Is vitamin D deficiency a risk factor for osteonecrosis of the jaw in patients with cancer? A matched case–control study

Alberto Bedogni [a, *], Giordana Bettini [a], Giorgio Bedogni [b], Daniela Basso [c], Davide Gatti [d], Silvia Valisena [e], Antonella Brunello [f], Marco Sorio [g], Tamara Berno [h], Sandro Giannini [i], Filippo Navaglia [c], Mario Plebani [c], Pier Francesco Nocini [j], Stella Blandamura [k], Giorgia Saia [a, 1], Francesco Bertoldo [l, 1]

[a] Unit of Maxillofacial Surgery, Department of Neuroscience-DNS, University of Padua, Padua, Italy
[b] Clinical Epidemiology Unit, Liver Research Center, Basovizza, Trieste, Italy
[c] Unit of Laboratory Medicine, Department of Medicine-DIMED, University of Padua, Padua, Italy
[d] Unit of Rheumatology, Department of Medicine, University of Verona, Verona, Italy
[e] Service of Traumatology, Orthopedics and Hand Surgery, Regional Hospital of Bellinzona, Switzerland
[f] Medical Oncology, Istituto Oncologico Veneto-IRCCS, Padua, Italy
[g] Unit of Hematology, Department of Medicine, University of Verona, Verona, Italy
[h] Hematology and Clinical Immunology Branch, Department of Medicine-DIMED, University of Padua, Padua, Italy
[i] Unit of Internal Medicine, Department of Medicine-DIMED, University of Padua, Padua, Italy
[j] Unit of Oral and Maxillofacial Surgery, Department of Surgery, University of Verona, Verona, Italy
[k] Department of Medicine-DIMED, University of Padua, Padua, Italy
[l] Unit of Internal Medicine, Department of Medicine, University of Verona, Verona, Italy

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ABSTRACT

Purpose: A previous case–control histomorphometric study showed higher odds of osteomalacia in patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ). Vitamin D deficiency causes osteomalacia and may therefore be involved in the pathogenesis of BRONJ. The present case–control study aimed at testing such hypothesis.

Materials and methods: BRONJ+ and BRONJ− patients treated with bisphosphonates were matched by sex (same) and age (within 5 years). Serum 25-hydroxy-vitamin D (25-OH-D), parathyroid hormone, bone alkaline phosphatase, total procollagen type 1 amino-terminal propeptide, carboxy-terminal collagen crosslinks, Dickkopf WNT signaling pathway inhibitor 1 and sclerostin were measured.

Results: The main outcome was vitamin D deficiency defined as 25-OH-D < 50 nmol/l. A total of 51 BRONJ+ and 73 BRONJ− patients were studied. The frequency (95% CI) of vitamin D deficiency was 59% (45%−72%) in BRONJ+ and 62% (48%−75%) in BRONJ− patients. This amounts to a difference of −3% (−22%−16%, p = 0.77) for BRONJ+ patients. Serum 25-hydroxy-vitamin D and parathyroid hormone were similar in BRONJ+ and BRONJ− patients. Among the bone metabolism markers, only sclerostin differed between the two groups, being higher in BRONJ+ patients.

Conclusion: The present matched case–control study suggests that vitamin D deficiency is not a risk factor for BRONJ.

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1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is an adverse drug reaction due to nitrogen-containing bisphosphonates (NBP), denosumab and antiangiogenics (Yarom et al., 2010; Troeltzsch et al., 2012; Fedele et al., 2015). Bisphosphonate-related

osteonecrosis of the jaw (BRONJ) develops in up to 10% of patients treated with intravenous high-potency bisphosphonates (Fedele et al., 2015).

The diagnosis and management of BRONJ is challenging, mostly because its pathogenesis is not completely understood (Campisi et al., 2014). The most commonly hypothesized pathogenetic mechanisms are bone turnover inhibition, bone infection, angiogenesis inhibition, soft-tissue toxicity, and immune dysfunction (Pazianas, 2011; Reid, 2012; Zhang et al., 2013; Campisi et al., 2014; Kalyan et al., 2014). Such mechanisms are not mutually exclusive and may work at different points of the pathogenetic pathway leading to BRONJ.

