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ORIGINAL ARTICLE

Vitamin D3 deficiency and MRONJ: insights from a Bi-Center Study in Argentina. A preliminary cross-sectional study

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Abstract:

Objetive: The aim of this study is to describe Vitamin D3 levels in patients diagnosed with MRONJ from two centers in Argentina. **Methods:** A cross-sectional study was conducted on patients from two Oral Medicine centers in Argentina. Patients diagnosed with Medication-related osteonecrosis of the jaw between 2016 and 2022 were included. Vitamin D3 levels were measured in plasma. The STROBE guidelines for reporting cross-sectional studies were followed. **Results:** The final sample consisted of 53 individuals. Among them, 60.4% had oncological-based diseases while 39.6% were diagnosed with osteoporosis. Oncological patients with Medication-related osteonecrosis showed lower vitamin D3 levels (23.9 ng/mL) compared to the osteoporosis group (32.9 ng/mL) (p=0.03). **Conclusion:** These preliminary findings described the levels of vitamin D3 in patients diagnosed with MRONJ, highlighting the relevance of investigating the role of vitamin D3 and its clinical outcomes in these patients. Future research in this area could provide valuable insights for a comprehensive understanding of this role.

Key words: Osteonecrosis; Cancer; Osteoporosis; Vitamin D3.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is an adverse effect associated with the administration of antiresorptive therapy (AT) and antiangiogenic or immunomodulatory treatments, which can be severe. It is characterized by the presence of exposed necrotic bone or an identifiable fistula in the maxillofacial region, persisting for a minimum period of 8 weeks, without a history of radiotherapy in the head and neck area[1-3]. The incidence and prevalence of MRONJ are relatively low, although they are clearly higher in cancer patients receiving high-dose AT or angiogenesis inhibitors rather than osteoporosis patients receiving oral bisphosphonates or denosumab[4].

The potential risk of MRONJ in each patient may vary depending on the potency and cumulative dose of the medication, with reported values ranging from 0.01% to over 20%. The 2022 position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS) indicates that the incidence or risk of MRONJ is very low in patients with osteoporosis (between 0.02% and 0.05%) and variable in cancer patients receiving antiresorptive or antiangiogenic therapy, with an average risk not exceeding 5%[3]. In contrast, other researchers suggest that the incidence or risk of MRONJ is underestimated, with real-world data indicating values around 1–2% for osteoporosis patients and frequently above 10% for oncologic patients[5,6].

Statement of Clinical Significance
This preliminary study describes serum variations of Vitamin D3 in patients with MRONJ. The observed trend toward Vitamin D3 insufficiency, particularly among oncologic MRONJ patients, highlights the need for further investigation into its role in bone metabolism and disease progression. Future research should focus on evaluating the efficacy of Vitamin D3 supplementation in improving clinical outcomes in MRONJ patients, thereby contributing to the development of more effective treatment strategies.

The inhibition of osteoclastic resorption and remodelling, reduction in bone vascular supply, and microbial invasion by odontogenic infection are considered the main etiological events. Antiresorptive drugs are indicated for skeletal disorders characterized by increased bone resorption, including osteoporosis,

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osteopenia, bone metastases from solid tumors, and multiple myeloma[7]. Several studies on this topic have hypothesized that Vitamin D3 may play a pivotal role in the etiological pathways of MRONJ[8,9]. Furthermore, multiple comorbidities are associated with Vitamin D deficiency and other concomitant outcomes of MRONJ. Given its low cost, dietary supplementation with Vitamin D could be a practical strategy for MRONJ prevention[8].

