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ORIGINAL ARTICLE

Key insights into antiresorptive drug use and osteonecrosis in osteoporotic patients undergoing tooth extractions: A clinical and CBCT assessment

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Abstract

Summary This study investigates the effects of antiresorptive drugs and risk factors for medication-related osteonecrosis of the jaws in osteoporotic patients undergoing tooth extraction. Among the findings, antiresorptive-treated patients had thicker lamina dura and longer healing times. Additionally, corticosteroid intake and multi-rooted teeth carried a higher osteonecrosis risk. Bone sequestrum indicated osteonecrosis.

Purpose To describe the effects of antiresorptive drugs (ARD) in the maxilla and mandible and risk factors for medication-related osteonecrosis of the jaws (MRONJ) in osteoporotic patients undergoing tooth extractions using clinical data and cone beam computed tomography (CBCT).

Methods This retrospective cohort study collected clinical and CBCT data from 176 patients. The study group ($n=78$; 224 extractions) received ARD treatment, underwent tooth extraction, and had a pre-operative CBCT. Additionally, age-, sex-, and tooth-matched controls were selected ($n=98$; 227 extractions). Radiographic examinations were performed independently by three calibrated examiners. Statistical analysis included Chi-square, Fisher's exact, Mann–Whitney *U*, and *t*-tests to contrast clinical and radiographic data between study and control, MRONJ + and MRONJ − , and bisphosphonate and denosumab patients/sites. Significance was set at $p \leq 0.05$.

Results From the study group, 4 patients (5%) and 5 sites (2%) developed MRONJ after tooth extraction. ARD-treated patients exhibited significantly more thickening of the lamina dura and a longer average mucosal healing time (4.4 weeks) than controls (2.6 weeks). In the study group, MRONJ risk significantly increased with corticosteroid intake and in multi-rooted teeth. No significant differences between bisphosphonates and denosumab use were seen in the tomographic features ($p > 0.05$). Lastly, bone sequestrum was exclusively observed in osteoporotic patients, who exhibited post-operative exposed bone or histological evidence of osteonecrosis.

Conclusion Osteoporotic patients under ARD may exhibit thickening of the lamina dura and prolonged post-operative healing. Among these patients, multi-rooted teeth are at higher risk for MRONJ than single-rooted teeth. Sequester formation is a radiographic indicator of osteonecrosis.

Keywords Cone-beam computed tomography · Denosumab · Diphosphonates · Osteonecrosis · Osteoporosis · Tooth extraction

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Introduction

Osteoporosis is a systemic skeletal disorder characterized by decreased bone mass and microarchitectural deterioration, which is a growing concern in an aging population [1]. Antiresorptive drugs (ARDs), including bisphosphonates and denosumab, play a crucial role in managing osteoporosis by inhibiting bone resorption and reducing fracture risk [1, 2]. However, their prolonged use has been associated with a rare but severe complication known as medication-related osteonecrosis of the jaw (MRONJ) [2, 3].

MRONJ is an oral pathology characterized by exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the oral cavity persisting for more than 8 weeks in patients with current or previous treatment with ARD or antiangiogenic agents and with no history of radiation therapy to the jaws or metastatic disease to the jaws [4]. Although MRONJ incidence is relatively low, affecting between 0.001 and 0.4% of the ARD-treated osteoporotic patients [5–7], studies have reported an increased risk after tooth extractions, ranging from 2.3 to 3.4% [8–10].

As osteonecrosis can significantly affect an individual's quality of life, it is crucial not only to promptly diagnose MRONJ but also to identify predisposing factors or latent lesions when tooth extractions are necessary and plan the best perioperative approach [11]. Factors such as the duration of ARD treatment [10], corticosteroid use, and diabetes mellitus [3] have been associated with MRONJ. Additionally, concerning dental extractions, local risk factors for this condition, such as osteosclerosis or osteolysis, teeth with furcation involvement or untreated dentinal caries, multi-rooted teeth, and mandibular extraction sites, have been recognized [12].

