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Research Article

Serum Crosslaps (CTX) and 25hydroxyvitamin D Levels as Risk Predictors of Bisphosphonate-Related Osteonecrosis of the Jaw

Picardo SN[1], Rodriguez Genta SA[2], Seijo M[3], Zeni SN[4] and Rey EA[5]*

[1]Oral and Maxillofacial Surgery Department II, School of Dentistry, University of Buenos Aires, Department of Dentistry, Favaloro Foundation University Hospital, Argentina

[2]Oral and Maxillofacial Surgery Department II, School of Dentistry, University of Buenos Aires, Argentina

[3,4]Metabolic Bone Diseases Laboratory, Institute of Immunology, Genetics, and Metabolism (INIGEM), School of Pharmacy and Biochemistry, San José de San Martin Clinical Hospital (CONICET-UBA) Buenos Aires, Argentina

[5]President of the National Academy of Dentistry, Consultant to the National Academy of Medicine, Former Professor of Oral and Maxillofacial Surgery School of Dentistry University of Buenos Aires, Argentina

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***Corresponding author:** PhD Rey EA, President of the National Academy of Dentistry, Consultant to the National Academy of Medicine, Former Professor of Oral and Maxillofacial Surgery School of Dentistry University of Buenos Aires, Argentina

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Summary

Bisphosphonates (BPs) are anticatabolic drugs of choice for treating bone diseases, including bone metastases. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is one of the possible complications. Crosslaps (CTX) could be used as biochemical marker for risk of developing ONJ. Vitamin D (VD) may be involved in this condition. VD status and CTX levels were evaluated and compared in BP-treated women without BRONJ (Group I; n=28) and with BRONJ (Group II; n=58). Women were older and duration of BP use was longer in Group II (p=0.0000036). No differences in calcemia, phosphatemia, or CTX levels were observed; BAP levels were significantly higher and 25OHD were significantly lower in Group II (p=0.040 and p=0.035, respectively). The percentage of subjects with CTX levels between 100 and 149mg/mL was similar in both groups. VD deficiency was observed in 18% of subjects in Group II but in none of the subjects in Group I. No significant differences in the percentage of subjects with VD insufficiency and sufficiency were observed between groups (Group I: 50%; Group II: 40%). Conclusion: CTX levels did not prove useful as predictors of risk for developing BRONJ. The high percentage of women with VD deficiency who developed BRONJ suggests a possible relationship between both conditions and highlights the importance of assessing Vitamin D status.

Keywords: Bisphosphonates; Osteonecrosis of the jaw; Women; Vitamin D; CTX

What are Glucocorticoids?

Bisphosphonates (BPs) are the anti-catabolic treatment of choice for osteoporosis and other bone diseases [1]. Therapeutic response to BPs is affected by Vitamin D (VD) status, which is determined by 25hydroxyvitamin D (25OHD) levels [2].

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is one of the possible complications of chronic oral or intravenous treatment with aminoBPs [3]. In 2007, the American Association of Oral and Maxillofacial Surgeons (AAOMS) defined this side effect of BP treatment as an area of exposed bone in the maxillofacial region in a patient on BP therapy for more than eight weeks and who has not had radiation therapy to the head and neck region [4]. Although the etiology of BRONJ is multifactorial, the marked decrease in bone remodeling would be one of the main risk factors for its development [5].

Bone remodeling involves two highly coordinated events, namely bone formation due to osteoblastic activity and bone resorption caused by osteoclastic activity. Bone cell activity can be assessed using biochemical markers of bone formation and resorption. These markers are used routinely to evaluate response to antiresorptive treatment. Through their action on the mevalonate pathway, BPs block osteoclast activity and favor cell apoptosis inhibiting bone resorption. Bone remodeling starts with a resorption event, so that inhibition of bone resorption dramatically decreases bone tissue remodeling [6].