Vitamin D3 (dihydroxycholecalciferol) is essential for calcium homeostasis and bone mineralization. Hypovitaminosis D3 is associated with diseases characterized by altered bone metabolism, such as osteoporosis and cancer. The metabolisms of vitamin D are complex and difficult processes, involving UVB radiation, which is the predominant source for vitamin D in humans and hydroxilating enzymes for synthesis and catabolism. UVB radiation with a wavelength between 290 and 315 nm initiates the synthesis of vitamin D in the skin. Additionally vitamin D can be obtained directly from the diet, which usually represents only 10–20% from the total intake[9-11]. Consequently, recommended Vitamin D3 levels vary between countries due to differences in solar exposure related to geographical latitude. In Argentina, the recommended levels are above 40 mg/100 ml[12]; however, there are no studies describing Vitamin D3 levels in patients with MRONJ in South America. A retrospective study documented lower serum Vitamin D levels in MRONJ patients and an increased prevalence of the disease in patients undergoing AT[9]. The aim of this study is to describe Vitamin D3 levels in patients diagnosed with MRONJ from two centers in Argentina.

MATERIAL AND METHODS

Study design

A cross-sectional study was conducted on patients who sought care at the Oral Medicine Department, Universidad Nacional de Córdoba and the Oral Medicine Department, Faculty of Health Sciences, Universidad Católica de Córdoba, Argentina.

The STROBE guidelines for reporting cross-sectional studies were followed (10) (Supplementary Materials Table S1).

Participants and recruitment

The inclusion criteria were: patients with a clinical and/or histopathological diagnosis of MRONJ[3] who attended between 2016 and 2022. Clinical data were extracted from the medical history and complementary studies databases of both institutions.

The exclusion criteria included patients with osteoradionecrosis (head and neck radiation therapy), and patients with bone metastasis in the maxilla or mandible. Patients who received additional Vitamin D3 supplementation during AT were also excluded in this study.

Variables and measurement

Vitamin D3 levels were measured in plasma, along with laboratory studies of the patient's general assessment and/or presurgical analyses at the moment of the first consultation and initial MRONJ diagnosis.

Data collection

Data extraction was conducted by two independent researchers (G.G. and N.L.), both blinded to the outcomes of the patients. In cases of discrepancies, the researchers discussed their findings with a third investigator (G.F.) to reach a consensus. After final agreement, the relevant data for each case was recorded in an ad-hoc spreadsheet

Analysis of results

A descriptive statistical analysis was conducted using Infostat 2020 software with a significance level set at $p<0.05$. Qualitative and quantitative variables were described using means, standard deviations (SD), and absolute frequency values. Student's t-test was utilized for quantitative variables, while chi-square was employed for qualitative variables.

Ethical considerations

This preliminary cross-sectional study was developed in the framework of the doctoral thesis "Treatment Protocol of Stage 1 and Stage 2 MRONJ based on a pharmacological and surgical scheme", approved by the Health Ethics Committee of the University Clinic Reyna Fabiola (Córdoba, Argentina) Protocol Number 4364.

RESULTS

The final sample consisted of 53 individuals, with 40 (75%) females and 13 (25%) males, averaging 72.17 years (range: 49-85). Among them, 60.4% (n=32) had oncological-based diseases (Cancer Group), while 39.6% (n=21) were diagnosed with osteoporosis (Osteoporosis Group). The average AT duration was 3.85 years for the Cancer Group and 10.43 years

for osteoporotic patients. Zoledronate was the most common drug associated with MRONJ development (39.6%; n=21). Tooth extraction was the most frequent triggering factor, observed in 75% of cases (n=40). Regarding clinical features, 71% (n=38) of MRONJ cases affected the mandible, and 25% (n=13) affected the maxilla. Systemic comorbidities were prevalent in 36 patients (67.9%), with hypertension and diabetes being the most common (Table 1).

Oncological patients with MRONJ showed lower Vitamin D3 levels (23.9 ng/mL) compared to the osteoporosis group (32.9 ng/mL). Vitamin D3 levels also exhibited a distinct distribution between both groups, indicating that cancer patients developed MRONJ with Vitamin D3 Deficiency (p=0.03) (Table 2).

DISCUSSION

In this study, we present findings from a cohort of patients diagnosed with MRONJ from two diagnostic centres in Argentina. Our results align with similar characteristics reported in the literature and discussed in recent consensuses[3]. This holds significance as these patients may be influenced by sociocultural and environmental factors unique to our region, such as Vitamin D3 levels impacted by sunlight exposure, given Argentina's southern latitude.