A high frequency of BRONJ has been reported in zoledronate-treated patients with persistently low serum calcium and secondary hyperparathyroidism (Ardine et al., 2006; Hokugo et al., 2010, 2013). Murine studies have also reported an inverse association between serum vitamin D and BRONJ development (Hokugo et al., 2010, 2013). In a recent case−control study of BRONJ+ vs. BRONJ− patients, we have identified osteomalacia as a potential risk factor for BRONJ in cancer patients (Bedogni et al., 2012). Because vitamin D deficiency causes osteomalacia and is common in cancer patients, it may be causally linked to BRONJ (Holick, 2007).

We performed a matched case−control study to test whether vitamin D deficiency is more common in BRONJ+ than in BRONJ− cancer patients.

2. Materials and methods

2.1. Study design

We performed a matched case−control study in consecutive cancer patients followed at the Maxillofacial Clinics of the Padua and Verona University Hospitals. BRONJ was defined as exposed or non-exposed osteonecrosis of the mandible or maxilla (Ruggiero et al., 2009, 2014; Fedele et al., 2010). Cases were BRONJ+ patients treated with NBP, and controls were BRONJ− patients also treated with NBP. BRONJ+ and BRONJ− patients were matched on sex (same) and age (within 5 years) using many-to-many coarsened

exact matching (Iacus et al., 2011). BRONJ + patients were eligible for the study if they were ≥18 years of age, had cancer, and treatment with NBP because of the underlying cancer. Patients were excluded from the study if they had previous radiation treatment to the jaws, previous supplementation with vitamin D, HIV infection, HBV infection, or HCV infection. (Patients with HIV, HBV or HCV infection were excluded because of their high frequency of vitamin D deficiency.) The enrollment of patients took place between 1 January 2011, and 30 June 2012 in Verona and between Nov 01 2011 and 31 Dec 2012 in Padua. The Ethical Committees of the participating Clinics approved the study (resolutions CE VR-2100 and CE PD-2443P), and all patients gave their written informed consent.

2.2. Outcomes

The main outcome of the study was the frequency of vitamin D deficiency in BRONJ+ vs. BRONJ− patients. Vitamin D deficiency was defined as serum 25-hydroxy-vitamin D (25-OH-D) < 50 nmol/l (Holick, 2007). The secondary outcomes were the between-group (BRONJ+ vs. BRONJ−) differences in the serum levels of: 1) 25-OH-D; 2) parathyroid hormone (PTH); 3) calcium; 4) phosphate; 5) magnesium; 6) bone alkaline phosphatase (bALP); 7) total pro-collagen type 1 amino-terminal propeptide (P1NP); 8) carboxy-terminal collagen crosslinks (CTX); 9) Dickkopf WNT signaling pathway inhibitor 1 (DDK-1); and 10) sclerostin.

2.3. Clinical examination

All clinical data were collected during a single visit at the outpatient facility of the two participating Clinics. A detailed patient history was taken and an oral examination was performed. Photographs of the oral cavity were always taken (Nikon Finepix S1 Pro; Nikon, Tokyo, Japan). The following data were obtained directly from the patients and/or from their clinical charts: 1) age; 2) sex; 3) reason for NBP usage; 4) NBP type; 5) duration of NBP treatment; 6) cumulative dose of NBP; 7) concurrent use of steroids; 8) concurrent use of chemotherapy drugs; 9) concurrent use of antiangiogenics; 10) concomitant diseases and; 11) risk factors

Table 1
Measurements of patients with and without BRONJ.

	BRONJ+[a] (n = 51)			BRONJ−[a] (n = 73)		
	P_{50}	P_{25}	P_{75}	P_{50}	P_{25}	P_{75}
Age (years)	69	64	74	69	62	76
Time from last BP (months)	21	12	37	1	1	18
25-OH-D (nmol/l)[b]	39	18	62	38	21	61
PTH (ng/l)[b]	24	11	38	22	4	35
Calcium (ng/l)	2.32	2.23	2.37	2.24	2.18	2.33
Phosphate (pmol/l)	1.05	0.90	1.28	0.99	0.79	1.24
bALP (U/l)	60	52	74	56	43	90
Magnesium (mmol/l)	0.81	0.74	0.90	0.82	0.73	0.87
P1NP (ng/ml)	23	17	37	23	16	48
CTX (ng/ml)[b]	0.124	0.033	0.213	0.062	0.033	0.217
DKK1 (pmol/l)	32.5	18.9	50.9	37.6	14.3	54.3
Sclerostin (pmol/l)	43.7	34.0	55.4	32.0	25.8	48.6
Urea (mmol/l)	6.4	5.0	7.8	5.7	4.5	7.3
Creatinine (μmol/l)	79	64	92	72	59	87
Glomerular filtration rate (ml/min/m²)	73	61	88	82	67	103
Zoledronate cumulative dose (mg)[c]	88	52	156	92	20	120
Pamidronate cumulative dose (mg)[c]	0	0	0	0	0	0