C-terminal telopeptide of collagen type I (CTX or Crosslaps) is currently considered the most sensitive and specific marker of bone resorption to assess changes in bone remodeling. Serum CTX levels decrease markedly within the first weeks or month after initiating anti catabolic treatment [7]. A new role for CTX has been suggested over the last years. According to Marx RE et al., very low serum CTX levels in patients on chronic BP therapy would indicate potential risk for developing BRONJ [8]. Other authors, however, found no relation between CTX levels and development of BRONJ [9,10] and the clinical utility of CTX as a predictor of BRONJ remains controversial to date [11-14].

Bedogni A et al. [15] found that 77% of patients with BRONJ but only 5% of BP-treated patients who did not develop BRONJ had osteomalacia [15]. Inadequate Vitamin D status has therefore been proposed as an additional risk factor for ONJ in patients on long-term treatment with bisphosphonates.

Based on the above, the present study sought to evaluate and compare the VD status and CTX levels of women on chronic BP therapy with and without BRONJ.

Materials and Methods

Subjects

The subjects were recruited from a population of 25.538 male and female patients, mean age 55±12 treated at the Oral and Maxillofacial Traumatology and Surgery Department II of the School of Dentistry, University of Buenos Aires (FOUBA), between 2007 and 2013. The present study included all the female patients aged more than 20 years referred for oral surgery by their attending dentist or physician during the study period. All subjects signed a written informed consent form prior to enrollment.

The present study was conducted in keeping with ANMAT 5330/97 guidelines and regulations, and in compliance with the Helsinki declaration and UNESCO bioethics principles. The study was approved by the Ethics Committee of the institution (Resolution (CD) 399).

Methods

From a total 253 women on long-term treatment with BPs (mean age: 62.4±6.7 years) referred for oral surgery to the department within the study period, 86 complied with the study inclusion criteria and were assigned to one of two groups according to the presence of BRONJ.

Group I (n=28): women receiving BPs who did not develop BRONJ.

Group II (n=58): women receiving BPs who developed BRONJ.

Clinical diagnosis of BRONJ was made according to the 2014 update of the American Association of Oral and Maxillofacial Surgery position papers on medication-related osteonecrosis of the jaw [3]. Based on these guidelines, patients with a history of radiation therapy to the head and neck, presenting a systemic disease that alters normal physiology of bone tissue, and/or who did not consent to participate in the study or to undergo the biochemical assessments of bone and phospho-calcium metabolism were excluded from the study. BRONJ diagnosis was confirmed by clinical assessment.

At the first consultation of each participant, a patient interview was conducted and oral examination was performed to assess clinical signs and symptoms, neural signs and symptoms, and presence of oral lesions. The patient's medication, underlying disease (osteoporosis, Paget's disease, cancer) prompting BP therapy, and type of BP and duration of use regardless of dose were recorded. In the case of referred patients, their referring physician was reached to inquire about BP therapy. Post-operative follow up was performed at 1, 2, 4, 8, and 10 weeks post-surgery, and additional follow up visits were scheduled when necessary.

Phosphatemia (sPi) (mg/dL) was determined by colorimetry at 340nm using an autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA). Intra- and interassay coefficients of variation (CVs) were 0.5-5% and 0.3-0.6%, respectively. Bone alkaline phosphatase (BAP) (IU/L) was determined by colorimetry at 520nm (optimized Alkaline Phosphatase, Wiener SA) after precipitation of the bone isoform with wheat germ lectin. Intra- and interassay CVs were between 4-8% and 6-8%, respectively.

Levels of 25 hydroxyvitamin D (25OHD) (ng/mL) were determined by competitive protein binding radioimmunoassay (DiaSorin, Stillwater, MN, USA). Intra- and interassay CVs were 10% and 15%, respectively. C-terminal telopeptide of Collagen type I (CTX) (ng/mL) was determined by enzyme immunoassay using monoclonal antibodies (Osteometer BioTech, Herlev, Denmark). Intra-assay CV was 6%.

Statistical analysis

Normality of the studied variables was tested using Shapiro-Wilk test. Homogeneity of variances was determined using Levene's test. Student's t test was used to compare the differences between the studied groups. All statistical analyses were performed using SPSS 19.0 for Windows (SPSS, Inc. Chicago, IL). Statistical significance was set at a value of p below 0.05 ($p<0.05$).

