SYSTEMATIC REVIEW

Prevalence of radiographic findings on jaws exposed to antiresorptive therapy: a meta-analysis

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Objectives: Determine the prevalence of radiographic findings (RF) on both jaws among patients receiving antiresorptive bone therapy.

Methods: Six electronic databases and partial grey literature were searched. Data was collected based on predetermined criteria. The key features from the included studies were extracted. The MASTARI tool assessed the potential risk of bias (RoB) among the studies, while the GRADE approach determined the level of evidence.

Results: 29 studies were identified and included in the qualitative analysis, totalling 1133 patients. 27 studies had sufficient data to be included in a series of meta-analysis reporting 12 types of radiographic findings, and were split in two groups based on their study design. G1 comprised descriptive observational studies and G2 analytical cross-sectional studies. Two studies presented a high RoB, 16 had a moderate RoB, and 11 had low RoB. The overall level of evidence identified was very low. The most frequent RF were mixed lytic-sclerotic areas (73.88%), followed by osteolytic changes (66.18%), osteosclerosis (65.75%), cortical bone erosion (50.83%), persisting alveolar socket (45.77%), periodontal ligament (PDL) widening (44.69%), and inferior alveolar canal (IAC) involvement (43.40%). Less frequent, but equally important, were the periosteal reaction (34.27%), lamina dura thickening (32.97%), sequestrum (29.94%), pathologic fracture (20.90%), and density confluence of cortical and cancellous bone (16.61%). 20 patients reported no signs.

Conclusions: RF prevalence was high and mainly included mixed lytic-sclerotic areas, osteolysis, osteosclerosis, cortical bone erosion, persisting alveolar socket, PDL-widening, IAC-involvement. Due to the very low level of evidence (GRADE) caution should be exercised when considering these findings.

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Introduction

Antiresorptive bone therapy consists of regularly administration of antiresorptive drugs, such as bisphosphonates (BP). BP are synthetic drugs commonly prescribed intravenously for treating many osseous diseases involving lytic bone, such as multiple

myeloma, bone metastasis of solid tumors, osteitis deformans (Paget's disease), and osteogenesis imperfecta, as well as prescribed orally for treatment and prevention of osteoporosis.^{1,2} These drugs are potent inhibitors of osteoclast-mediated bone resorption acting through the inhibition of bone remodeling capability, and indirectly preventing the loss of bone mass, pathologic fractures, pain or hypocalcemia; all

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of which markedly improve the quality of life of the affected patients.^{3,4}

Bone disease progression is typically first evidenced through a radiographic examination, and it is reasonable to expect that antiresorptive treatment would lead to changes in radiodensity of maxillomandibular structures visible on dental radiographs.⁴ In this regard, careful review of radiographs of patients receiving antiresorptive treatment is necessary to assess increased structural radiodensity, which may have implications during risk assessment of potential complications during and following dental procedures.

Radiographic findings (RF) related to antiresorptive bone therapy have already been reported, including alveolar bone loss (not associated with chronic periodontal disease), trabecular bone alterations, persistent alveolar sockets, sclerotic changes of the lamina dura, and inferior alveolar canal narrowing.⁵ From this point, if therapy continues, destructive bone changes were often progressive, from the lamina dura or cortical plate to the medullar bone, and finally, to affect the entire cross-sectional area of the jaw bone.⁶ A better understanding of the significance of radiographic manifestations of such therapy may assist in the identification of patients at increased risk of developing these complications.⁵ The possibility of an early diagnosis through imaging can make a significant difference in the management of the underlying disease; enabling better treatment and prevention of new potential cases.⁵ Moreover, high-resolution imaging could be helpful allowing comparison of affected to non-affected areas, while asymptomatic areas can also be detected early.⁶ Therefore, properly timed imaging should be mandatory, even in advanced cases, for assessing the extent of damaged bone.

Despite being a pathologic bone condition, there are no established diagnostic maxillomandibular radiographic criteria for alterations caused by antiresorptive therapy. Previous studies have reported RF from panoramic radiography, CT, and cone-beam CT (CBCT).^{7–11} However, the frequency and consistency of these findings remain unclear. Based on these premises, the goal of this systematic review was to answer the following focused question: “Among patients receiving antiresorptive bone therapy, what is the prevalence of RF on the jaws?”

