. The combination of *F. nucleatum* and pamidronate affected gingival fibroblast and keratinocyte growth factor (essential for epithelial regeneration), which resulted in delayed epithelial healing combined with bone death. Collectively, these findings in humans and animals suggest a role of dental infection in BRONJ development.

In the present study, all participants were cancer patients receiving multiple chemotherapy regimens and were at least 50 years old. Both advanced age and chemotherapy-induced immunosuppression are risk factors for periodontal disease.^{32,33} Consistent with previous reports, we found that the number of BP infusions was significantly associated with BRONJ development.^{3,34,35} Barasch et al have suggested that risk for BRONJ begins within 2 years of BP initiation and increases four-fold after 2 years of BP therapy.³⁶ We also noted that

tooth extraction was a common inciting factor for BRONJ development. This is in agreement with other published reports that have frequently noted BRONJ following extraction of un-restorable teeth including teeth with active periodontal disease or periapical infection.^{4,11,25,37} In the absence of effective bone resorption, conditions like tooth extraction and dental infection might result in tissue death, vascular loss, and eventually osteonecrosis. Furthermore, we noted BRONJ cases had more missing teeth than controls. It is unknown if BRONJ cases in the present study lost their teeth due to periodontal disease, dental caries or other factors. Also, it is unknown how many individuals in each group received periodic periodontal therapy during their BP treatment phase.

Recently, two studies have found that preventive dental measures initiated before the start of BP therapy reduced the incidence of BRONJ in cancer patients.^{38,39} Dimopoulos et al. followed 90 multiple myeloma patients who received dental treatment and oral preventive care before receiving zoledronic acid.³⁴ When compared to a group who had not received any prior dental interventions, these investigators found that the treated group had a three-fold reduction in BRONJ incidence. Similarly, Ripamonti et al. found a lower incidence of BRONJ in solid tumor patients who received preventive dental measures before BP initiation when compared to an earlier group that did not receive pre-infusion dental care.³⁵ In both studies, however, patients who were followed before and after preventive dental measures differed in terms of type and duration of BP treatment, which could have confounded the study results. In general though, these findings reinforce the notion that early removal of potential sources of infection (for example, tooth extraction) reduces the incidence of BRONJ development. Furthermore, the American Dental Association recommends that patients on antiresorptive therapy who have active periodontal disease should receive appropriate forms of nonsurgical periodontal therapy combined with periodontal re-evaluation every four to six weeks.^{40,41} Since tooth extractions constitute a risk factor for BRONJ, patients are advised to receive frequent dental care to minimize the risk for tooth loss from caries or progressive periodontitis. Furthermore, when possible, practitioners are advised to use atraumatic techniques to minimize dentoalveolar manipulation.^{40,41}

In conclusion, results from this case-control study indicate that higher BP infusions, increased missing teeth, and larger CAL and alveolar bone loss are associated with BRONJ risk. Antibiotics and chlorhexidine mouth rinse usage in BRONJ participants may have eliminated or reduced the differences in GI, PI, BOP, and PD between BRONJ cases and controls. Despite attempts to match cases and controls according to BP exposure, the number of BP infusions differed significantly between BRONJ cases and controls. Nevertheless, differences between cases and controls in the unadjusted analysis have a similar trend to those in analyses adjusted for age, sex, smoking, and BP infusions. Adjusting for age, sex, smoking, and number of BP infusions significantly increased the estimated differences between cases and controls in average CAL and percent of sites with CAL ≥ 3 mm compared to analyses adjusted only for age, sex, and smoking. The effect of adjusting for number of BP infusions could be attributed to the antiresorptive function of BPs, which has been shown to improve periodontal disease status and bone turnover.^{16–18} Furthermore, it is unclear if discontinuation of BP therapy in BRONJ cases before study enrollment could have affected our results. As a standard practice, patients are advised to discontinue BP treatment and are prescribed antibiotics and chlorhexidine mouth rinse as soon as they are diagnosed with BRONJ. The causative role of periodontitis in BRONJ development needs to be further explored in future prospective trials.