Vitamin D3, also known as dihydroxycholecalciferol, plays a crucial role in maintaining calcium homeostasis and bone mineralization[13]. Low levels of Vitamin D3 have been associated with an increased risk of diseases characterized by altered bone metabolism[9]. Although maintaining optimal levels of Vitamin D3 has been shown to reduce morbidity and mortality in cancer patients[14], its specific role in preventing MRONJ remains unclear. The parameter used to evaluate the body's vitamin D status is the serum concentration of dihydroxycholecalciferol. In cases of severe hypovitaminosis, the level of dihydroxycholecalciferol remains within the normal range (pg/ml) due to secondary hyperparathyroidism. The reference values commonly used in our setting are as follows: desirable >40 ng/ml, hypovitaminosis D <40 ng/ml, insufficiency <20 ng/ml, deficiency <10 ng/ml[12]. Our study observed a trend toward insufficiency of Vitamin D3, with statistically significant differences between the oncological and osteoporosis MRONJ groups (p=0.03).

The alleged association between vitamin D deficiency and jaw osteonecrosis is an intriguing

Table 1. Demographic and clinical variables.

	n (%)
Total	53 (100)
Sex	
Female	40 (75)
Male	13 (25)
Reason for antirresorptive treatment	
Cancer (Group I)	32 (60.4)
Breast Cancer	16 (30.2)
Prostate Cancer	9 (17)
Multiple Myeloma	3 (5.6)
Bladder Cancer	1 (1.9)
Kidney Cancer	1 (1.9)
Lung Cancer	1 (1.9)
Myelodisplastic Syndrome	1 (1.9)
Osteoporosis (Group II)	21 (39.6)
Antirresorptive treatment duration (median)	
Cancer	3.85 years (SD 2.35)
Osteoporosis	10.43 years (SD 7.51)
Medication	
Zoledronate	21 (39.6)
Alendronate	10 (18.8)
Ibandronate	6 (11.3)
Pamidronate	1 (1.9)
Denosumab	4 (7.5)
Zoledronate + Denosumab	4 (7.5)
Ibandronate + Denosumab	4 (7.5)
Other combination of BP	3 (5.9)
Triggering factor for MRONJ	
Dental Extraction	40 (75.5)
Non-identificable (Spontaneous)	8 (15.1)
Anatomical Location	
Mandible	38 (71,5)
Posterior región	33 (62,1)
Anterior region	4 (7,5)
Multifocal involving both regions	1 (1,9)
Upper Maxilla	13 (24,5)
Posterior region	9 (17)
Anterior region	4 (7,5)
Both maxilla and mandible	2 (4)
MRONJ – Stage	
Stage 0	2 (3,7)
Stage 1	23 (43,4)
Stage 2	22 (41,5)
Stage 3	6 (11,4)
Comorbidities	
No	17 (32,1)
Yes	36 (67,9)
Vitamin D3 dosage	
D3 Vitamin dosage Cancer Group	23.9 ng/ml (SD 11)
D3 Vitamin dosage Osteoporosis Group	32.9 ng/ml (SD 13)

SD: standard deviation. BP: bisphosphonates.

Table 2. Differences among Cancer and Osteoporosis in medication related osteonecrosis of the jaw patients.

Total	Cancer (n)	Osteoporosis (n)	OR (95%CI)	p-value
	32	21		
Sex				
Females	19	21		**0.0008***
Males	13	0		
Age				
Mean (SD)	72.41 (8.77)	71.81 (7.77)		
Median	73	74		0,80†
Range	49–85	58–83		
Triggering factor for MRONJ				
Dental extraction	26	14		
Non-identificable	4	4		0.45*
Other factors	2	3		
Anatomical location				
Mandible	22	16		
Upper maxilla	8	5		0.49*
Both	2	0		
MRONJ – Stage				
Stages 0–1	11	14	3.8 (1.2–12.2)	**0.021***
Stages 2–3	21	7		
Comorbidities				
No	8	3	0.5 (0.11–2.15)	0.49‡
Yes	24	18		
D3 Vitamin dosage Mean (SD)	23.9 ng/ml (SD 11)	32.9 ng/ml (SD 13)		**0.03**†