Result

Data corresponding to the 86 women included in the study are shown in Figure 1. Twenty-seven of the 28 women in Group I were prescribed BPs for osteoporosis and one for Paget's disease, whereas 40 of the 58 women in Group II were prescribed BPs for osteopenia/osteoporosis and 18 for cancer treatment. Twenty-four women in Group I had undergone tooth extraction and one had had dental implant surgery. Eighty-six percent of patients (n=50) in Group II, 34 of whom had osteoporosis and 16 had a neoplasm, developed BRONJ after tooth extraction or dental implant therapy; the remaining 8 patients in this group, six of whom had osteoporosis and 2 had a neoplasm, developed ONJ spontaneously.

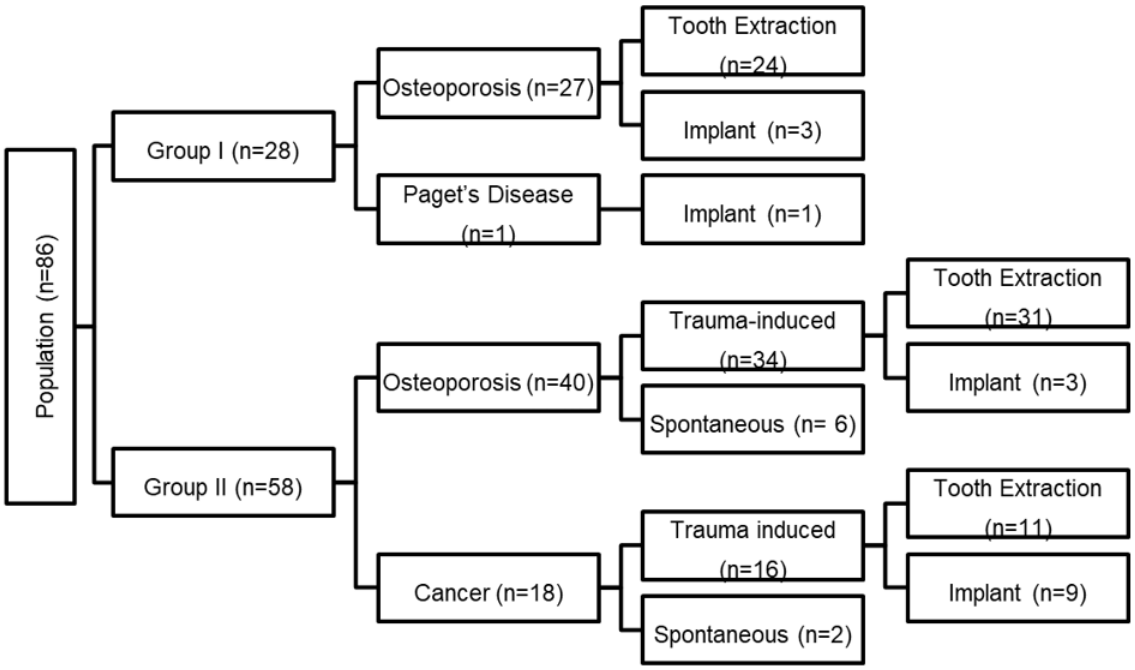

Figure 1: Distribution of women in Groups I and II according to underlying disease, type of oral treatment, and occurrence of bisphosphonate related osteonecrosis of the jaw.

Comparison between women with and without BRONJ

Comparison between groups showed women with BRONJ were older and duration of BP use was significantly longer (p=0.00001) in the group of women with BRONJ. No significant differences in serum calcium, phosphate, or CTX levels were observed between groups, whereas BAP levels were significantly higher and 25OHD levels were significantly lower in the group of women who developed BRONJ (p=0.040 and p=0.035, respectively) Table 1. In view of the highly significant differences in duration of use between groups I and II, all the above parameters were analyzed in a subset of patients with BRONJ whose duration of BP use was similar to that of Group I, i.e., women who did not develop BRONJ. As observed when comparing the entire Group I with Group II, mean age of the Group II subset was higher than mean age of Group I, but no significant differences in serum calcium, phosphate, or CTX levels were observed between the Group II subset and Group I (data not shown).