Several studies have employed diagnostic imaging to investigate the effects of ARDs on the jaw and their potential contribution to osteonecrosis development [13]. While some investigations have utilized panoramic radiographs [12, 14], the utilization of cone beam computed tomography (CBCT) images for this purpose in osteoporotic patients has been relatively uncommon. Existing CBCT studies have primarily focused on the mandibular cortical area [15, 16], resulting in a gap in the comprehensive evaluation of broad-spectrum changes in this patient population. Therefore, the objective of this retrospective cohort study is to characterize the effects of ARDs on the maxilla and mandible and to identify risk factors for osteonecrosis development in osteoporotic patients undergoing tooth extractions, utilizing clinical data and CBCT assessment. This study aims to address two research questions: (1) Are there clinical and radiographic disparities between patients with and without ARD treatment? and, (2) What are the clinical and local radiographic risk factors associated with MRONJ development? We hypothesize that even low doses of ARDs can lead to detectable changes in the maxillary bones, which will be reflected in clinical data and three-dimensional imaging. Additionally, we anticipate that CBCTs will aid in the identification of local risk factors for MRONJ.

Material and methods

Study design and settings

Before commencing this retrospective cohort study, we sought approval from the ethical committee of UZ/KU Leuven (protocol number: S63934). The study adhered to the ethical standards outlined in the Declaration of Helsinki and the institutional review board. Reporting of the study followed the STROBE guidelines [17].

Participant selection

The medical records of 525 patients who received ARD treatment and underwent CBCT imaging at the oral and maxillofacial surgery department of University Hospitals Leuven between 2010 and 2020 were revised. The inclusion criteria comprised patients who (1) had osteoporosis and were on active or prior treatment with ARDs, (2) underwent tooth extraction(s) within 1 year after CBCT imaging, and (3) had documented clinical follow-up. Exclusion criteria included patients with (1) prior head and neck radiation, (2) bone exposure or prior MRONJ at the extraction site, and (3) poor image quality.

Subsequently, patients from the same imaging department who had undergone CBCT imaging and tooth extractions but had no history of ARD treatment were selected as controls. This control group was matched with the study group in terms of age, sex, and extracted tooth, and also complied with the same exclusion criteria. Tooth extractions followed the methodology outlined by Moreno-Rabié et al. 2023 [12]. Specifically, patients in the study group who were on active ARD therapy did not undergo a drug holiday at the time of tooth extractions. Additionally, the study group was prescribed amoxicillin 875 mg/clavulanic acid 125 mg or clindamycin 300 mg three times daily starting 2 days prior to surgery for a duration of 1 week, and a 0.12% chlorhexidine mouthwash to start the day after the extraction for 2 weeks.

Clinical data selection

The patient's electronic medical records were reviewed, including clinical data and diagnostic images. Collected information included age, sex, systemic condition (i.e., comorbidities), concomitant medication, antiresorptive drug scheme

(i.e., type, dose, duration, and time since the last ARD administration), smoking status [18], alcohol habits, date of CBCT acquisition, extracted teeth (i.e., surgery date, indication for extraction, and clinical follow-up), use of leukocyte- and platelet-rich fibrin (L-PRF), prophylactic antibiotics, antiseptic mouthwash, and, if developed, date of MRONJ diagnosis, stage [4], and date of mucosal healing (i.e., "epithelial continuity obtained by granulation of the extraction socket with no fistula connected to the underlying bone" [19, 20]).

CBCT assessment

The imaging assessment protocol has been previously described by Moreno-Rabie et al. 2023 [21]. In summary, CBCT images were acquired using 3D Accuitomo 170 (J. Morita Corp., Kyoto, Japan) or Newtom VGi evo (Cefla Dental Group, Imola, Italy). Image analysis was conducted using IMPAX software (version 6.5.5, Agfa-Gevaert, Mortsel, Belgium).

Three independent oral and maxillofacial radiologists, blinded to the study variables, evaluated the CBCT images. Prior to the imaging assessment, a calibration session was conducted to establish diagnostic consensus using 21 CBCTs external to this study sample. Parameters assessed at each tooth extraction site included alveolar bone loss, furcation involvement, lamina dura, periodontal ligament space, endodontic treatment, periapical lesion, root remnant, and trabecular bone pattern. Additionally, measurements of the mandibular cortical width (MCW) were performed bilaterally at the level of the mental foramen. Intra-observer agreement was assessed by re-evaluating 49 extraction sites 1 month after the initial assessment completion.

Statistical analysis

Statistical analyses were performed using RStudio software (version 2023.3.1.446, RStudio, Boston, MA, USA). The collected data were grouped by patient and extraction site and categorized into control and study groups, as outlined in Tables 1 and 2. Imaging assessment was conducted solely at the extraction site level (Table 3). Comparisons were made between control and antiresorptive-treated patients/sites, as well as between MRONJ + and MRONJ − patients/sites within the study group.