MRONJ: medication related osteonecrosis of the jaw; OR: odss ratio; SD: standard deviation; DMB: denosumab; BP: bisphosphonates.
*according to χ^2 test; †according to T test; ‡according to Fisher Test.
No data: patients excluded from statistical tests. Bold indicates statistically significant p-values.

topic. In fact, some researchers did not find such an association, while others have observed that low vitamin D levels are risk factors for the development of MRONJ[15]. Our results align with previous studies from other regions of the world, including Germany and Iran. These studies have identified vitamin D3 deficiency in patients with MRONJ and have evaluated their characteristics to determine key factors that could justify vitamin D3 supplementation, aiming to improve clinical outcomes in MRONJ. Heim et al. documented significantly lower serum vitamin D levels in subjects with stage 2 MRONJ compared to patients without exposed bone. The prevalence of MRONJ in patients receiving AT appears to be increased by low serum vitamin D levels. The authors reported a measurable trend suggesting a role of vitamin D in MRONJ development, leading to the recommendation of adequate vitamin D supplementation in patients undergoing AT[16]. Moreover, the Iranian study reported that the control group (under AT but without MRONJ diagnosis) had significantly higher serum vitamin D levels compared to the MRONJ group (63.99 ng/mL±29.80 vs. 29.51 ng/mL±23.72, respectively), with statistically significant differences[17]. Demircan et al. conducted a case-control study to evaluate the levels of several bone markers in MRONJ induced by bisphosphonates. They found higher PTH levels and lower TSH, osteocalcin, and vitamin D levels in MRONJ patients compared to the control groups[18].

The mechanisms that explain the connection between vitamin D deficiency and MRONJ are multifactorial and involve various biological pathways. Understanding these processes is critical to determining how vitamin D deficiency can exacerbate the development and progression of MRONJ. The pathophysiological mechanisms involved are closely linked to bone health and healing. Vitamin D is essential for calcium homeostasis, bone mineralization, and immune modulation. It exerts its effects primarily through the activation of vitamin D receptors (VDRs) in osteoclasts, osteoblasts, and immune cells. A deficiency in vitamin D leads to impaired calcium absorption in the intestines, resulting in decreased serum calcium levels. This triggers secondary hyperparathyroidism, which increases parathyroid hormone (PTH) levels, enhancing bone resorption and reducing bone mineral density. The imbalance between bone formation and resorption creates an environment highly susceptible to osteonecrosis, particularly in the presence of antiresorptive medications such as bisphosphonates and denosumab. Furthermore, vitamin D plays a key role in modulating immune responses and inflammation, both of which are critical factors in the pathogenesis of MRONJ. Vitamin D deficiency can impair the immune system's ability to combat bacterial infections in the oral cavity, increasing the risk of infection following dental procedures such as extractions. The combination of altered bone metabolism, reduced immune function, and compromised healing creates a "perfect storm" for the development of MRONJ in patients with vitamin D insufficiency[8-10,19].

Notably, during the Sars-Cov 2 pandemic, four cases of MRONJ associated with underlying malignancies, that were diagnosed before March 2020, showed clinical worsening coinciding with marked Vitamin D3 deficiency (<10 ng/ml). This deterioration occurred despite maintaining antibiotic regimens, suggesting a potential link between vitamin D3 deficiency and MRONJ progression. The enforced social isolation measures resulted in a significant reduction in sunlight exposure and malnutrition, which is essential for the desirable levels of Vitamin D3. This decrease in sun exposure, combined with the lack of regular clinical follow-up, may have contributed to the worsening of MRONJ (Figure 1). Although the relationship between Vitamin D3 and MRONJ pathogenesis requires further study, additional supplements may present beneficial effects in increasing bone density[20]. Experimental evidence suggests that Vitamin D3 analogues may inhibit local inflammatory conditions leading to MRONJ[21].

