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Dental risk factors for osteonecrosis of the jaws: A CONDOR case–control study

A. Barasch, DMD, MDSc[1], **J. Cunha-Cruz, DDS, PhD**[2], **F. Curro, DMD, PhD**[3], **T. DeRouen, PhD**[4], **G. H. Gilbert, DDS, MBA**[5], **P. Hujoel, MSD, PhD**[6], **M. M. Safford, MD**[7], **D. A. Vena, BS**[8], **A. E. Voinea-Griffin, DDS, MHSA, MBA**[9], **H. Wu, MPH**[10], and **for the CONDOR Collaborative Group**

[1]Chair, Dept. of Dental Medicine, Winthrop University Hospital, Mineola, NY [2]Research Assistant Professor, University of Washington School of Dentistry, Seattle [3]Clinical Professor, New York University College of Dentistry, New York [4]Professor and Acting Dean, University of Washington School of Dentistry, Seattle [5]Professor and Chair, Dept. of General Dental Sciences, University of Alabama at Birmingham School of Dentistry, Birmingham, Alabama [6]Professor, University of Washington School of Dentistry, Seattle Statistician, The EMMES Corporation, Rockville, Maryland [7]Associate Professor at University of Alabama at Birmingham School of Medicine [8]The EMMES Corporation, Rockville, Maryland [9]PhD candidate, University of Alabama at Birmingham [10]The EMMES Corporation, Rockville, Maryland

Abstract

Background—Reports of osteonecrosis of the jaw (ONJ) have associated this lesion to treatment with bisphosphonates (BPs) and dental procedures. In this study, we investigated the association of specific dental diagnoses and procedures with ONJ among patients with past BP use.

Methods—Dentists from three Practice-Based Research Networks provided ONJ cases and controls (1:3). Data gathered from patients and dental offices with two respective standard questionnaires included demographic, medical, pharmaceutical, and dental information. Diagnoses and procedures up to three years prior to ONJ (prior to interview for controls) were analyzed within risk strata, defined by BP use and cancer status, using interaction terms within conditional logistic regression models.

Results—We enrolled 191 ONJ cases and 573 controls from 119 dental offices. Among participants who had used *only oral BP*, extraction was the only dental risk factor for ONJ (OR=12, p=0.01). Suppuration was also more prevalent in cases (18%) than in controls (9%), but not statistically significant (OR=9, p=0.06).

Among participants who had *not used either oral or IV BP* (a majority of whom received RT to the head and neck), suppuration was the only dental risk factor for ONJ (prevalence=34% for cases and 8% for controls; OR=7, p=0.01). The prevalence of extractions in this group was also higher, but not statistically significant (44% vs 10%; OR=3). Limited power precludes definitive findings among participants exposed to IV BP.

Conclusions—Among patients taking oral BP, extraction was the only dental procedure associated with subsequent ONJ development.

Corresponding author: Dr. Andrei Barasch, Winthrop University Hospital, 222 Station Plaza N, suite 408, Mineola, NY 11501, abarasch@winthrop.org.

The authors declare no conflict of interest.

Clinical Relevance—Results of this study suggest that routine dental procedures are not associated with development of ONJ in patients exposed to BPs.

Keywords

Osteonecrosis; jaws; bisphosphonates; dental diagnosis; dental treatment; risk factors

INTRODUCTION

Since 2003, an unusually large number of case reports and case series have described what appeared to be either spontaneous osteonecrosis of the jaws (ONJ)[1] or more commonly, ONJ following dental treatment among individuals with a history of exposure to bisphosphonates (BPs).[2–7] Bisphosphonates are a commonly used class of drugs that inhibit osteoclast activity and may have antiangiogenic properties.[8–10] BP effects on suppressing bone remodeling make these drugs a prime suspect for osteonecrotizing processes.[11,12] However, the etiology of jaw bone osteonecrosis in patients exposed to BPs has not been fully elucidated. Postulated mechanisms of disease include endothelial damage,[10–12] overmineralization of bone and microcracks.[13] The exact role of each of these processes remains unclear.