Table 1: Data of the women included in the study.

	Group I (n=28)	Group II (n=58)
Age	61.0±8.2	66.2±9.8
Duration of BP use	36.8±23.3	63.9±41.7**
Calcemia (mg/dL)	9.4±0.4	9.4±0.6
Phosphatemia (mg/dL)	3.4±0.7	3.4±0.5
BAP (IU/L)	60.2±24.4	73.7±34.3*
CTX (ng/mL)	226±171	224±151
25OHD (ng/mL)	32.5±9.7	28.4±9.4*

*P <0.05; **p<0.00001 : Group I vs. Group II

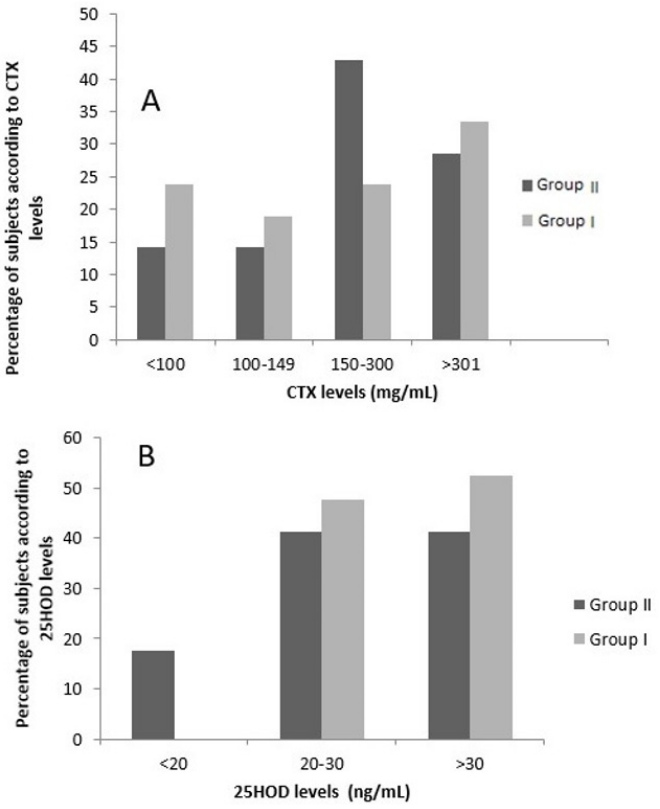

Figure 2: Percentage of women in Groups I and II according to CTX (A) and according to 25OHD levels (B).

Distribution of patients in Groups I and II according to serum CTX levels stratified as high, low, or minimal risk for BRONJ (8)

is shown in Figure 2. No statistically significant differences in the percentage of women with CTX levels between 100 and 149mg/mL (14.3% and 19.0%) or between women with CTX >301 mg/mL (28.5% vs. 33.4%) were observed between groups. However, 50% of women in Group II had CTX levels <100mg/mL (14.3% vs. 23.8%), and the number of women with CTX levels in the 150-300mg/mL range (42.9% vs. 23.8%) was twofold higher in Group II as compared to Group I.

Comparison of duration of use and 25OHD levels between groups according to range of CTX showed significantly lower duration of use ($p<0.0001$) in each of the CTX ranges, and significantly higher 25OHD levels ($p<0.05$) in the <100 and 150-300 mg/mL CTX ranges in Group I Table 2.

Table 2: Data of women with and without BRONJ according to CTX levels.

