

Clinical Study

Osteoporosis and Bisphosphonate-Related Osteonecrosis of the Jaw Bone

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The aim of this longitudinal study is to present data from 76 female patients treated with bisphosphonates (BPs) for postmenopausal osteoporosis and referred to the Unit of Oral Diagnosis and Day Surgery of the University of Milano for diagnosis and treatment. All patients received a thorough oral examination. The diagnosis of osteonecrosis of the jaw bone (ONJ) was made from radiographic and clinical findings. 9% of individuals had BRONJ at first visit. Patients with dental or periodontal abscess were significantly more likely to develop BRONJ (OR: 2.9, 95% CI 0.5–15.9). Patients with osteoporosis receiving BPs may develop BRONJ, especially in the presence of an active infectious process in the mouth. Clinicians should carefully follow up on individuals receiving bisphosphonates therapy to avoid the occurrence of osteonecrotic lesions.

1. Introduction

Postmenopausal osteoporosis is a systemic skeletal condition that affects many millions of women around the world. The National Institutes of Health Consensus Conference defined osteoporosis as a disease of increased skeletal fragility accompanied by microarchitectural deterioration and low bone mineral density (a T score for bone mineral density below -2.5) [1]. Osteoporosis prevention and treatment have relied on hormonal treatments such as estrogens and selective estrogen-receptor modulators, and on anticatabolic drugs and bone resorption inhibitors including bisphosphonates. Bisphosphonates are the most widely used anticatabolic agents in the pharmacological management of postmenopausal osteoporosis [2]. These compounds are potent suppressors of osteoclast activity, improve trabecular and cortical architecture, and increase bone mineral density thereby [3] reducing the risk of fracture in women osteoporosis [4].

Since 2003, numerous reports proposed an association between bisphosphonate use and osteonecrosis of the jaw bone as a long-term side effect of this class of agents [5]. According to the American Association of Oral and Maxillofacial

Surgeons' position paper [6], patients may be considered to have bisphosphonates-related osteonecrosis of the jaw (BRONJ) if all of the following three characteristics are present: (1) current or previous treatment with a bisphosphonate, (2) exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks, and (3) no history of radiation therapy to the jaws.

Although BRONJ is a dose-related side effect and it is more common in cancer patients [7], a recent paper showed that the frequency of osteoporosis patients on oral BPs affected by BRONJ was higher than previously reported ($N = 470$, 7.8%) [8]. The purpose of this longitudinal study is to present data from 76 female patients treated with bisphosphonates for postmenopausal osteoporosis and referred to the Unit of Oral Diagnosis and Day Surgery of the University of Milano for diagnosis and treatment.

2. Materials and Methods

Starting in 2005, all female osteoporotic patients treated with BPs were referred to the Unit of Oral Diagnosis and Day Surgery for evaluation and management. Before the visit

and treatment, all patients gave written informed consent. This study was approved by the Director of the Clinic in accordance with the Declaration of Helsinki. Each patient received a thorough oral, dental, and periodontal examination. Each tooth was probed at four sites (three buccally and one lingually) using a North Carolina probe to measure probing pocket depth and recession. Recession was measured using the cemento-enamel junction as a reference point. Clinical attachment level (CAL) was then calculated as probing depth plus recession. Periodontitis was based on measures of the presence and extent of CAL in at least 20% of the sites probed, $CAL > 4$ mm. Relevant clinical data regarding BPs treatment, comorbidities, oral findings, dental treatment plan, and past and present dental therapies, were assessed. Patients were followed up every three months for routine clinical examination, oral hygiene instructions and debridement; restorative care, periodontal and dentoalveolar procedures were provided when needed according to the American Association of Oral and Maxillofacial Surgeons guidelines [9]. Adjustment of any ill-fitting dentures was performed, when necessary.

2.1. BRONJ Diagnosis and Staging. BRONJ diagnosis was made from radiographic and clinical findings. Patients were classified as having stage 0, I, II, or III. Briefly, patients with no clinical evidence of necrotic bone were considered stage 0. Individuals were included in the stage I group if they had asymptomatic exposed bone without any evidence of infection. Stage II group patients had exposed necrotic bone with clinical evidence of infection. Finally, patients were included in the stage III group if they had exposed necrotic bone with evidence of infection, pain, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border of the mandible or sinus floor.