Methods and materials

Protocol registration

This systematic review conformed to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist.¹² The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under CRD 42016038055.¹³

Eligibility criteria

Inclusion criteria:

- Studies that evaluated patients that underwent antiresorptive therapy and were at least exposed to one of following radiographic methods: CBCT, intraoral radiographs or panoramic radiographs were included.
- In order to reduce publication and retrieval bias, we did not restrict our search by language, date or publication status.

Exclusion criteria:

- Studies that did not assess RF on patients that underwent antiresorptive therapy.
- Reviews, case reports, letters, personal opinions, book chapters, conference abstracts, guidelines, and pilot studies.
- Studies conducted using animal models.
- Studies that evaluated other diagnostic methods.
- Studies conducted in patients with bone diseases such as Paget’s disease, rheumatoid arthritis, osteogenesis imperfecta.
- Studies in which the jaw bones were not assessed.
- Studies in which the RF were not clearly reported.
- Full copy of potentially usable studies irretrievable.

Information sources and search

Detailed individual search strategies for each of the following bibliographic databases were developed on April 20, 2016: EMBASE, Latin American and Caribbean Health Sciences (LILACS), PubMed, Science Direct, Scopus, and Web of Science. An email alert was created at all databases for new references that appeared after this initial search. A final updated search was done on July 7, 2017. A partial grey literature search was performed on Google Scholar, Open Grey, and ProQuest. In addition, a hand-search was done on the reference lists of selected articles.

Appropriate key words and Medical Subject Heading (MeSH) terms were applied using the following MeSH terms: “antiresorptive therapy” AND “dental radiograph” AND “jaw” OR “head and neck”. The search was adapted for each database with the aid of a specialized librarian from health sciences (Supplementary Material 1, available at online). All references were managed, and the duplicated hits were removed using reference manager software (Endnote X7, Thompson Reuters, New York, NY).

Study selection

Two reviewers (KLD, LFH) independently screened titles and abstracts of all identified electronic database citations. The same authors applied the eligibility criteria on the full-text assessment of the selected articles. Any disagreement was resolved by discussion. A third author (MC) was involved, when required, to make a final decision.

Data items and collection process

The data collection was also completed by two reviewers (KLD, LFH) independently. The following information was recorded for all the included studies: study characteristics (authors, year, country of publication, and study model), sample characteristics (size, age range, sex, bisphosphonate-related osteonecrosis of the jaws (BRONJ) case sites and trigger factors, and underlying disease), intervention characteristics (antiresorptive therapy type and time of exposure-months and imaging type), and RF. The third reviewer (MC) crosschecked the collected information and confirmed its accuracy.

Summary measures

The prevalence of RF on the jaws among patients receiving antiresorptive bone therapy was the main outcome evaluated. Prevalence was reported or calculated as a percentage. For meta-analysis purposes, the studies were grouped based on their study design following the Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI) critical appraisal tool.¹⁴ Since these groups reflect different clinical scenarios and infer the RF prevalence differently.

Synthesis of results

A qualitative analysis of results based on the prevalence of RF was performed. In order to decrease heterogeneity among studies, results were separated according to study design.

The individual RF results were combined by means of a series of meta-analysis if sufficient data were available following the appropriate Cochrane Collaboration guidelines and were performed using MedCalc (MedCalc Software Ostend, Belgium) for Windows. A random-effect model was used in all cases.

Heterogeneity within studies was evaluated either by considering clinical (differences about participants, type of interventions and results), methodological (design, and risk of bias) and statistical characteristics (effect of studies) or by using inconsistency indexes (I^2).¹⁵ A value greater than 50% was considered an indicator of substantial heterogeneity among studies.¹⁶ The significance level was set at 0.05.

Post hoc subgroup analysis were performed to investigate possible sources of between-study heterogeneity in meta-analyses with a minimum of 10 included studies. The mixed effects analysis was carried out by using the Comprehensive Meta-analysis software (version 3). In this analysis, the random effect model is used to estimate pooled effect sizes for each subgroup, thereafter, differences within subgroups are tested for heterogeneity.