CTX levels	<100		100-149		150-300	
	Group I	Group II	Group I	Group II	Group I	Group II
CTX (mg/mL)	57±23	49±26	115±18	127±18	222±49	214±36
Age (years)	64.8±12.2	61.4±9.4	55.8±4.6*	69.6±11.2	60.4±9.3	68.0±10.6
Type of Oral tr.	32.6±23.6*	59.4±66.4	27.0±11.5*	65.8±26.6	42.8±27.1*	64.9±38.2
BAP (IU/L)	56.0±13.8*	83.0±38.8	59.0±10.5	61.0±15.8	60.8±4.3*	80.8±43.7
25OHD (ng/mL)	31.4±5.0	31±8.2	30.1±4.6	33.8±4.9	37.7±12.7*	27.5±10.0

Vitamin D status (sufficiency, insufficiency, deficiency) in each group is shown in Figure 1. Whereas none of the subjects in Group I had deficient VD levels, 18% of those in group II had 25OHD levels below 20 ng/ml. The percentage of women with VD sufficiency/insufficiency did not differ significantly between groups, and accounted for 50% of women in Group I and 40% of those in Group II.

Comparison of duration of use in patients with VD sufficiency and insufficiency between groups, showed that duration of use was significantly lower ($p<0.001$) in patients with VD sufficiency and insufficiency in Group I. It was not possible to compare duration of use in patients with Vitamin D deficiency since there were no cases of Vitamin D deficiency in Group I Table 3.

Table 3: Data of women with and without BRONJ according to 25OHD levels.

25OHD levels	<20		20-30		>30	
	Group I	Group II	Group I	Group II	Group I	Group II
25OHD (ng/mL)	-	15.6±3.0	23.2±1.9	26.6±2.9	39.3±8.9	37.4±3.4
Age (years)	-	63.5±10.6	60.0±3.0	68.6±8.7	60.7±8.9	65.9±10.4
Type of Tr.	-	46.0±24.1	46.0±27.8	74.2±45.1	34.8±24.6	58.9±43.9
BAP (IU/L)	-	88.3±29.9	72.5±42.0	77.2±41.5	55.9±10.0	68.6±27.9
CTX (mg/mL)	-	212±90	317±239	292±192	208±138	206±149

Comparison of parameters according to onset of BRONJ showed that CTX levels were significantly higher (264±169 *vs*. 189±87mg/mL; $p<0.05$) in women who developed BRONJ after invasive dental treatment as compared to those who developed BRONJ spontaneously, and though the difference did not reach statistical significance, duration of use (71.8±19.7 *vs*. 62.2±45.0 months) was also longer (71.8±19.7 *vs*. 62.2±45.0 months) in the former sub-set of women with BRONJ. No differences in age or in the remaining biochemical parameters were observed between these two sub-sets.

As regards underlying disease prompting BP therapy, no significant differences in serum calcium (9.3±0.4 vs. 9.7±0.8mg/dL), phosphate (3.4±0.6 vs. 3.4±0.9mg/dL), BAP (73.1±31.2 vs. 79.3±38.5), or 25HOD (29.5±8.5 vs. 28.4±9.3mg/dL) levels were observed between women with BRONJ receiving BPs for osteoporosis and those receiving BPs for cancer treatment. Mean CTX levels were higher in women with BRONJ receiving BPs for cancer treatment than in those receiving BPs for osteoporosis (225±121 vs. 291±222mg/mL, respectively), though the difference did not reach statistical significance. Duration of use was significantly higher in BRONJ patients with osteoporosis than in those with a neoplasm (74.4±42.6 vs. 44.6±31.9 months, respectively: $p<0.01$).

The percentage of patients with BRONJ receiving BPs for osteoporosis and for cancer treatment according to serum CTX and 25OHD values is shown in Figure 3. The percentage of osteoporosis and cancer patients with CTX levels indicating high or moderate risk for BRONJ was similar (33.3% vs. 33.4%), whereas the percentage of cancer patients with CTX levels below 100mg/mL was higher than that of women with osteoporosis (16.7% vs. 9.6%). The percentage of subjects with deficient/inadequate VD levels was higher in the group of cancer patients (58.8% vs. 67.7%). Comparison of parameters according to mode of delivery (oral vs. intravenous administration) showed that serum Ca, BAP, CTX,

and 25OHD levels were higher and serum phosphate levels were lower in women receiving intravenous BPs, though only BAP levels differed significantly (70±5 *vs*. 97±10 IU/L; p<0.05).