Abbreviations: BRONJ = bisphosphonate-related osteonecrosis of the jaw; $P_x = X^{th}$ percentile; BP = bisphosphonate; 25-OH-D = 25-hydroxy-vitamin D; PTH = parathormon; bALP = bone alkaline phosphatase; P1NP = total procollagen type 1 amino-terminal propeptide; CTX = carboxy-terminal collagen crosslinks; DKK1 = Dickkopf WNT signalling pathway inhibitor 1.

[a] BRONJ+ and BRONJ− patients were matched by sex (same) and age (5 years) using many-to-many coarsened exact matching.

[b] Values under the lower limit of detection were set at the lower limit of detection for descriptive purposes but censoring was accounted for by tobit regression in inferential analysis (see Statistical analysis for details).

[c] The dose of patients not taking the drug was set equal to 0.

for BRONJ. The clinical data were entered into a standardized electronic case report form.

2.4. Laboratory measurements

Blood samples were stored at −80 °C, and laboratory measurements were performed in batch at a single time point. Internal and external quality controls were employed for all assays. The laboratory of Padua University Hospital measured the following: 1) 25-OH-D (chemiluminescent immunoassay, Liaison, DiaSorin, Saluggia, Italy); 2) PTH (chemiluminescent immunoassay, Liaison, DiaSorin, Saluggia, Italy); 3) calcium (colorimetric method, Cobas 8000, Roche, Milan, Italy); 4) phosphate (colorimetric method, Cobas 8000, Roche, Milan, Italy); 5) magnesium (colorimetric method, Cobas 8000, Roche, Milan, Italy); 6) bALP (colorimetric method, Cobas 8000, Roche, Milan, Italy); 7) urea (enzymatic assay method, Cobas 8000, Roche, Milan, Italy); 8) creatinine (Jaffa colorimetric assay, Cobas 8000, Roche, Milan, Italy). The laboratory of Verona University Hospital measured: 1) CTX (chemiluminescent immunoassay, IDS-iSYS Multi Discipline automated analyzer, Immunodiagnostics System, Boldon, UK); 2) P1NP (chemiluminescent immunoassay, IDS-iSYS Multi Discipline automated analyzer, Immunodiagnostics System, Boldon, UK; 3) sclerostin (ELISA, Biomedica Medizinprodukte GmbH & Co KG, Wien, Austria); 4) DKK-1 (ELISA, Biomedica Medizinprodukte GmbH & Co KG, Wien, Austria). In our laboratories, reference values are: 4.6–26.8 ng/l for PTH; 28–128 mg/ml for P1NP; and 0.100–0.300 ng/ml for CTX. Glomerular filtration rate (GFR) was estimated from creatinine using Levey formula (Levey, 1999).

2.5. Statistical analysis

Continuous variables are reported as 50th (median), 25th and 75th percentiles because of skewed or censored distributions. Categorical variables are reported as numbers and proportions. CEM was used to perform a many-to-many matching between BRONJ+ and BRONJ− patients by sex (same) and age (within 5 years) (Iacus et al., 2011). Logistic regression was used to evaluate the association between vitamin D deficiency (0 = no; 1 = yes) and BRONJ (discrete, 0 = no; 1 = yes) (Hosmer et al., 2013). Ordinary least square (OLS) regression was performed to compare continuous uncensored variables (P1NP, sclerostin and DDK-1) between BRONJ+ and BRONJ− patients (Weisberg, 2014). Tobit regression was used to compare continuous censored variables (25-OH-D, PTH and CTX) between BRONJ+ and BRONJ− patients (Cameron and Trivedi, 2019). Censoring was performed at the lower limit of the detection method, i.e., 10 nmol/l for 25-OH-D, 4 ng/l for PTH and 0.033 ng/ml for CTX. All continuous variables were log_e-transformed prior to regression analysis to ensure the homoscedasticity of residuals. CEM was taken into account in all descriptive and inferential statistics using CEM-related weights (Iacus et al., 2011). Robust 95% confidence intervals (95%CI) were calculated for all regression models (Iacus et al., 2011). Statistical analysis was performed using Stata 15.1 (Stata, College Station, TX) together with the user-written CEM command (Blackwell et al., 2009).