2.2. BRONJ Management. The management of BRONJ aimed to reduce lesion size, soft and hard tissue inflammation and to alleviate pain. Nonsurgical treatment included wide spectrum antibiotics, antifungal agents, and mouthwashes with an antimicrobial solution. Surgical treatment included debridement without mucosal elevation and removal of loose segments of bony sequestra.

2.3. Statistical Analysis. We described the distribution of participants' characteristics, including demographics, smoking status, medical history, and the prevalence and clinical features of BRONJ.

We performed a logistic regression analysis to estimate odds ratios (ORs) and 95% CI for exposures of interest such as diabetes, hypertension, dental or periodontal abscess, multiple dental decays, periodontitis, dental extraction, and the presence of ONJ. All analyses had a significance level of 0.05.

3. Results

A total of 76 Caucasian women were included in this analysis. At the time of enrollment, patients ranged in age from 51 to

TABLE 1: Patients' characteristics, osteonecrosis of the jaw and dental treatments.

	Total (N = 76) n (%)
Age category	
50–60	14 (18.4)
61–70	27 (35.5)
71–79	28 (36.9)
80+	7 (9.2)
Median (IQR)	69 (62–74)
Smoking status	
Never	56 (73.7)
Current	9 (11.8)
Former	11 (14.5)
Medical history	
Hypertension	
No	50 (65.8)
Yes	26 (34.2)
Cardiovascular disease	
No	60 (78.9)
Yes	16 (21.1)
Immunosuppressant	
No	72 (94.7)
Yes	4 (5.3)
Previous radio/chemotherapy	
No	73 (96.1)
Yes	3 (3.9)
BPs and BRONJ	
BPs treatment	
Alendronate	47 (61.8)
Clodronate	16 (21.1)
Ibandronate	3 (3.9)
Risedronate	10 (13.2)
ONJ at first visit	
No	69 (90.8)
Yes	7 (9.2)
ONJ Stage	
0	57 (89.1)
I	3 (4.7)
II	4 (6.3)
ONJ Site	
Maxilla	1 (14.3)
Jaw Bone	6 (85.7)
Oral care	
Minor ONJ surgery	
No	72 (94.7)
Yes	4 (5.3)
Dental treatment	
No	31 (40.8)
Yes	45 (59.2)

ONJ: Osteonecrosis of the jaw; BPs: Bisphosphonates.

91 years, with a median age of 69 years (interquartile range 62–74) (Table 1). Approximately 12% of the women reported current smoking.

TABLE 2: Univariate analysis of associations with osteonecrosis of the jaw bone.

	Total (N = 76) n (%)	ONJ		Odds ratio (95% CI)	P value
		No (N = 69) n (%)	Yes (N = 7) n (%)		
Diabetes					
No	72 (94.7)	66 (91.7)	6 (8.3)	1.0	.26
Yes	4 (5.3)	3 (75.0)	1 (25.0)	3.7 (0.3–40.9)	
Hypertension					
No	50 (65.8)	44 (88.0)	6 (12.0)	1.0	.24
Yes	26 (34.2)	25 (96.2)	1 (3.8)	0.3 (0.1–2.6)	
Suppuration					
No	70 (92.1)	69 (98.6)	1 (1.4)	1.0	<.01
Yes	6 (7.9)	0 (0.0)	6 (100.0)	∞ (<0.001–∞)	
Multiple dental decays					
No	29 (38.2)	24 (82.8)	5 (17.2)	1.0	.06
Yes	47 (61.8)	45 (95.7)	2 (4.3)	0.2 (0.1–1.2)	
Periodontitis					
No	17 (22.4)	17 (100.0)	0 (0.0)	1.0	.05
Yes	59 (77.6)	52 (88.1)	7 (11.9)	∞ (<0.001–∞)	
Dental extraction					
No	39 (51.3)	37 (94.9)	2 (5.1)	1.0	.20
Yes	37 (48.7)	32 (86.5)	5 (13.5)	2.9 (0.5–15.9)	

ONJ: Osteonecrosis of the jaw.

In addition, 34.2% suffered from hypertension, 21.1% had cardiovascular disease, 5.3% of patients reported having diabetes, 5.3% were in treatment with an immunosuppressant agent, and 3.9% previously underwent chemo- and radiotherapy. Multiple dental decays and periodontitis were present in 61.8% and 77.6% of the individuals, respectively.

All patients were affected by osteoporosis and were treated with bisphosphonates.