Interstingly, a recent study underscore the importance of individualized approaches in the prevention and management of MRONJ, by indicating vitamin D supplementation during surgical procedures, particularly tooth extraction in patients undergoing AT. This study that Vitamin D influence the progression of bone necrosis and help mitigate the severity of MRONJ. This highlights the positive role of vitamin D in maintaining healthy bone tissue, where cellular processes and blood supply are not disrupted. The preventive supplementation of vitamin D in patients treated with AT is critical, as deficiency in vitamin D increases the risk of developing severe MRONJ[22]. Therefore, our findings, coupled with these data, highlight the relevance of investigating the osteoprotective role of vitamin D3 supplementation in the clinical outcomes of patients with or at risk of MRONJ.

The results of this study should be interpreted with caution due to the preliminary nature of the findings. Furthermore, this study has several limitations that warrant consideration. The relatively small sample size may limit the statistical power and reduce the generalizability of the results to broader populations. Given the design of our research, it has some limitations. Uncontrolled variables such as dietary habits, vitamin supplementation, or comorbidities could influence vitamin D3 levels and were not analysed in the study. Numerous factors may affect the variability of vitamin D3 dosage. Since data were collected at a single point in time, it is difficult to determine whether vitamin D3 deficiency preceded the development of MRONJ or resulted from the underlying disease and its treatment. Moreover, cancer patients may present lower vitamin D3 levels due to the disease itself or other factors, such as reduced sun exposure or dietary alterations and restrictions. Further follow-up studies are needed, monitoring vitamin D3 levels throughout the entire follow-up period of patients with MRONJ, while adjusting for some of the confounding variables influencing D3 hypovitaminosis described above. To strengthen these findings, future studies should include control groups comprising cancer and osteoporosis patients without MRONJ, enabling a more robust evaluation of the hypothesis.