To assess the independence of clinical data and radiographic features, the Chi-square/Fisher's exact test was used for categorical data, the Mann–Whitney *U* test for ordinal variables, and the *t*-test for continuous data. Additionally, the Pearson correlation test was employed in the study group to analyze the association of ARD duration with MCW and time until mucosal healing. The association between specific antiresorptive drugs (i.e., bisphosphonates and denosumab) and radiographic features was also investigated within the study group. For this analysis, patients who had exclusively been exposed to one type of drug were selected, and the distribution of radiographic characteristics was compared using the aforementioned tests.

Inter-observer agreement was calculated using Fleiss' Kappa test, while Cohen's Kappa test was used to evaluate intra-observer agreement [22]. The significance level was set at $p \leq 0.05$.

Results

Characteristics of the selected patients

A total of 78 osteoporotic patients who underwent 224 tooth extractions were included in the present study. Additionally, 98 patients with 227 tooth extractions were selected for the control group. Both groups exhibited no significant differences in patient age ($p = 0.260$), sex ($p = 0.827$), type of extracted tooth ($p = 0.997$), or presence of systemic diseases ($p = 0.583$). Four patients with osteoporosis (5%; five sites (2%)) and zero controls developed MRONJ. Other peri- and post-operative complications included seven oroantral communications, three inflammations, three post-operative bleedings, and one abscess. All complications were successfully treated.

Clinical data assessment

The clinical characteristics investigated as risk factors for MRONJ are described in Table 1 at the patient level and in Table 2 at the tooth level. These tables also provide comparative data with the control group.

A significantly higher risk of developing MRONJ was observed at the patient level among those with respiratory diseases, including sarcoidosis and chronic obstructive pulmonary disease (n MRONJ + = 3; n MRONJ − = 10; $p = 0.014$). Two of these patients were treated with a budesonide inhaler. Corticosteroid treatment was also identified as a risk factor for MRONJ ($p = 0.021$), although the treatment duration did not show significant differences ($p = 0.225$). No other variable proved to be a predisposing factor for MRONJ. However, it is important to note that all patients with osteonecrosis had been treated with injectable antiresorptive drugs (i.e., subcutaneous or intravenous). Three of them had been on these drugs for at least 4 years, and two had received their last administration less than 6 months before tooth extraction.

When examining the extraction sites, it was observed that molars developed significantly more osteonecrosis than premolars and single-rooted teeth ($p = 0.041$). All sites that developed osteonecrosis exhibited spontaneous and percussion pain at the time of extraction. Among these, two showed radiographic signs of moderate periodontitis, and three had dentinal caries.