Quality assessment

The methodology of the selected studies was evaluated using MAStARI critical appraisal tool.¹⁴ Two reviewers (KLD, LFH) independently completed the appraisal assessing each domain in terms of the potential risk of bias. Different MAStARI questionnaires were used

based on the included studies designs, among them, the checklist for observational descriptive studies, checklist for observational analytical studies (cohort and case-control), and checklist for analytical cross sectional studies. All of them consisted of eight or nine questions, with possible answers as “yes”, “no”, “unclear”, or “not applicable”. Risk of bias (RoB) was categorized by the authors as high when the study reached up to 49% of a “yes” score, moderate when the study reached 50 to 69% of a “yes” score, and low when the study reached more than 70% of a “yes” score. A third reviewer (MC) resolved any disagreement. Figures of the quality assessment were generated with Review Manager 5.3 (RevMan 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark).

RoB across studies

Studies were separated as per RoB score (low, moderate, or high) and the meta-analysis was performed to determine if the RF prevalence varied based on that.

Level of evidence

Two authors (KLD, LFH) rated the quality of the evidence as well as the strength of the recommendations according to the following aspects: risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, plausible confounding, and dose response gradient. A summary of overall strength of evidence available was presented using “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) Summary of Findings (SoF) tables, from GRADEpro software (McMaster University, Hamilton, Canada).^{17,18}

Results

Studies selection

The initial search on databases identified 2708 citations from databases. From the updated search, an additional 69 studies were detected. Only three studies were included from the grey literature. No additional study was included from the reference lists. After the initial selection phase, 177 studies were selected for full-text assessment. From these, 148 studies were later excluded due to different reasons (Supplementary Material 2). Hence 29 studies were included for qualitative and 27 for quantitative synthesis. A flowchart summarizing this process of identification, inclusion, and exclusion of studies is shown in [Figure 1](#).

Study characteristics

The included studies examined 1133 patients. All of them recruited patients that had been treated with antiresorptive bone therapy for either oncological or non-oncological reasons. The studies were observational studies either descriptive^{3,5-7,9,19-34} or analytical cross-sectional,^{10,35-39} analytical cohort,⁴⁰ or analytical case-control.⁴¹

Figure 1 Flow diagram of literature search and selection criteria (adapted from PRISMA).

Only one included study was an analytical cohort,⁴⁰ as well as, only one analytical case-control⁴¹ study was found. Qualitative analysis was not possible as only one study for these study types was identified. The remaining included studies were split into two groups for meta-analysis purposes based on their study design as follows: the observational descriptive studies

were grouped in Group 1 ($n = 21$), and the analytical cross-sectional comprised the Group 2 ($n = 6$).

All included studies used the confirmed diagnosis of BRONJ according to American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria. From the 27 studies identified, BRONJ patients were first recognized and then their RF were described; whereas only Rugani

et al⁴⁰ and Popovic et al³³ followed patients under antiresorptive bone therapy without BRONJ diagnosis and later described the RF incidence. A summary of the descriptive characteristics of the studies can be found in Table 1.

Results of individual studies

Two articles were not included in the meta-analysis as there was only one study per category. Klingelhöffer et al⁴¹ developed an analytical case-control study aiming to find a correlation between certain RF in dental panoramic radiographs and the risk for developing BRONJ in patients taking antiresorptive therapy. The authors found that RF as visible alveolar socket (OR = 5; $p = 0.001$), enhancement of lamina dura (OR = ∞; $p < 0.001$), enhancement of the mandibular canal (OR = 4.8; $p = 0.025$), proliferative periostitis (OR = ∞; $p = 0.05$), and osteolytic processes at the cortex (OR = 19.7; $p < 0.001$) were seen significantly more often in patients undergoing antiresorptive bone therapy than in the control group consisted of dental panoramic radiographs from patients without antiresorptive treatment. Rugani et al⁴⁰ developed an analytical cohort study investigating a homogenous group of premenopausal early breast cancer treated sample with a cumulative dose of 28 mg zoledronic acid, with an average follow-up period of 4 years and 8 months.⁴⁰ This study did not reveal any case of BRONJ Stage 1 to 3, however, a high prevalence of early findings of BRONJ was detected, 10.4% (five patients) showed BRONJ stage 0 with clinical and radiological signs, and another five patients (totaling 20.8 %) only radiological signs.^{4,40} The control group consisted of patients that did not receive BP therapy or other relevant medications like antiangiogenetics or had local radiation therapy. From them, five patients showed unspecific radiological signs that are associated with BRONJ in patients with a history of BP therapy. No clinical signs were detected. Statistical evaluation revealed no statistically significant difference between groups, although a tendency was visible (Fisher's exact test, $p = 0.098$). Comparing the frequency of clinical signs, Fisher's exact test was significant. (Five patients in the study group versus 0 patients in the control group, $p = 0.023$).