An increasing body of evidence suggests that BP therapy is a true risk factor for ONJ[14,15] and that “dental problems” may play a significant role in the development of these lesions. A recent comprehensive review of existing studies concluded that risk factors for ONJ consisted of exposure to nitrogen-containing BP, dental extractions and trauma from inadequate dentures.[16] Nevertheless, in most of the reviewed publications dental histories were poorly documented, if documented at all.[15,16] As a consequence, practice guidelines for dentists treating patients on BP are based on anecdotal data.

The current case–control study was performed in three U.S.-based dental Practice-Based Research Networks (PBRNs) with the overall objective of determining risk factors for ONJ, including demographics, medical conditions, drug exposures, and dental diseases and treatments[14]. This article investigates the hypothesis that specific dental diseases and treatments are independently associated with ONJ within subsets of patients who have been exposed to BP and within those not exposed to BP or radiation therapy to the head and neck (RT).

METHODS

This 1:3 case–control study was a collaboration of three NIH-funded dental PBRNs, which are centered at the University of Alabama at Birmingham (DPBRN), New York University (PEARL), and the University of Washington at Seattle (NW PRECEDENT). These programs have an established infrastructure for practice-based research, and between them include more than 3,000 academic and community dentists. A common protocol was formulated and implemented at all sites between September 2006 and March 2009. The joint protocol was approved by each PBRN’s ethics committee.

Methods for this study are described in detail elsewhere[14] and are briefly described herein. Study subjects were primarily drawn from community dental practices within the geographic areas served by the PBRNs. General dentists and dental specialists, both from among and beyond the members of the networks, were informed about the study through mass mailings and word of mouth. Practitioners who had diagnosed ONJ cases and were interested in participating were asked to contact the respective network.

Case selection

Inclusion criteria were age 40 years or older and a diagnosis of ONJ made by a participating dentist. Exclusion criteria were a history of recent facial trauma or sickle cell disease. An ONJ lesion was defined as maxillary or mandibular exposed bone of any size that clinically appeared necrotic, without regard to duration or causation. Radiographic or microscopic findings were not considered in the definition of ONJ, as their reliability and consistency have not been proven.[17] The cases originated from primary, secondary, or tertiary care centers. Subsequent to the identification of a case, the treating practitioners were asked to contact the patient verbally to ask permission for contact by the researchers, who then obtained informed consent.

Control selection

We aimed to select controls from the same primary care practice where a case was initially diagnosed. Patients treated in the practice and of age 40 years or older represented the sampling frame for selection of controls. Patients were selected from this frame and invited to participate until 3 controls were enrolled for every case. For ONJ cases that were sampled from secondary care centers, controls were selected from the general dental practice that referred the case or, if this was not possible, from a general practice in the same geographic area. For ONJ cases that were sampled from tertiary care centers, the controls were selected from the patient's primary dental practice or from a participating dental practitioner in the same geographic area.

Data collection

Two standardized instruments (a dental history form and a patient questionnaire) were used to collect medical, dental, and sociodemographic information. Both forms are publicly available at http://www.dentalpbrn.org/users/publications/Supplement.aspx. The dental history form was completed by the dentist and focused on oral clinical signs, symptoms, diagnoses, and procedures rendered between 2000 and 2007 that preceded the diagnosis of ONJ by a maximum of 3 years. For example, if a patient was diagnosed with ONJ in 2007, the questionnaire covered the period from 2004 to 2007. We obtained data on oral hygiene, tooth loss, periodontal disease, caries, endodontic problems, gingival bleeding, suppuration, pain or sensitivity, as well as neurosensory disturbances. Information on dental procedures and dates of their performance was also collected. For quality control purposes, 10% of dental charts were reabstracted by a trained research assistant, and a 98% concordance was found with the initially abstracted data. Additional information was found in 2% of the reabstracted charts.

The patient questionnaire was a standardized telephone interview conducted by trained research assistants at each PBRN. It assessed ONJ characteristics (location in the mouth, date of onset, size, pain, duration, healing), as well as oral hygiene, oral diseases, and dental treatments performed after January 1, 2000 (extraction, surgeries, dentures, endodontics, orthodontics, periodontics, trauma), medical history (cancers, radiotherapy, bone diseases), occupational exposures (chemical industry work, white phosphorus exposure), demographics, education, and lifestyle (race/ethnicity, alcohol and smoking history), and medications (oral and/or IV bisphosphonates, chemotherapy, antiretroviral medication, steroids, regular use of other drugs).