3. Results

3.1. Patients

A total of 51 BRONJ+ patients were matched with 73 BRONJ− patients using many-to-many CEM. Table 1 gives the main measurements of the patients, and Table 2 gives the distribution of sex, concomitant disease, and risk factors for BRONJ.

As expected, the time elapsed between NBP withdrawal and enrollment was longer in BRONJ + than in BRONJ− patients (Table 1). The main indication for NBP treatment was breast cancer (35% of BRONJ+ and 21% of BRONJ− patients) (Table 2).

3.2. Main outcome

The frequency (95% CI) of vitamin D deficiency was 59% (45%–72%) in BRONJ+ and 62% (48%–75%) in BRONJ− patients. This amounts to a difference of −3% (−22%–16%, $p = 0.77$) for

Table 2
Distribution of sex, concomitant disease, and risk factors for BRONJ.

	BRONJ+[a]		BRONJ−[a]	
	N	%	N	%
Sex				
Female	30	58.8	43	58.8
Male	21	41.2	30	41.2
Diabetes				
No	46	90.2	68	93.2
Yes	5	9.8	5	6.8
Hypertension				
No	29	56.9	35	47.7
Yes	22	43.1	38	52.3
Chronic renal failure				
No	36	70.6	61	83.3
Yes	15	29.4	12	16.7
Cardiovascular disease				
No	41	80.4	64	87.7
Yes	10	19.6	9	12.3
Chronic pulmonary insufficiency				
No	50	98.0	69	94.9
Yes	1	2.0	4	5.1
Osteoporosis				
No	47	92.2	67	92.3
Yes	4	7.8	6	7.7
Coagulopathy				
No	46	90.2	63	86.2
Yes	5	9.8	10	13.8
Other disease				
No	40	78.4	67	92.1
Yes	11	21.6	6	7.9
Steroids				
No	45	88.2	54	73.9
Yes	6	11.8	19	26.1
Antiangiogenics				
No	45	88.2	72	98.8
Yes	6	11.8	1	1.2
Hormonotherapy				
No	38	74.5	56	77.1
Yes	13	25.5	17	22.9
Maxillary involvement				
No	33	64.7	73	100.0
Yes	18	35.3	0	0.0
Mandible				
No	10	19.6	73	100.0
Yes	41	80.4	0	0.0
Trigger				
Dental extraction	25	49.0	—	—
Dental/periodontal infection	17	33.3	—	—
Dentures	5	9.8	—	—
Implant/perimplant infection	2	3.9	—	—
Other	1	2.0	—	—
Unknown	1	2.0	—	—
Not available	0	0.0	73	100.0
Cancer				
Breast	18	35.3	15	20.7
Kidney	6	11.8	0	0.5
Lung	3	5.9	1	0.9
Non-Hodgkin lymphoma	0	0.0	1	0.9
None	18	35.3	45	61.9
Prostate	6	11.8	11	15.2