All remaining studies ($n = 27$) were split into two groups based on the study design for meta-analysis purposes. Group 1 ($n = 21$) was comprised of observational descriptive studies whose BRONJ patients were identified and the prevalence of RF described. In Group 2 ($n = 6$), analytical cross-sectional studies selected BRONJ and control patients and reported the prevalence of RF. All of them classified BRONJ cases according to the staging system of AAOMS 2009.

In Group 1 three studies evaluated the diagnostic potential of various radiological techniques (CBCT, panoramic or periapical radiography) to detect mild osteonecrosis, describing the RF. They did not report BRONJ Stage 0, but rather the nomenclature “early as

Stage 1” was used instead.^{6,10,34} Accordingly, as early as Stage 1 “destruction of the trabecular structure of the cancellous bone” was a frequent radiological sign of BRONJ in CBCT scans.³⁴ “Cortical bone erosion” and “sclerotic changes of the *lamina dura*” can also often occur even in the low-stage (Stage 1).^{6,34} “Sequestration” and “Osteosclerosis” of the jaw bone can be seen across all stages, but is more frequent in severe BRONJ cases, Stages 2 to 4.^{6,34} “Periosteal bone proliferation” occurred only in higher-stage BRONJ sites (Stages 3 and 4),³⁴ as well as mixed lytic-sclerotic areas, IAC involvement, and pathologic fracture.⁶ One study identified only stage 0 disease.⁵ Another study only reported RF for advanced Stage 3 patients as follows: fracture, osteolytic changes, and periosteal bone proliferation.²² Two studies staged BRONJ cases in 1 to 3¹⁹; however, they did not report the RF prevalence individually. Finally, the other 15 studies did not stage the BRONJ cases and reported the RF altogether.

In Group 2, Treister et al,¹⁰ reported radiographic features for Stages 1 to 3 using panoramic radiography, and osteosclerosis, surface irregularity, persistent alveolar socket, and osteolysis were seen in all stages, except for sequestrum that was found only in Stages 2 and 3. Two studies staged BRONJ cases in 0 to 3^{35,39}; however, did not report the RF prevalence individually. Finally, the other 3 studies did not stage the BRONJ cases and reported the RF altogether.^{36–38}

Synthesis of results

Among all included studies, 27 studies described RF in patients receiving antiresorptive bone therapy and had enough data to be included in our quantitative analysis (meta-analysis). These studies were grouped by their study design and random effects meta-analysis was performed for each RF reported in each group. Forest plots were constructed for the prevalence of each RF for observational descriptive studies (Group 1; Figures 2 and 3), and prevalence of each RF for analytical cross-sectional studies (Group 2; Figure 4). High heterogeneity between the studies was found in the meta-analyses for both groups. Group 1 had an inconsistency (I²) of 63.95 to 97.33%, and Group 2 had an I² of 0.00 to 93.70%.

Results from the meta-analysis in Group 1 (observational descriptive studies) showed an RF prevalence as follow: mixed lytic-sclerotic areas 73.88% (CI:50.94 to 91.44; $n = 81$); osteolysis 66.18% (CI:43.03 to 85.83; $n = 503$); osteosclerosis 65.75% (CI:38.07 to 88.59; $n = 466$); cortical bone erosion 50.83% (CI:33.63 to 67.92; $n = 272$); persisting alveolar socket 45.77% (CI:24.72 to 67.65; $n = 175$); PDL widening 44.69% (CI:15.68 to 75.86; $n = 38$); IAC involvement 43.40% (CI:20.59 to 67.81%; $n = 200$); periosteal reaction 34.27% (CI:18.93 to 51.52; $n = 86$); lamina dura thickening 32.97% (CI:14.14 to 55.23; $n = 139$); sequestrum 29.94% (CI:14.90 to 47.64; $n = 460$); pathologic fractures 20.90% (CI:11.55 to 32.15; $n = 197$); density confluence of cortical and

Table 1 Summary of descriptive characteristics of included articles ($n = 29$). Data are numbered unless otherwise stated.