Exposures

The exposures addressed in this article are more descriptive of private practice and include BP treatment, dental diagnoses and procedures, and a history of head and neck cancer treatment with ionizing radiation. Other exposures captured in this study are presented

elsewhere[14] and include diagnosis of cancer or osteoporosis, coexisting chronic diseases, and long-term use of systemic corticosteroid medication. Duration, frequency, dose, and dose scheduling of each bisphosphonate and the specific details of exposure were collected using the patient interview.

Dental procedures occurring prior to lesion development but within the same dental quadrant as the ONJ were labeled as "matched" procedures, whereas those in uninvolved quadrants were "unmatched." Data on all dental visits, diagnoses, and procedures were abstracted from the primary dentists' charts. If patients were referred for treatment elsewhere, those providers were contacted and information was obtained regarding additional diagnoses and procedures.

Statistical considerations

Conditional logistic regression models were used to evaluate the predictive ability of oral hygiene habits, oral conditions, and dental treatments on the development of ONJ (SAS procedure LOGISTIC, SAS Institute, Cary, NC) in a matched case/control setting. Main effects analysis was used to identify the primary factors associated with ONJ. BP use was classified as none, only oral BP (no IV BP), and any IV BP (including 24 subjects who had received both oral and IV BP). Interaction analysis of BP use classification with each potential dental risk factor, adjusted for observed main effects, was used to evaluate the relationship between ONJ and oral hygiene habits, specific oral conditions, and dental treatments.

RESULTS

The three networks identified 308 ONJ cases, of which 117 either refused participation or could not be contacted for interviews. One hundred ninety-one cases completed the survey and were eligible for final analyses together with 573 controls. Demographic characteristics and associations of BP, other medications, and medical conditions are presented in detail elsewhere.[14] Briefly, all BP medications were significantly associated with development of ONJ. These ORs were greater for the more potent BPs typically administered intravenously to cancer patients (>999.9), but still quite large for the orally administered BPs as well (12.2). Two other covariates were associated with ONJ after regression analysis: head and neck therapeutic radiation and anemia.[14]

Before the onset of ONJ, 51% of the cases had used intravenous (IV) BP (with or without oral BP) (n=98), 30% had used only oral BP (n=57) and 17% had not used BP (n=32). Before the index date, 1% of the controls had used intravenous BP (with or without oral BP) (n=7), 14% had used only oral BP (n=79) and 83% had not used BP (n=475). BPs containing a nitrogen chain or ring conferred significantly higher risk for ONJ (OR 15.2 and 178.4, respectively, $p<0.001$).[14] Within those not exposed to BP, 56% of cases and 4% of controls had received radiation to the head and neck, while 12% of cases and 9% of controls had received RT in the oral BP only group, and 20% of cases and no controls in the IV BP group.

ONJ lesion characteristics among the 191 cases are presented within BP use group in Table 1. Overall, most cases were single lesions (76%) diagnosed in 2006–2007 (54%), and smaller than a dime in size (59%). Regarding duration, lesions had been present for longer than 8 weeks in 64% of the cases, less than 8 weeks in 15%, and undetermined in 21% of the cases. Most lesions (58%) were asymptomatic prior to bone exposure, but became painful by the time of diagnosis (64%). ONJ characteristics were similar across the three subgroups although the IV BP patients reported fewer healed lesions (23%) than those not exposed to BP (47%) and those on oral BP (53%).

Distribution of oral hygiene characteristics, oral conditions, dental treatments, and radiation to the head and neck within case/control and BP use categories are provided in Table 2. Both the oral only and IV BP groups were older (64 and 60 vs. 53 years old), had more females (89% and 76% vs. 69%) compared with the No BP subgroup. A history of cancer was reported among 22% of the No BP subgroup vs. 40% and 92% of the oral only and any IV BP subgroups, respectively.