Abbreviations: BRONJ = bisphosphonate-related osteonecrosis of the jaw.
[a] BRONJ+ and BRONJ− patients were matched by sex (same) and age (5 years) using many-to-many coarsened exact matching.
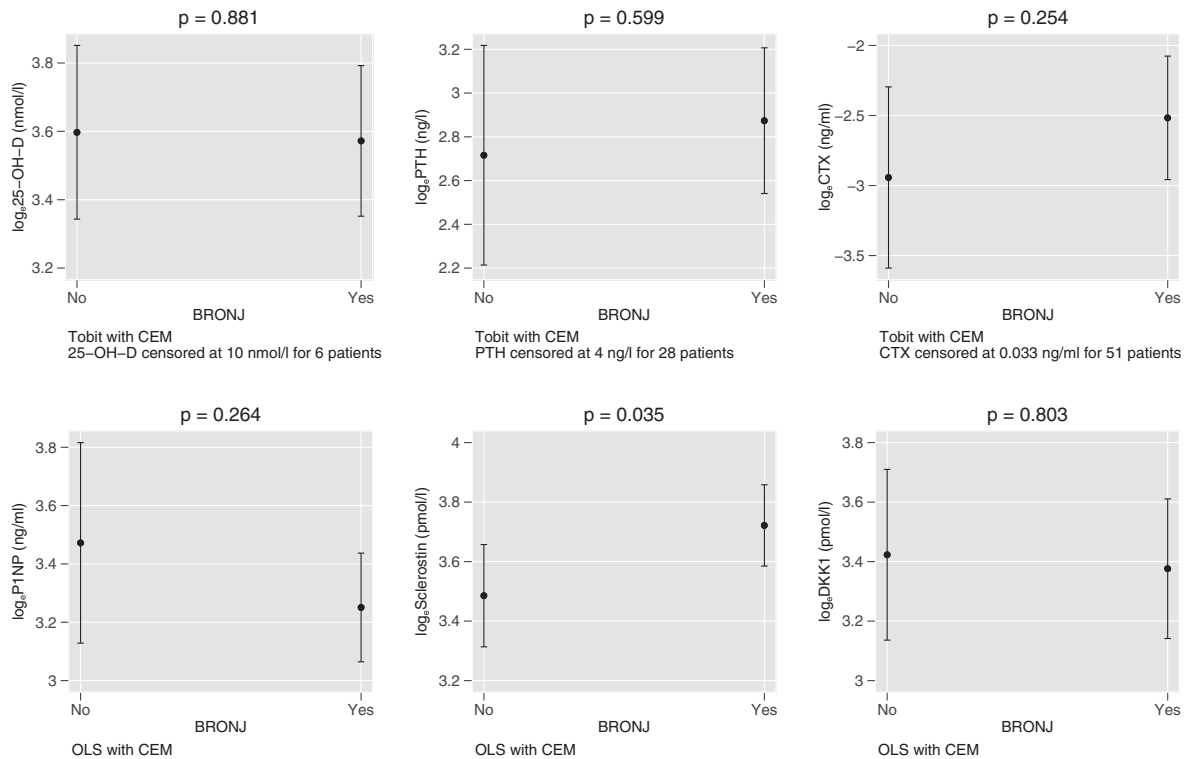
Fig. 1. 25-OH-D, PTH, and markers of bone metabolism. Mean and 95% confidence intervals of the $\log_e$-transformed values of 25-OH-D, PTH and markers of bone metabolism in patients with and without BRONJ matched by sex (same) and age (within 5 years) using many-to-many coarsened exact matching. Values for censored variables are obtained from tobit regression and those for uncensored variables from ordinary least square regression. BRONJ = bisphosphonate-related osteonecrosis of the jaw; CEM = coarsened exact matching; 25-OH-D = 25-hydroxy-vitamin D; $\log_e$ = natural logarithm; OLS = ordinary least squares regression; PTH, parathyroid hormone; P1NP = total procollagen type 1 amino-terminal; Tobit = tobit regression.

BRONJ+ patients. The point estimate of the difference (3%) is too low to be clinically relevant. Because of the relatively low sample size, the 95%CI of such estimate are wide, covering any effect between a reduction of 22% and an increase of 16% of vitamin D deficiency for BRONJ+ vs. BRONJ− patients.

3.3. Secondary outcomes

Fig. 1 compares the $\log_e$-transformed values of 25-OH-D, PTH, CTX, P1NP, sclerostin, and DKK1 in BRONJ+ vs. BRONJ− patients.

Only sclerostin was significantly different in BRONJ+ patients ($p = 0.035$). Even though a pathogenetic role for sclerostin in BRONJ can be hypothesized, the interpretation of this finding must proceed with caution because of the number of multiple comparisons.

4. Discussion

Vitamin D deficiency is common among cancer patients and has been identified as potential risk factor for some cancers (Abbas et al., 2008; Ahn et al., 2008; Gupta et al., 2011; Lauter and Schmidt-Wolf, 2015). However, there is no evidence from the available randomized controlled trials that vitamin D supplementation reduces mortality in subjects with cancer (Goulão et al., 2018).

In a recent histomorphometric case—control study of BRONJ+ vs. BRONJ− cancer patients, we have identified osteomalacia as a potential risk factor for BRONJ (Bedogni et al., 2012). Because vitamin D deficiency is a known cause of osteomalacia and is associated with BRONJ development in rats (Hokugo et al., 2010), we performed a case—control study to test the hypothesis that