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Table 1

Patient characteristics

Characteristic	BRONJ (N=25)	Non-BRONJ (N=48)	P-value
Age - mean (sd), in years	66.3 (10.3)	64.4 (11.7)	0.50
Sex – no. (%)			
Female	16 (64%)	34 (71%)	0.60
Race – no. (%)			1.00
White	24 (96%)	46 (96%)	
Black	1 (4%)	2 (4%)	
Malignant Disease – no. (%)			0.020
Breast cancer	13 (52%)	27 (56%)	
Multiple myeloma	4 (16%)	15 (31%)	
Prostate cancer	2 (8%)	6 (13%)	
Lung cancer	2 (8%)	0 (0%)	
Renal cell carcinoma	3 (12%)	0 (0%)	
Others	1 (4%)	0 (0%)	
Pre-existing medical conditions – no. (%)			
Diabetes mellitus	1 (4%)	5 (10%)	0.66
Hypertension	11 (44%)	26 (54%)	0.47
Hypercholesterolemia/Hyperlipidemia	11 (44%)	15 (33%)	0.45
Hypothyroidism	7 (28%)	10 (21%)	0.56
Previous medications – no. (%)			
Corticosteroids	14 (56%)	32 (67%)	0.45
Smoking Status – no. (%)			0.11
Current	5 (20%)	3 (6%)	
Former	11 (44%)	18 (38%)	
Never	9 (36%)	27 (56%)	
Type of Bisphosphonates – no. (%)			0.71
Zoledronate	16 (64%)	32 (67%)	
Pamidronate	2 (8%)	6 (13%)	
Pamidronate + Zoledronate	7 (28%)	10 (21%)	
Bisphosphonate infusions – mean (sd)			
All cancer	38.4 (26.3)	18.8 (7.2)	< 0.0001
Duration of Bisphosphonate exposure – mean (sd) in months			
All cancer	45.1 (29.7)	37.7 (21.9)	0.23

Table 2

BRONJ Characteristics

Characteristics	BRONJ (N=25)
Location – no. (%)	
Maxilla	7 (28%) [*]
Mandible	20 (80%)
Anterior sextant	4 (16%)
Posterior sextant	22 (88%)
BRONJ onset – no. (%)	
Tooth extraction	16 (64%)
Spontaneous	6 (24%)
Other [†]	3 (12%)
BRONJ Treatment – no. (%)	
Antibiotics at enrolment	12 (48%)
Antimicrobial rinse at enrolment	21 (84%)

^{*} Some participants had BRONJ in more than one location

[†] Other events precipitating BRONJ onset included implant placement, root canal therapy, and crown preparation

Table 3
Comparisons of Clinical Periodontal Measurements [mean (SD)] Between Cases and Controls

	Unadjusted average (SD)		P-value for case vs. control		
Characteristic	BRONJ (N=25)	Non-BRONJ (N=48)	Unadjusted Analysis	Adjusted Analysis 1 [†]	Adjusted Analysis 2 [¶]
Number of missing teeth [*]	7.8 (8.2)	3.1 (4.6)	0.002	0.011	0.004
Mean Plaque Index	0.40 (0.29)	0.55 (0.41)	0.13	0.064	0.41
Mean Gingival Index	0.54 (0.25)	0.58 (0.31)	0.62	0.47	0.84
Bleeding on Probing (%)	12.0 (15.4)	14.9 (12.8)	0.42	0.37	0.62
Mean full-mouth PD (mm)	2.07 (0.34)	2.11 (0.31)	0.60	0.40	0.81
Mean full-mouth CAL (mm)	2.18 (1.55)	1.56 (0.99)	0.047	0.11	0.016
% Sites PD 4–6 mm	5.0 (4.6)	4.8 (6.5)	0.87	0.76	0.70
% Sites CAL ≥ 3 mm	39.0 (35.9)	23.3 (25.3)	0.039	0.10	0.015

^{*} Out of 28, i.e., not counting 3rd molars. Teeth extracted shortly before BRONJ development are not counted as missing

[†] Adjusted for age, sex, and smoking status (ever vs. never)

[¶] Adjusted for age, sex, smoking status (ever vs. never), and number of BP infusions (analyses excludes six BRONJ cases who received 60 or more infusions)

Comparisons of Radiographic Alveolar Bone Height [mean (SD)] Between Cases and Controls (N=66)[‡]

Characteristic	Unadjusted average (SD)		P-value for case vs. control		
	BRONJ (N=25)	Non-BRONJ (N=48)	Unadjusted Analysis	Adjusted Analysis 1 [†]	Adjusted Analysis 2 [¶]
Average bone height*	0.59 (0.06)	0.62 (0.03)	0.0041	0.0224	<0.0001
Fraction teeth bone height 0.50*	0.20 (0.23)	0.06 (0.09)	0.0013	0.0115	<0.0001

[‡] Seven participants were excluded from the analysis: three were edentulous and four did not have bone height measures

* Considering a maximum of 28 teeth, i.e., not counting 3rd molars

[†] Adjusted for age, sex, and smoking status (ever vs. never)

[¶] Adjusted for age, sex, smoking status (ever vs. never), and number of BP infusions (analyses excludes six BRONJ cases who received 60 or more infusions)