Interaction analyses, adjusted for radiation to the head and neck, suppuration, and extraction are presented in Table 3. Among participants who had used only oral BP, extraction was the only dental risk factor for ONJ (prevalence= 39% for cases and 8% for controls; OR=12, p=0.01). Suppuration also was more prevalent in cases (18%) than in controls (9%), but was not statistically significant (OR=9, p=0.06). Among participants who had not used BP, neither oral nor IV, suppuration was the only dental predictor for ONJ (prevalence=34% for cases and 8% for controls; OR=7, p=0.01). Extraction also was more prevalent in cases (44%) than in controls (10%), but was not statistically significant (OR=3, p=0.13).

Conditional logistic regression with an interaction term between radiation therapy to the head and neck and each dental risk factor adjusting for suppuration, extraction, and BP use is presented in Table 4. Among patients who did not receive radiation, both suppuration (OR=8, p<0.001) and extraction (OR=5, p<0.001) were associated with an increased risk of ONJ.

Due to the small number of controls who had used *IV BP* (n=7), the effect of oral conditions and treatments on ONJ among the participants who had used IV BP could not be reliably estimated. Among patients with IV BP, 21% had suppuration, 43% had extraction and 15% had endodontic treatment, while no controls who had used IV BP had suppuration, extraction or endodontic treatment.

DISCUSSION

The first report of ONJ associated with BP treatment was published in 2003[7] and was quickly followed by others.[5,6] These articles described patients with metastatic bone disease or multiple myeloma who had developed necrotic lesions (mostly dental treatment–related, but also spontaneous) of their jawbones. Following these initial articles, similar reports were published in quick succession, showing ONJ in BP-treated patients to be more common than anticipated.[1–4,20] Most of these publications described non–population-based, case reports, retrospective studies, or case series, and few were able to provide clear epidemiological associations. We present here results of dental factors associated with development of ONJ in subgroups of patients selected to help guide dentists treating patients who present for dental procedures in the presence of BP use.

The fact that dental extractions and local suppuration were associated with ONJ is not surprising and confirms previous findings.[15] However, our results also suggest that oral hygiene, and common dental diseases and treatments are not significant risk factors for lesion development. These results must not be generalized though, as some specific dental procedures (e.g. implants) had a low prevalence in our population and hence, the power was insufficient to detect effects.

Suppuration was observed as the only significant factor among ONJ patients not using BP, although a majority of these cases had been exposed to radiation therapy to the head and neck. Extraction was a significant risk factor (OR=13) for ONJ among oral only BP users, while suppuration was marginally significant with an OR=9. Surgical procedures other than extractions were not associated with ONJ.

The current study was not designed to determine the prevalence or incidence of ONJ. A recent article[21] analyzed previously published data for ONJ among BP treated osteoporosis patients and reported an incidence of 0.028% to 4.3%. However, new analyses of two large datasets produced an estimated incidence of 0.02% and 0% among the same type of patients. These retrospective results have numerous limitations and are likely to underestimate the true incidence of disease due to strict inclusion criteria. In their report, Otto et al[22] found that 7.8% of the ONJ lesions among an European cohort of bisphosphonates-treated patients were in oral only BP users. Hence, the incidence of ONJ may vary but appears to be quite low in patients exposed to oral BP. Nevertheless, results of our study strongly suggest that oral BPs are a significant risk factor for development of the lesion.

The presentation of lesions in this study largely confirms previous findings,[15,23,24] as in most patients they were single, relatively small, and longer than 8 weeks in duration. We note however that 15% of the cases had a documented duration of fewer than 8 weeks. As the diagnosis of ONJ is clinical and the appearance of necrotic bone is distinct, we believe that these lesions are bona fide ONJ and should not be excluded solely on the basis of their duration.

All cases of osteonecrosis were analyzed in the current study in light of our desire to include all possible risk factors for development of such lesions. As expected, therapeutic radiation for head and neck cancer was significantly associated with development of necrosis in the jawbone. This finding confirms that osteoradionecrosis remains a possible side effect of radiation therapy in the age of intensity-modulated exposure and that post-radiation extractions may be a major risk factor.[25]

Results of this study must be interpreted considering its limitations, which include the case-control study design and heterogeneity of its clinician-investigators and patient population.