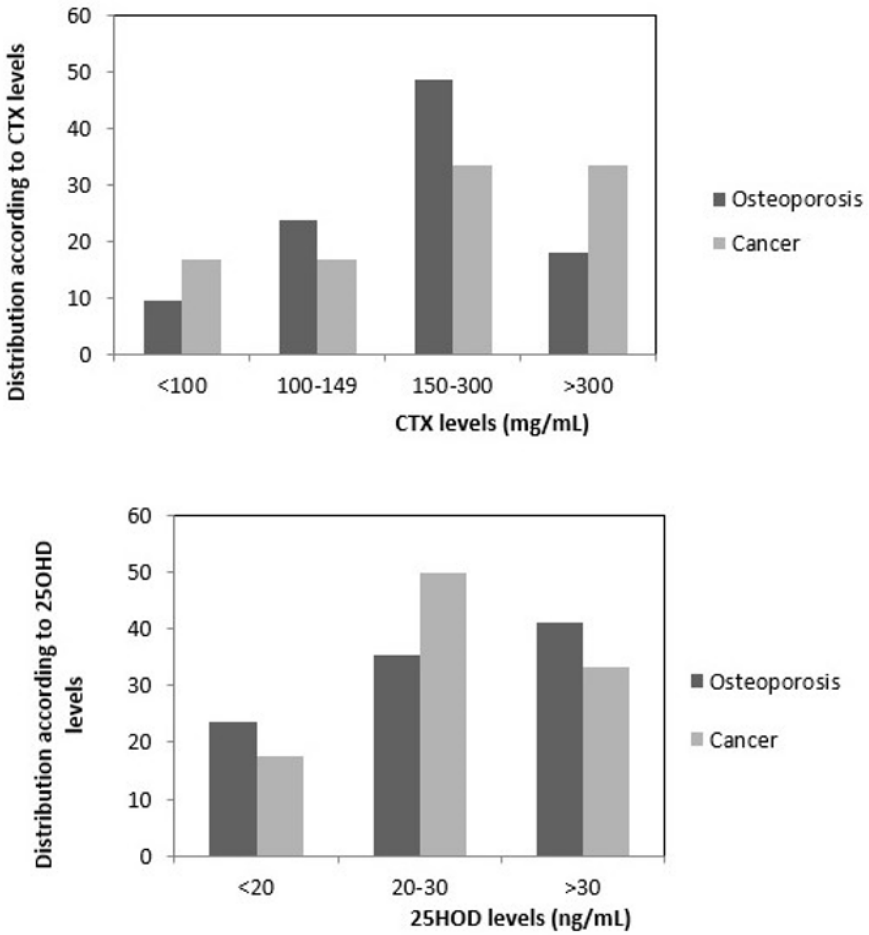

Figure 3: Percentage distribution of women with osteoporosis and cancer according to CTX and 25OHD levels (A and B, respectively).

Discussion

Serum CTX levels were not found to predict risk for ONJ. Of note, a high percentage of patients on long-term BP treatment, including those who developed BRONJ and those who did not, had inadequate VD status.

The degree of bone turnover can be assessed using biochemical markers of bone remodeling, which include osteoblastic bone formation and osteoclastic bone resorption markers. When bone formation and resorption are coupled and coordinated, it is sufficient to determine one in order to assess total bone remodeling. CTX is currently considered one of the most specific and sensitive markers of bone resorption [16,17]. CTX levels decrease dramatically one or two months after initiation of oral or intravenous antiresorptive BP treatment. This decrease prevents bone mass loss, and the risk of fracture therefore decreases. However, suppression of bone remodeling for a prolonged period of time can cause adverse secondary effects such as atypical fractures and BRONJ [3].

Bisphosphonate-related osteonecrosis of the jaw is a complex condition of multifactorial origin, involving a number of mediators. The marked decrease in bone remodeling resulting from BP treatment is considered one of the key risk factors for the development of this disease [18]. However, there is a wide range of individual variability among patients receiving the same dose and even the same BP [14], likely due to genetic susceptibilities [19].