Table 1 Data at a patient level for osteoporotic and control subjects

Characteristic		Osteoporosis under ARD						Control	
Number of patients, *n*		78						98	
Development of osteonecrosis, *n* (%)		MRONJ +		MRONJ −		Total	*p*-value	NA	*p*-value
		4	5%	74	95%	78			
Age (years)	Mean (range)*	70.3 (51–82)		67.4 (16–92)		67.6 (16–92)	0.496	66.2 (45–86)	0.260
Sex, *n* (%)	Female	4	6%	60	94%	64	1.000	78	0.827
	Male	0	0%	14	100%	14		20	
Extracted teeth, *n*	Mean (range)*	2.0 (1–3)		2.9 (1–16)		2.9 (1–16)	0.828	2.3 (1–13)	0.182
Systemic disease, *n* (%)	Yes	4	8%	47	92%	51	0.292	59	0.583
	No	0	0%	27	100%	27		39	
Antiresorptive drug type, *n* (%)	Bisphosphonate	1	2%	45	98%	46	0.112	NA	NA
	Denosumab	1	5%	19	95%	20		NA	
	Both	2	17%	10	83%	12		NA	
Specific antiresorptive drug used, *n* (%)	Zoledronic Acid	1	6%	15	94%	16	0.889	NA	NA
	Denosumab	3	9%	29	91%	32		NA	
	Alendronate	1	3%	32	97%	33		NA	
	Pamidronate	0	0%	4	100%	4		NA	
	Ibandronate	0	0%	9	100%	9		NA	
	Risedronate	0	0%	8	100%	8		NA	
	Etidronate	0	0%	1	100%	1		NA	
Number of sequential ARD, *n* (%) *	1	3	5%	56	95%	59	0.964	NA	NA
	2	1	8%	12	92%	13		NA	
	3	0	0%	6	100%	6		NA	
Time on ARD (months)	Mean (range)*	55.8 (6–124)		68.9 (3–266)		68.2 (3–266)	0.865	NA	NA
Time since last administration of ARD (months), *n* (%)	Not stopped	0	0%	17	100%	17	0.571	NA	NA
	Mean (range)*	7.4 (2–19)		20.8 (1–97)		19.9 (1–97)	0.205	NA	
	Mean B.P. (range)*	19		30.4 (1–97)		30 (1–97)	1.000	NA	
	Mean D.B. (range)*	3.6 (2–4)		10.9 (1–47)		10.1 (1–47)	0.106	NA	
Corticosteroid use (months), *n* (%)	Yes	3	20%	12	80%	15	*0.021*	7	*0.029*
	No	1	2%	62	98%	63		91	
	Mean (range)*	44.1 (17–63)		88.5 (18–161)		79 (17–161)	0.225	46.8 (1–154)	0.127
Alcohol consumption, *n* (%) *	No consumption	1	4%	25	96%	26	0.829	26	0.684
	1–2 units week	2	9%	21	91%	23		39	
	3–4 units week	0	0%	3	100%	3		4	
	> 5 units week	0	0%	11	100%	11		18	
	Ex-abuser	0	0%	2	100%	2		2	
	Unknown	1	8%	12	92%	13		9	
Tobacco use, *n* (%)	Never smoker	2	5%	39	95%	41	0.415	68	0.092
	Current smoker	1	8%	11	92%	12		10	
	Former smoker	0	0%	22	100%	22		18	
	Unknown	1	33%	2	67%	3		2	

The *p*-values correspond to the outcomes of the Chi-square/Fishe's exact test for comparing MRONJ + and MRONJ − sites in the study group, and the latter with the control group. Variables marked with an asterisk (*) indicate ordinal/numerical data analyzed using the Mann–Whitney *U/t* test. Significant *p*-values ($p \leq 0.05$) are indicated in *italics*

MRONJ, medication-related osteonecrosis of the jaws; *ARD*, antiresorptive drugs; *B.P.*, bisphosphonates; *D.B.*, denosumab; *NA*, not applicable

Finally, when analyzing the time taken to observe mucosal healing, a longer healing time was observed in the study group, with a mean of 4.4 weeks (ranging from 1 to 86 weeks), while the control group took 2.6 weeks (ranging from 1 to 7 weeks) ($p < 0.001$). Specifically, the bisphosphonate-exposed sites took 4.1 weeks (ranging from 1 to 11 weeks) for mucosal closure, while denosumab-exposed sites took an average of 4.4 weeks (ranging from 1 to 86 weeks). No significant correlation was found between the period on ARDs and the time until mucosal healing ($r = -0.022$, $p = 0.849$).

Table 2 Summary of the data at a tooth level in the osteoporotic and control groups

Characteristic		Osteoporosis under ARD						Control	
Number of extracted teeth, *n*		224						227	
Development of osteonecrosis, *n* (%)		MRONJ +		MRONJ −		Total	*p*-value	NA	*p*-value
		5	2%	219	98%	224			
Extraction indication, *n* (%)	Caries	1	1%	67	99%	68	0.282	77	0.333
	Cyst	0	0%	2	100%	2		1	
	Difficult Hygiene	0	0%	0	0%	0		3	
	Fracture	1	5%	21	95%	22		14	
	Internal resorption	0	0%	0	0%	0		1	
	Pericoronitis	0	0%	0	0%	0		2	
	Periodontitis	1	1%	86	99%	87		81	
	Root remnant	2	7%	28	93%	30		33	
	Trauma	0	0%	2	100%	2		1	
	NA	0	0%	13	100%	13		14	
Type of teeth, *n* (%) *	Incisors + canines	0	0%	84	100%	84	*0.041*	77	0.178
	Premolars	1	2%	53	98%	54		46	
	Molars	4	5%	82	95%	86		104	
Arch, *n* (%)	Maxilla	2	1%	143	99%	145	0.348	136	0.338
	Mandible	3	4%	76	96%	79		91	
Region, *n* (%)	Anterior maxilla	0	0%	64	100%	64	0.280	51	0.454
	Posterior maxilla	2	2%	79	98%	81		85	
	Anterior mandible	0	0%	20	100%	20		26	
	Posterior mandible	3	5%	56	95%	59		65	
Antibiotic prophylaxis, *n* (%)	Yes	5	2%	209	98%	214	1.000	25	*< 0.001*
	No	0	0%	10	100%	10		202	
Antiseptic mouthwash, *n* (%)	Yes	5	2%	212	98%	217	1.000	227	*0.007*
	No	0	0%	7	100%	7		0	
Use of L-PRF, *n* (%)	Yes	3	2%	148	98%	151	0.662	3	*< 0.001*
	No	2	3%	71	97%	73		224	
Time until mucosal healing, *n* (%)	0– ≤ 4 weeks	0	0%	111	100%	111	NA	205	0.059
	> 4– ≤ 8 weeks	0	0%	108	100%	108		22	
	> 8 weeks	5	100%	0	0%	5		0	
	Mean (weeks)*	26.61		3.88		4.40	*< 0.001*	2.59	*< 0.001*
MRONJ worse stage, *n* (%)	Stage 1	3	60%	NA		NA	NA	NA	NA
	Stage 2	2	40%	NA		NA		NA	
	Stage 3	0	0%	NA		NA		NA	