CONCLUSIONS

Results of this study add to the evidence base for ONJ and can help dental providers draw the profile of patients at high risk for developing the lesion. Patients exposed to oral or IV BP are at significantly higher risk for developing ONJ after dental extractions. However, other common dental procedures such as restorative, endodontic and periodontal procedures, do not appear to increase the risk for ONJ. Suppuration should always be considered an important clinical finding and may be even more relevant for those patients on BP.

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TABLE 1

ONJ characteristics by BP use

ONJ Characteristics	No BP (n=32)	Only Oral BP (n=57)	Any BP (n=98)
Number of quadrants with lesions			
Missing	3%	4%	5%
0	6	2	5
1	81	81	70
2	6	12	15
≥3	3	2	4
Maximum length of bone exposure (weeks)			
Missing	25%	16%	24%
< 2	3	2	0
2–3	0	4	3
4–5	6	5	2
6–7	6	9	3
≥ 8	59	65	67
Maximum size of all lesions			
Missing	25%	21%	26%
Dime or smaller	56	58	61
Quarter	9	14	6
Larger than a quarter	9	7	7
Lesion characteristics			
Any tingling pain prior to lesion	50	28	36
Spontaneous bone exposure	53	54	48
Pain at the time bone became exposed	56	65	57
Medication use for ONJ	84	72	69
Healed	47	53	23

Table 2

Description of cases and controls by BP use *(note: few cases and controls had perio surgery, endo and implants)*

		CASES				CONTROLS			
		BP use				BP use			
		None	Only oral	Any IV	All	None	Only Oral	Any IV	All
		N = 32 %	N = 57 %	N = 98 %	N = 187 %	N = 475 %	N = 79 %	N = 7 %	N = 561 %
Age	Mean (SD)	59.8 (11.6)	67.2 (10.4)	60.1 (10.9)	62.1 (11.3)	52.9 (11.0)	62.1 (10.2)	55.9 (12.2)	54.2 (11.4)
Gender									
	Male	75	14	23	29	39	9	29	35
	Female	25	86	77	71	61	91	71	65
Brushing									
	Missing						1	.	
	Once or more per day	94	100	95	96	96	95	86	95
	Less than once per day	6	.	5	4	4	4	14	4
Flossing									
	Missing	.	2	1	1	.	1	.	
	Once or more per day	28	39	35	35	34	37	29	34
	Less than once per day	72	60	64	64	66	62	71	66
Rinsing									
	Missing	66	37	33	39	11	14	.	11
	4 or more times per week	13	21	21	20	26	33	43	27
	3 or less times per week	22	42	46	41	63	53	57	62
Periodontal disease									
	Missing	16	30	17	21	17	11	.	16
	Yes	28	9	11	13	12	16	14	13
	No	56	61	71	66	71	72	86	71
Gingivitis									
	Missing	13	25	16	18	7	11	14	8
	Yes	31	30	38	33	44	41	29	43

		CASES				CONTROLS			
		BP use				BP use			
		None	Only oral	Any IV	All	None	Only Oral	Any IV	All
		N = 32 %	N = 57 %	N = 98 %	N = 187 %	N = 475 %	N = 79 %	N = 7 %	N = 561 %
	No	56	46	46	48	49	48	57	49
Suppuration									
	Missing	9	21	15	16	9	11	29	9
	Yes	34	18	21	22	8	9	.	8
	No	56	61	63	62	84	80	71	83
Endodontic problems									
	Missing	9	21	16	17	9	15	14	10
	Yes	31	32	35	34	27	20	29	26
	No	59	47	49	50	64	65	57	64
Caries									
	Missing	13	19	15	16	7	11	29	8
	Yes	50	46	40	43	51	46	14	50
	No	38	35	45	41	42	43	57	42
Extraction									
	Missing	.	.	.					
	Region matched to ONJ	44	39	43	42	10	8	.	9
	No/ mismatched treatment	56	61	57	58	90	92	100	91
Perio surgery									
	Missing	.	2	.	1				
	Region matched to ONJ	13	4	.	3	2	3	.	2
	No/ mismatched treatment	88	95	100	96	98	97	100	98
Endodontic treatment									
	Missing	.	2	.	1				
	Region matched to ONJ	13	14	15	14	9	5	.	9
	No/ mismatched treatment	88	84	85	85	91	95	100	91
Implants									