61.8% of patients were receiving Alendronate, 21.1% Clodronate, 3.9% Ibandronate, or 13.2% Risedronate. Patients had received BPs consecutively for a mean duration of time of 191 weeks (95% CI, 150.9–230.7).

3.1. BRONJ Patients. Of these 76 patients, seven (9.2%) had active ONJ at first visit and were being treated in our clinics (Table 1). Three patients were classified as being stage I, and four individuals were stage II. Among these, the majority (85.7%) was in the mandible while 14.3% had ONJ in the maxilla. The triggering events for ONJ were identified as previous dentoalveolar surgery ($n = 2$), local trauma from dentures ($n = 3$), and periodontal infection ($n = 2$).

All BRONJ patients received wide spectrum antibiotic therapy, and four patients underwent surgical debridement. No alternative treatments were chosen.

3.2. Treatment Outcome. Closure of the exposure and complete remission was obtained in 4 cases out of 7.

At present none of the non-ONJ patients submitted to invasive dental treatments developed ONJ signs and/or symptoms.

3.3. BRONJ-Associated Factors. Individuals with dental or periodontal abscess were significantly more likely to develop ONJ (Table 2). A borderline association was present among individuals with periodontitis ($P = .05$). Women with a positive history for diabetes had a significant increase in the odds of having ONJ (OR: 3.7, 95% CI 0.3–40.9). Patients who underwent dental extraction while receiving BPs therapy were three times more likely to develop ONJ (OR: 2.9, 95% CI 0.5–15.9).

No significant associations were observed for the following variables: age, smoking status, type of BPs used, hypertension, cardiovascular disease, immunosuppressant, previous radio- and chemotherapy, and multiple dental decays.

4. Discussion

Bisphosphonates are the most widely prescribed drugs for the treatment of osteoporosis, with more than 190 million prescriptions dispensed worldwide [10]. The results of our analysis showed that the incidence of ONJ attributable to the use of bisphosphonates was 9%. Our findings are in agreement with those of Otto et al. [8], who conducted a large multicenter trial on the relationship between ONJ and the use of BPs and showed that 7.8% of cases ($N = 470$) were associated with oral BPs therapy due to osteoporosis.

Patients with diabetes were four times more likely to develop ONJ. The risk increased also for patients who underwent dental-alveolar procedures and for those women who had periodontal disease and dental or periodontal abscess. Our results are also consistent with those from a paper by the M. D. Anderson Cancer Center group [11], which reported

that patients who had a dental or periodontal abscess and were taking bisphosphonates, were at a seven-fold increased risk for developing BRONJ.

Individuals who had dental extractions were three times more likely to be diagnosed with BRONJ. Data presented by Hoff et al. [12] showed that cancer patients with a positive history of dental extractions were associated with a significant increase in the odds of detecting ONJ (OR: 13.2; 95% CI 3.7–47.3; $P < .0001$). However, our odds ratios are lower than those reported by Hoff and colleagues. It may be suggested that cancer patients have a slower healing process than cancer-free but osteoporotic patients; both radiation therapy and chemotherapy can affect the ability of cells to reproduce, which slows the healing process in the mouth [13]. In addition, chemotherapy may reduce the number of white blood cells and weaken the immune system, making it easier for the patient to develop an infection. As such, the risk of ONJ is significantly increased.

Though small numbers limited our ability to fully evaluate the risk factors for ONJ, no associations were observed for tobacco use, presence of multiple decays, previous radiotherapy and/or chemotherapy, or concomitant use of immunosuppressant medications. Another limitation to note for this study is that our study population was hospital based. Therefore, our results may not be generalizable to the population at large. In order to overcome these sample-size issues, multicentric population-based case-control studies are warranted.

5. Conclusions

Our findings indicate that patients with osteoporosis receiving BPs may develop osteonecrosis of the mandible, especially in the presence of an active infectious process in the mouth such as periodontal disease or suppuration. In addition, management of this condition requires the use of prolonged medical treatment and may require oral surgical procedures. As such, there is an urgent need to fill a knowledge gap in better characterizing this condition, identifying the main cause, and determining individual susceptibility for the intervention and prevention of BRONJ. To follow up on our findings, additional large clinical trials that aim to find how to overcome bisphosphonate-associated ONJ and to predict who may benefit from bisphosphonate treatment without accompanying risk of ONJ are warranted. In the meantime, patients receiving bisphosphonates therapy should be followed carefully to avoid the occurrence of extended osteonecrotic lesions.

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