The *p*-values described under osteoporosis and control correspond to those obtained with the Chi-square/Fisher's exact test or Mann–Whitney *U* test (*) when data were ordinal. Comparisons were made between MRONJ + and MRONJ − sites in the study group, and between study and control groups. Significant *p*-values ($p \leq 0.05$) are *italicized*

MRONJ, medication-related osteonecrosis of the jaws; L-PRF, leukocyte- and platelet-rich fibrin; NA, not applicable

CBCT assessment

All tooth extractions occurred within 12 months of CBCT acquisition, with an average of 3 months for osteoporotic patients and 2 months for the control group.

Inter-observer agreement was substantial ($K = 0.695$), and there was no significant difference between the observer's MCW measurements ($p = 0.921$). Furthermore, intra-observer agreement ranged from substantial to almost perfect ($K_{OBSERVER1} = 0.829$, $K_{OBSERVER2} = 0.979$, $K_{OBSERVER3} = 0.790$). There was also no significant difference in the reproducibility of MCW measurements ($p_{OBSERSER1} = 0.923$, $p_{OBSERVER2} = 0.960$, $p_{OBSERVER3} = 0.538$).

The radiographic findings at each extraction site are summarized in Table 3. When comparing the control and study groups, it was observed that the latter exhibited significantly more thickening of the lamina dura ($p < 0.001$). In contrast, the control group had significantly more periapical

Table 3 Pre-operative CBCT characterization of the tooth extraction sites in the study (MRONJ + and MRONJ −) and control groups

Observed parameter		Osteoporosis under ARD						Control	
Number of extracted teeth, *n*		224						227	
Development of osteonecrosis, *n* (%)		MRONJ +		MRONJ −		Total	*p*-value	NA	*p*-value
		5	2%	219	98%	224			
Horizontal bone loss	Absent/initial	3	2%	137	98%	140	1.000	150	0.487
	Moderate/severe	2	2%	82	98%	84		77	
Angular bone defect	Absent	4	2%	171	98%	175	1.000	187	0.309
	Present	1	2%	48	98%	49		40	
Furcation involvement	Absent	5	3%	189	97%	194	1.000	180	0.053
	Present	0	0%	30	100%	30		47	
Lamina dura	Normal	3	2%	124	98%	127	1.000	183	*< 0.001*
	Thickened	2	2%	95	98%	97		44	
Periodontal ligament space	Normal	2	3%	71	97%	73	0.662	92	0.098
	Widened	3	2%	148	98%	151		135	
Endodontic treatment	Absent	4	3%	138	97%	142	0.533	143	0.979
	Adequate filling	1	3%	32	97%	33		35	
	Inadequate filling	0	0%	49	100%	49		49	
Periapical lesion size*	Absent	3	2%	155	98%	158	0.852	138	*0.009*
	Small (≤ 3 mm)	2	7%	27	93%	29		22	
	Large (> 3 mm)	0	0%	37	100%	37		67	
Periapical lesion cortical*	Absent	3	2%	156	98%	159	0.917	138	*0.009*
	None	2	13%	14	87%	16		14	
	Thinning	0	0%	18	100%	18		22	
	Expansion	0	0%	7	100%	7		9	
	Destruction	0	0%	24	100%	24		44	
Root remnant	Absent	3	1%	201	99%	204	0.064	196	0.151
	Present	2	10%	18	90%	20		31	
Osteoclerosis*	Normal	2	1%	144	99%	146	0.285	105	*< 0.001*
	Localized sclerosis	1	6%	17	94%	18		16	
	Extended sclerosis	2	3%	58	97%	60		106	
Osteolysis*	Absent	4	2%	205	98%	209	0.253	213	0.775
	Localized lysis	1	11%	8	89%	9		13	
	Extensive lysis	0	0%	6	100%	6		1	
Periosteal reaction*	Absent	5	2%	217	98%	222	0.847	226	0.559
	Localized reaction	0	0%	1	100%	1		0	
	Extensive reaction	0	0%	1	100%	1		1	
Sequestrum formation*	Normal	3	1%	218	99%	221	*< 0.001*	227	0.081
	Localized sequester	0	0%	1	100%	1		0	
	Extensive sequester	2	100%	0	0%	2		0	