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			CASES				CONTROLS			
			BP use				BP use			
			None	Only oral	Any IV	All	None	Only Oral	Any IV	All
			N = 32 %	N = 57 %	N = 98 %	N = 187 %	N = 475 %	N = 79 %	N = 7 %	N = 561 %
		Missing	.	4	.	1	.	.	.	
		Region matched to ONJ	.	7	1	3	1	1	.	1
		No/ mismatched treatment	100	89	99	96	99	99	100	99
History of cancer										
	Yes		63	46	96	75	19	35	43	22
	No		37	54	4	25	81	65	57	78
Radiation to the head and neck										
		Missing	0	2	2	2	0	1	0	0
		Yes	56	12	20	25	4	9	0	5
		No	44	86	78	74	96	90	100	95

Table 3

Interaction between BP use and dental risk factors*

	OR of ONJ among No BP use				OR of ONJ among Only oral BP use				OR of ONJ among IV BP use (+-oral)			
	OR	**95%**	**CI**	**p-value**	**OR**	**95%**	**CI**	**p-value**	**OR**	**95%**	**CI**	**p-value**
Brushing	0.54	0.05	5.60	0.61					2.37	0.10	58.04	0.60
Flossing	1.41	0.42	4.75	0.58	2.35	0.55	10.04	0.25				
Rinsing	0.71	0.11	4.76	0.72	0.66	0.11	4.05	0.65	0.68	0.04	13.17	0.80
Perio disease	2.24	0.50	9.96	0.29	0.98	0.08	12.42	0.99	0.12	0.00	12.88	0.38
Gingivitis	0.39	0.10	1.55	0.18	0.52	0.14	1.91	0.33				
Suppuration	7.43	1.71	32.28	0.01	9.21	0.92	92.01	0.06				
Endodontic problems	1.63	0.47	5.70	0.44	0.59	0.14	2.48	0.47	43.47	0.00	>999.9	0.43
Caries	0.72	0.15	3.48	0.69	0.74	0.14	4.00	0.73				
Extraction (matched region)	2.84	0.73	11.06	0.13	12.65	1.69	94.49	0.01				
Perio surgery (matched region)					-				-			
Endodontic treatment (matched region)	1.13	0.20	6.49	0.89	1.37	0.17	11.11	0.77				
Implants (matched region)					21.78	0.00	>999.9	0.51				

*adjusted for significant main effects: , radiation to the head and neck

Table 4

Interaction between radiotherapy and dental risk factors*

	OR of ONJ among No radiation				OR of ONJ among Radiation			
	OR	**95%**	**CI**	**p-value**	**OR**	**95%**	**CI**	**p-value**
Brushing	3.59	0.46	28.00	0.22	1.33	0.01	185.88	0.91
Flossing	2.51	0.95	6.67	0.06	0.13	0.01	2.38	0.17
Rinsing	0.94	0.23	3.77	0.93	0.19	0.01	4.21	0.30
Perio disease	3.00	0.66	13.61	0.15				
Gingivitis	0.54	0.19	1.53	0.25	0.04	0.00	0.95	0.05
Suppuration	8.17	2.12	31.53	0.00	6.11	0.13	281.03	0.35
Endodontic problems	1.47	0.55	3.94	0.45	0.15	0.01	3.74	0.25
Caries	0.86	0.24	3.12	0.81				
Extraction (matched region)	4.86	1.68	14.08	0.00	13.38	0.73	246.06	0.08
Perio surgery (matched region)	3.40	0.21	55.04	0.39				
Endodontic treatment (matched region)	1.21	0.32	4.57	0.78				
Implants (matched region)	1.08	0.07	15.73	0.96				

*adjusted for significant main effects: , BP use