Biochemical determination of CTX levels reflects total bone resorption activity, rather than resorption at a specific skeletal site. In this regard, it must be kept in mind that the bone remodeling process in the jaws differs from that of the axial skeleton, and the jaws also differ in their response to aminobisphosphonate therapy. It has therefore been posited that BRONJ cannot develop without significant suppression of bone remodeling. Should the latter occur, minor trauma as is tooth extraction could trigger the disease. In this regard, Mark RE et al. concluded that the risk of BRONJ in patients on BP therapy for more than three years was high when their CTX levels were <100pg/mL, moderate with CTX levels 100 to 150pg/

mL, and minimal with CTX values 150 a 299pg/mL. Based on the above, the 2009 update of the AAOMS guidelines recommended discontinuing BP therapy for three months prior to dental surgery (bisphosphonate holiday) in order to minimize risk of developing BRONJ [20]. However, due to their high affinity for hydroxyapatite, aminobisphosphonates remain in the bone microenvironment over long periods of time, with the more potent BPs remaining in the body up to10 years. It would therefore be unlikely for the concentration of BP in the bone to change at such short times. A number of researchers [21-23] have also lent support to the utility of CTX levels as a potential risk predictor of BRONJ, though more recent studies seem to challenge this conclusion [22,24]. In their 2011 report, the American Dental Association Council on Scientific Affairs (ADAC) concluded that there was not sufficient evidence to consider the different levels of biochemical markers of bone remodeling as risk predictors for developing BRONJ [25]. The 2014 update of the AAOMS further supported the lack of validation of a systemic marker of bone remodeling to assess the risk for BRONJ [3].

In agreement with the above reports, we found no difference in average CTX levels or in the percentage of women with CTX levels in the low, moderate, and high risk ranges between patients with and without BRONJ. CTX levels were only found to differ within the group of BRONJ patients, and were lower in those who developed BRONJ spontaneously than in those who developed BRONJ after invasive dental treatment. Fifty percent of women with spontaneous BRONJ but only 25% of those with dental treatment-induced BRONJ had CTX levels below 150mg/mL. According to the classification proposed by Mark RE et al., therefore, 50% and 75% of patients with spontaneous and trauma-induced BRONJ respectively were at minimal risk of developing the disease, though 100% of these patients in fact developed BRONJ [8].

Other additional risk factors for BRONJ that would affect CTX levels include age, invasive oral treatment, type of BP, dose, and duration of use [26]. Both groups of women treated with BPs were similar in age, and all underwent oral treatment (tooth extraction or implant surgery), but differed in duration of use and type of BP. Although there were no available data on the dose, it is well documented that the dose used to treat neoplasms or active Paget's disease is markedly higher than the dose used to treat osteopenia/osteoporosis. The mode of delivery also differs with regard to the aforementioned conditions: neoplasms and Paget's disease are usually treated with intravenously administered BPs, whereas osteoporosis/osteopenia are treated with oral BPs. Intravenous administration of BPs has been associated with high risk of developing BRONJ [27]. Nevertheless, our results showed no difference in mean CTX levels or in the percentage of women with CTX levels <150mg/mL when comparing women receiving intravenous and oral BPs (data not shown).

Because BPs deposit in the bone, the quantity of the drug that remains in the bone microenvironment will depend on duration of treatment. In the present study, duration of treatment with aminoBPs was two-fold higher in the group of women who developed BRONJ than in the group who did not. In addition, our results showed that duration of use was shorter among the cancer patients than the osteoporosis patients who developed BRONJ. Despite these differences, according to reports in the literature, CTX levels stabilize after six weeks of treatment and are independent of treatment duration [23]. In line with these findings, our results showed that duration of treatment did not affect mean CTX levels or the percentage of women with CTX levels below 150mg/mL. The type of BP also differed. Intravenous zoledronate was the treatment of choice for neoplasms but zoledronate was not used for osteoporosis treatment (50% vs. 0%, respectively). Conversely, oral alendronate was not used to treat neoplasms but was the choice treatment for osteoporosis (0% vs. 38%, respectively). The observed difference in the type of aminoBP and mode of delivery did not affect mean CTX levels or the percentage of women with CTX levels below 150mg/mL (data not shown).