P-values obtained as results from the Chi-square/Fisher's exact test when comparing MRONJ + and MRONJ − patients in the study group, as well as the study and control groups. Variables denoted with an asterisk (*) represent ordinal/numerical data analyzed with the Mann–Whitney *U* test. Significant *p*-values ($p \leq 0.05$) are *italicized*. *NA*, not applicable

lesions (p = 0.009) and osteosclerosis at the extraction sites ($p < 0.001$). It should be noted that 55% of the control teeth with periapical radiopacities had periapical lesions, and 73% of the remaining teeth had thickened periodontal ligaments.

The presence of radiographic bone sequestrum was exclusively observed in the ARD-treated group, and it exhibited a significantly higher prevalence in extraction sites that subsequently developed post-operative osteonecrosis (Fig. 1) ($p < 0.001$). Notably, only one of these sites had a histopathological study using a sample taken during tooth extraction. This specific site was the sole one with bone sequestrum and did not manifest post-operative exposed bone (Fig. 2). The examination confirmed the presence of necrotic bone and a radicular cyst. At this site, complete mucosal healing was observed 5 weeks after surgery.

Fig. 1 Clinical (a) and CBCT reconstructions (b, c, d) of an 83-year-old female with osteoporosis treated with zoledronic acid. Clinically, there was spontaneous pain and suppuration from the root remnants of the mandibular left first and second molars. No evidence of exposed bone was observed. In the sagittal CBCT slice (b), the root remnants are pointed out by white arrows. While in the axial (c) and coronal (d) views, white arrows depict sequestrum formation. Tooth extractions were carried out under local anesthesia. Seven weeks postoperatively, bone exposure and loose sequesters were clinically observed. Therefore, sequestrectomy was performed. The duration from tooth extractions to mucosal healing was 11 weeks. No histopathological analysis was conducted