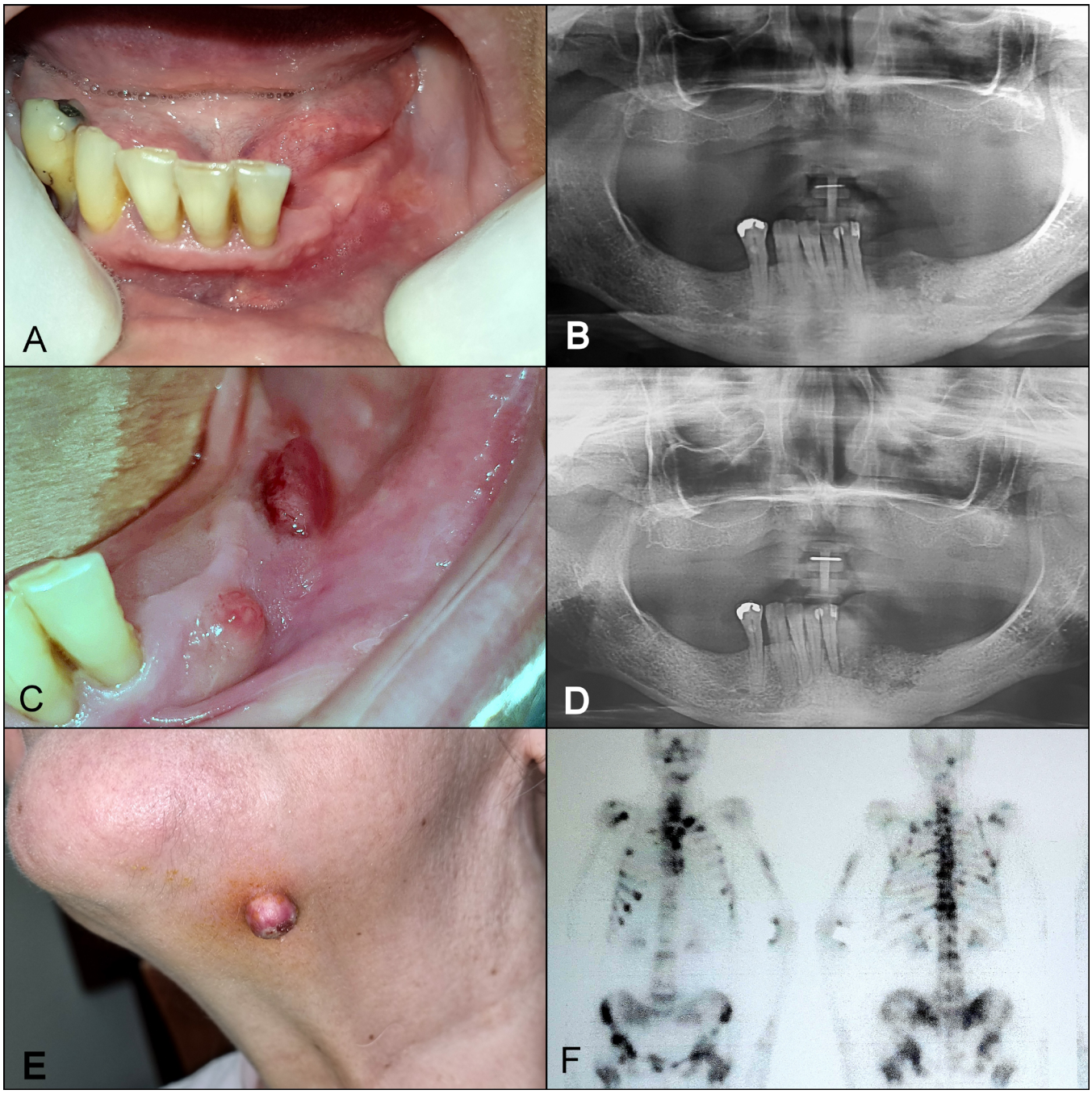

Figure 1. 72-year-old woman treated for 3 years with Zoledronate for breast cancer before the start of the Sars-Cov 2 pandemic with MRONJ stage 0. (A) She presented a slight increase in volume in the left jaw and absence of suppuration after a tooth extraction. (B) In the panoramic radiograph, an osteolytic lesion could be observed in the area adjacent to the lower lateral incisor. The patient was diagnosed with MRONJ Stage 0. (C) During admission to our service, the patient showed a Vitamin D3 dosage of 24 ng/ml. Antibiotic treatment was indicated but no intervention could be made due to the lockdown and quarantine due to the pandemic. She was monitored only 8 months later with an aggressive evolution of the disease. Multiple fistulas were observed accompanied by two bleeding lesions with active, very painful purulent discharge. (D) The radiographic analysis revealed an increase in mandibular osteolysis, with a pattern of moth-eaten bone involving adjacent teeth (which were clinically mobile). A diagnosis of MRONJ in Stage 3 was reached. (E) Infectious oral-cutaneous fistula associated with necrotic focus of the jaw. (F) A scintigram during the oncological follow-up showed new metastatic lesions in the clavicles, lower limbs, ribs, and skull. The vitamin D3 dosage was 18 ng/ml. The patient reported an absence of sun exposure during 8 months of isolation. The patient died 3 months after the last follow-up due to multisystem failure associated with her underlying oncological metastatic disease.

CONCLUSION

This study highlights Vitamin D3 hypovitaminosis in the management of MRONJ. The observed trend toward Vitamin D3 insufficiency, particularly in oncological MRONJ patients, underscores the need to further investigate its impact on bone metabolism and disease progression. Moreover, in accordance with previous publications, future research should focus on evaluating the efficacy of Vitamin D3 supplementation in improving MRONJ patient outcomes, thereby contributing to the development of more effective treatment.

AUTHORS' CONTRIBUTIONS

GG: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Writing – original draft. NL: Conceptualization, Formal analysis, Investigation, Resources, Writing – original draft. FG: Conceptualization, Data curation, Formal analysis. EP: Formal analysis, Investigation, Resources, Supervision, Validation, Visualization, Writing – review and editing. RP: Resources, Supervision, Validation, Visualization, Writing – review and editing.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: This study was approved by the Ethics Committee on Health of the Reyna Fabiola Clinic, Córdoba, Argentina, Protocol Number 4364.

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