It must be pointed out that although the present results do not lend support to the utility of serum CTX levels as predictor of risk for developing BRONJ, it is important to maintain the levels of this bone marker within reference range in order to prevent potential adverse effects of BP therapy.

Treatment with BPs can induce hypocalcemia and subsequently hyperparathyroidism [28]. According to reports in the literature, hyperparathyroidism may be involved in the complex etiology of BRONJ, since patients who develop BRONJ have persistent hypocalcemia and secondary hyperparathyroidism during the period before the onset of BRONJ [29]. Hellstein JW et al. [25] found that patients with higher immunoreactive PTH levels prior to or during BP treatment were more likely to develop BRONJ than those showing normal iPTH before PB treatment. Because PTH levels were not determined in all the women included in the present study, we were not able to evaluate the relation between PTH levels prior to BP treatment and development of BRONJ. Nevertheless, none of the women studied here had hypocalcemia, a specific marker of an increase in the parathyroid secretion.

Vitamin D deficiency has been considered a possible risk factor for BRONJ. In this regard, Hokugo A et al. [27] found VD deficient-rats treated with zoledronate to be at higher risk for BRONJ [27]. Clinical studies conducted by Beddoni A et al. showed a strong association between VD deficiency and risk for developing BRONJ [15]. Vitamin D deficiency and hyperparathyroidism are associated since insufficient 25OHD levels increase PTH levels through loss of negative feedback of VD on parathyroid hormone synthesis and secretion [27,30]. It is therefore relevant to consider whether increased iPTH levels, VD insufficiency, or both combined may play a role in the onset of BRONJ. As mentioned above, iPTH levels were not assessed in the present study. Nevertheless, given that the mean 25OHD levels of women with BRONJ were lower than those of women without BRONJ, it could be hypothesized that PTH levels might have been higher, though still within the reference range, at least in women with 25OHD levels in the insufficiency range. The

lower mean 25OHD levels observed in the group of women with BRONJ are accounted for not only by the higher percentage of women with inadequate VD status in this group but also by the fact that approximately 20% of women in this group had VD deficiency.

Badros A et al. [31] found that 40% of patients with multiple myeloma had VD deficiency (<14.4ng/mL) and 35% had VD insufficiency (14.4 a 30ng/mL) [31]. Lowe LC et al. [32] reported that 30.2% patients with breast cancer had VD insufficiency [32]. Multiple myeloma and cancer patients are usually treated with high doses of BPs, so that these patients on long term treatment with BPs could develop BRONJ. Although each of the aforementioned authors reported the percentage of multiple myeloma and cancer patients with vitamin D insufficiency/deficiency, respectively, they did not provide information regarding the presence of BRONJ among the patients they included in their study. It could be thought that their study population may have included subjects receiving high doses of BPs and who also had VD insufficiency/deficiency, and were therefore at risk for developing BRONJ. We found 45% of cancer patients who developed BRONJ in the insufficiency range. However, because 100% percent of the BP-treated cancer patients in our study developed BRONJ, we could not establish comparisons with BP-treated patients without BRONJ [33].

It is well documented that bone metabolism is directly affected by BP therapy, though in a complex manner on account of the number of mediators involved. It is therefore important to maintain the different mediators within reference ranges for the proper pharmacological action of BPs. In this regard, there is consensus that the therapeutic efficacy of BPs in decreasing fracture risk is suboptimal under conditions of VD deficiency [2]. In the present study, however, 60% of BP-treated women who developed BRONJ and 50% of those who did not were in the VD insufficiency range.

To conclude, the present results do not allow confirming the utility of serum CTX levels as predictor of risk for developing BRONJ. In addition, the high percentage of women with VD deficiency who developed BRONJ suggests the importance of determining the physiological status of bone metabolism in order to adjust calcium, VD, and PTH levels on account of the potential relation between these parameters and the development of BRONJ.

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