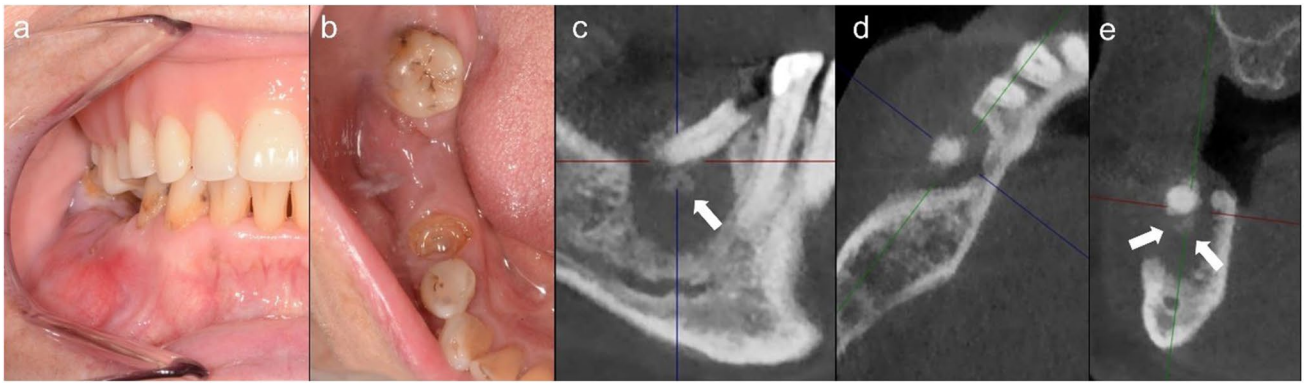

Fig. 2 Clinical (a, b) and CBCT reconstructions (c, d, e) of a 90-year-old female with osteoporosis treated with denosumab. A root remnant of the mandibular right second premolar with an accompanying vestibular abscess and absence of bone exposure were clinically observed. In the CBCT, a radiolucent lesion surrounding the tooth and a bony island (white arrows) can be seen. Tooth extraction and debridement of the alveolar socket were performed under local anesthesia. A sample of the bone and lesion were taken for histopathological analysis where the diagnosis of osteonecrosis and radicular cyst was confirmed. Complete mucosal healing and absence of inflammation were seen 5 weeks postoperatively

On average, the mandibular cortical width was 4 mm in the study group (MRONJ + 4.6 mm, MRONJ − 3.9 mm) and 4.2 mm in the control group. No significant differences were observed between the control group and study group ($p = 0.129$), MRONJ + and MRONJ − ($p = 0.639$), MRONJ + and control ($p = 0.774$), nor between MRONJ − and control patients ($p = 0.099$). Lastly, a non-significant correlation ($p = 0.827$, $r = -0.029$) was observed between the duration of ARDs and MCW.

Finally, to identify three-dimensional features associated with each type of ARD, 137 sites exposed exclusively to bisphosphonates and 52 to denosumab were selected. None of the three-dimensional characteristics observed showed an association with drug type ($p > 0.05$).

Discussion

The incidence of MRONJ in osteoporotic patients remains relatively low, ranging from 0.001 to 0.4% [5–7, 23]. However, tooth extractions elevate MRONJ risk to 3.4% [8–10, 23, 24]. Nonetheless, avoiding extractions solely due to

MRONJ concerns is unwarranted, as infection may be the primary cause of osteonecrosis [19]. Identifying risk factors for MRONJ in osteoporotic patients poses challenges due to the limited cases and restricted use of diagnostic images [25]. Thus, we aimed to describe the effects of ARDs on the maxilla and mandible and risk factors for the development of MRONJ using clinical data and CBCT in osteoporotic patients undergoing tooth extractions. Our findings indicate that patients under low doses of ARDs present thicker lamina dura and extended post-operative healing times and have a higher risk of MRONJ if under corticosteroid treatment or undergoing extractions of multi-rooted teeth. Moreover, sequestrum formation serves as a radiographic indicator for MRONJ.

Concurrent clinical risk factors for MRONJ during tooth extractions have been recognized, including osteoporotic patients older than 65 years [10, 11], females [26], prolonged ARD therapy [10, 11, 23], rheumatoid arthritis [23], corticosteroid use [9], and mandibular extraction sites [10, 11]. While Jeong et al. identified the mandible as a predisposing arch, no differences were found in dental arch location [10]. Although, the present results did not find a mandibular predilection, a preference for multi-rooted sites over single-rooted teeth was observed. This propensity can be attributed to alveolar socket size. In the absence of severe bone resorption, as seen in our MRONJ + teeth, the wound area can be twice as large in molars compared to canines or incisors [27].

Diverse tooth extraction protocols are reported, which may impact MRONJ development. Like ours, some employ prophylactic antibiotics [19, 26] and discourage discontinuation of ARD treatment [19, 20]. Lesclous et al. agreed that discontinuing ARD is not recommended due to increased fracture risk in the cessation period, especially with denosumab [20]. Our results support the finding that continued ARD treatment does not increase the risk of MRONJ. Besides, while some studies omit primary closure [19, 26], others compare the use of L-PRF and mucoperiosteal flaps [28]. Poxleitner et al. found no significant differences in healing outcomes between L-PRF and mucoperiosteal flap use, suggesting L-PRF as a minimally invasive, efficient, and cost-effective alternative, countering drawbacks of mucoperiosteal flaps such as invasiveness and reduced vestibular depth affecting dental rehabilitation [28]. Complementarily, a meta-analysis involving 2098 subjects found no significant differences in the effectiveness of L-PRF and alveolectomy for MRONJ prevention [25]. Likewise, our study did not demonstrate a significant protective effect of L-PRF use for MRONJ.