vitamin D deficiency is more common in BRONJ+ than in BRONJ− patients. The present study shows that this hypothesis is unlikely to be true. The frequency of vitamin D deficiency was in fact similar in BRONJ+ and BRONJ− patients, and not only serum 25-OH-D and PTH but also most bone turnover markers were similar in the two groups. Although case—control studies are only the first step on the difficult road of identifying cause—effect relationships (Keogh and Cox, 2014), our findings argue against the possibility that vitamin D deficiency is involved in the pathogenesis of BRONJ (Bedogni et al., 2012). Our results differ from those of a recently published retrospective study showing that low serum 25-OH-D is associated with maxillary BRONJ in patients undergoing antiresorptive treatment (Heim et al., 2017). The different study design and the different case mix of patients may partly explain the opposite findings of the two studies (Heim et al., 2017). A recent histomorphometric study suggested that osteomalacia occurs only in the presence of vitamin D deficiency (Priemel et al., 2010). In the present case—control study, the frequency of vitamin D deficiency was similar in BRONJ+ and BRONJ− patients. It can thus be argued that, if vitamin-D dependent osteomalacia were present, it should be equally frequent in BRONJ+ and BRONJ− patients. This seems to rule out vitamin D deficiency as an explanation for the osteomalacia that we detected in our previous case—control study of BRONJ+ vs. BRONJ− patients (Bedogni et al., 2012).

A high PTH is common in osteomalacia and has been suggested to play a role in BRONJ (Ardine et al., 2006). However, the available data are contradictory (Lehrer et al., 2009; Lazarovici et al., 2010; Kim et al., 2013). Because 25-OH-D and PTH were similar in our BRONJ+ and BRONJ− patients, it is unlikely that a systemic alteration of bone metabolism is involved in BRONJ. In agreement with

published data (Lee and Suzuki, 2010; Cremers and Farooki, 2011; Amadori et al., 2013), CTX and P1NP were similar among BRONJ+ and BRONJ− patients. If vitamin D deficiency is not responsible for BRONJ and for the mineralization deficit observed at the healthy margins of jawbone resection of bisphosphonate-treated patients (Bedogni et al., 2012), one could nonetheless hypothesize the existence of a "focal osteomalacia." Such osteomalacia may be produced by osteomyelitis by first causing a mineralization deficit spreading to bone margins and then osteonecrosis. Some data in support of this hypothesis come from animal studies showing that microcolonies of Staphylococcus aureus within the non-mineralized collagen matrix of bone promote osteoclast resorption and woven bone formation (Horst et al., 2012; Sanchez et al., 2013).

We detected higher sclerostin levels in BRONJ + than in BRONJ− patients. This is a novel finding that may have some pathophysiological relevance. Sclerostin is an antagonist of WNT signaling and the decrease in bone formation that follows long-term bisphosphonate therapy is associated with a dose-dependent increase in sclerostin (Gatti et al., 2012). The higher sclerostin levels of BRONJ + patients could reflect higher doses of bisphosphonates and/or could be a surrogate marker of osteomyelitis. Sclerostin is, in fact, known to inhibit osteoblastic differentiation, and may impair bone healing because of a mandibular trigger predisposing to bacterial osteomyelitis and eventually to BRONJ (Marriott, 2013; Taut et al., 2013; Napimoga et al., 2014).

A clear strength of the present study is that all patients were not supplemented with vitamin D. BRONJ patients are, in fact, becoming increasingly supplemented with vitamin D in clinical practice, making it very difficult to perform a study such as the present one. Another strength of the present study is that BRONJ+ and BRONJ− patients were matched for age and sex, which are known to influence 25-OH-D (Holick, 2007). A further strength of the present study is that the laboratory measurements were performed in batch at a single time point under strict quality control.

The present study nonetheless has some limitations. First, it is a case−control study, and as such it can only suggest, but not prove, a causal relationship (Keogh and Cox, 2014). Second, factors known to influence bone metabolism such as cancer type and drug treatment were not evenly distributed among BRONJ+ and BRONJ− patients. An adequate matching for these characteristics would require a much larger number of BRONJ patients, allowed only by multicenter studies. Third, in keeping with most studies (Santini et al., 2012; Günaldi et al., 2015), the median time from bisphosphonate withdrawal was longer in BRONJ + patients. On the other hand, it is well known that the withdrawal of antiresorptive therapy has little or no effect on the progression of BRONJ+. Finally, the 95% CIs of the difference in vitamin D deficiency in BRONJ+ vs. BRONJ− patients were large, because of the relatively low number of studied patients. However, if the point estimate of such difference, i.e., 3%, is the true effect size, an expansion of the sample size will reduce its variability without changing the fact that such effect is modest and biologically irrelevant.

5. Conclusion

In conclusion, in our matched case−control study, BRONJ+ and BRONJ− patients had the same frequency of vitamin D deficiency and the same levels of 25-OH-D, PTH, and most bone turnover markers. Our findings do not support the hypothesis that vitamin D deficiency is involved in the pathogenesis of BRONJ.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.03.007.

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