Few radiographic studies exist in osteoporotic patients investigating the local effects of ARDs on jawbones and their relationship with MRONJ. In this context, one of the most researched structures is the mandibular cortical width [14–16]. Three-dimensional examinations have revealed a notably thicker MCW in ARD-treated patients compared to controls [15, 16], averaging 4.3 mm and 3.4 mm, respectively [15]. Although, these differences are not evident in panoramic radiographs [14]. Similarly, our findings showed no significant contrasts between ARD-treated patients and the control group, nor was there a correlation between the duration of ARD treatment and the thickness of the MCW. This lack of association might arise from a treatment duration of less than 1 year with ARD in about 20% of the study patients, and from the fact that 25% of the study group and 20% of the control group lacked MCW measurements, as this structure was not visible on their CBCT scans.

One of the novel aspects of the present investigation is the comprehensive assessment of bony changes seen on CBCT images, which has been studied in oncologic patients treated with high doses of ARDs [21, 29] but to a lesser extent in patients treated with low doses. In osteoporotic patients under ARDs, no significant differences in the trabecular bone pattern have been demonstrated in two- [12] or three-dimensional examinations [16] when compared to a control group. Nevertheless, even low doses of ARD demonstrated significantly more thickening of the lamina dura in panoramic radiographs [12]. All findings are corroborated by our current results. In contrast, imaging outcomes related to oncologic ARD doses revealed not only a higher incidence of thickening of the lamina dura but also of osteosclerotic and osteolytic regions [30], which have been identified as local risk factors for MRONJ [30–32]. Lesser changes in the radiodensity of the bone trabeculae are consistent with a lower incidence of MRONJ observed in low-dose ARD treatment.

Among the examined radiographic features, only the presence of bone sequesters demonstrated an association with MRONJ development. Notably, all instances of radiographic sequestrum formation in our sample corresponded to sites with osteonecrosis. Two cases exhibited post-operative exposed bone, exceeding eight weeks, while the remaining case displayed histological osteonecrosis. In the latter case, tooth extraction and sequestrum removal within a single surgical procedure were curative, as post-operative bone exposure was absent. Shudo et al. advocated for biopsy during tooth extraction in suspected latent MRONJ cases [19]. Tooth extraction is not the trigger for MRONJ but rather the unveiling factor in these cases. Thus, combining perioperative biopsy and radiographic assessment could promptly identify a latent pathology.

While some studies observed no exposed bone postoperatively, they noted a longer healing period in osteoporotic patients on bisphosphonates [19, 20]. Shudo et al. linked longer bisphosphonate treatment to delayed mucosal healing, particularly beyond 5 years [19]. Similarly, Lesclous et al. found that ARD-treated patients experienced delayed healing, contrasting control healing within 4 weeks [20]. Our results showed controls achieved mucosal healing in an average of 2.6 weeks, whereas ARD-treated patients, whether

under bisphosphonates or denosumab, needed 4.4 weeks. Yet, no correlation was found between ARD treatment duration and healing time. Consistently, other studies also found no significant impact of ARD type or treatment duration [28], corticosteroids [19, 20], diabetes [19, 20], smoking [20], number or type of tooth extracted [28], or systemic diseases [28] on socket healing.

This retrospective design inherently holds limitations compared to prospective studies. While efforts were made to match controls, ideally, they would have been drug-naïve osteoporosis or osteopenia patients, which was unattainable. Furthermore, the study's limited sample size precluded comprehensive exploration of the effects of diverse bisphosphonate types. Additionally, different surgeons with varied experience levels performed the tooth extractions, despite surgeries taking place in the same center under similar protocols and materials. Lastly, due to the lack of histopathological reports, the incidence of MRONJ may be higher in this sample owing to dental infections rather than tooth extractions per se.

In conclusion, osteoporotic patients under low-dose ARDs showed a noticeable thickening of the lamina dura. Corticosteroid intake and the extraction of multi-rooted teeth were identified as risk factors for MRONJ. Sequestrum formation observed on CBCT scans can serve as a strong radiographic indicator of osteonecrosis. In addition, a prolonged post-operative healing period is expected in patients taking antiresorptive drugs, even when there is no development of exposed bone. These results contribute to understanding the effects of ARDs and osteonecrosis in osteoporotic patients undergoing tooth extractions.

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Declarations

Conflicts of interest Catalina Moreno-Rabié, Rocharles Cavalcante Fontenele, Nicolly Oliveira-Santos, Fernanda Nogueira-Reis, Tim Van den Wyngaert, and Reinhilde Jacobs declare that they have no conflict of interest.

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