Study characteristics			Sample			Intervention characteristics			Findings
Author, year, country	Study design	Size (N)	Age, mean range (years)	Gender	BRONJ site and trigger factors	Underlying disease	Antiresorptive therapy type and time exposure	Imaging type	Radiographic findings
Bagan et al. 2015–Spain	Analytical cross-sectional	43 BRONJ 43 controls	75	M 17 F 26	Tooth extraction 24 Implant 2 Prosthesis 1 Unknown 13	Breast Ca 13 Myeloma 7 Osteoporosis 12 Other Ca 3 Prostate Ca 8	Zo 30 oBPs 13 (58 mo)	CT	Cortical bone erosion 16 Fractures 2 IAC involvement 34 Osteolysis 37 Osteosclerosis 43 Sequestrum 23 Mixed lytic-sclerotic areas 26
Barragan-Adjemian et al. 2009–USA	Analytical cross-sectional	26 BRONJ U controls	NR	NR	NR	Ca 100%	iBPs i.v. 26 (8–60 mo)	CBCT	Cortical bone erosion 12 No signs 6 Persisting alveolar socket 6 Osteolysis 9 Sequestrum 1 Worm-eaten appearance 16
Beninati et al. 2013–Italy	Descriptive Observational	51 BRONJ	68	M 21 F 30	Apicectomy 1 Periimplantitis 3 Prosthetic trauma 12 Spontaneously 8 Tooth extraction 27	Oncological reasons 46 Non-oncological 5	Zo 31 31 (61%) Pa + Zo 15 15 (29%) Al 4 4 (8%) Ris 1 1 (2%) (48 mo; 24–84) 34 (67%)	Pano CT	Cortical bone erosion 12 No signs 6 Persisting alveolar socket 6 Osteolysis 9 Sequestrum 1 Worm-eaten appearance 16
Bianchi et al. 2007–Italy	Descriptive Observational	32 BRONJ	66 (48–84)	M 12 F 20	Mand 22 Max 10 Periimplantitis 1 Spontaneously 10 Tooth extraction 21	Breast Ca 15 Lung carcinoid 1 Myeloma 8 Non-hodgkin lymphoma 1 Prostate Ca 7	Zo 24 Zo, Pa 8 (4–196 mo)	Pano CT	Osteolysis 13 (CT); 6 (Pano) Cortical bone erosion 13 (CT); 6 (Pano) Osteosclerosis 13 (CT); 5 (Pano) Sequestrum 25 (CT); 12 (Pano) Periosteal reaction 13 (CT); 1 (Pano) No signs 2 (CT); 14 (Pano)
Bisdas et al., 2008–Germany	Descriptive Observational	32 BRONJ	63 (47–77)	M 13 F 19	U	Breast Ca 11 Multiple myeloma 9 Non-Hodgkin's lymphoma 1 Osteoporosis 2 Prostate Ca 4 Polyarthritis 2 Renal cell carcinoma 4	Zo 17 Al 11 Ib 4 (33 mo; 3–58)	CT	Osteolysis 28 Osteosclerosis 32 Fractures 16 Periosteal reaction 20 IAC involvement 32
Cardoso et al. 2017–Brazil	Retrospective Descriptive Observational	35 BRONJ	59 (24–95)	M 8 F 27	Mand 38 Max 7	Osteoporosis 2 Ca 33	Zo 27 Pa 3 Zo + Pa 2 Al 2 Ib 1 (42 mo; 6–288)	Pano	Osteolysis 28 Cortical bone erosion 12 Osteosclerosis 35 Sequestrum 9 Lamina dura thickening 17 IAC involvement 15 Persisting alveolar socket 12 Fracture 3

(Continued)

Table 1 (Continued)

Study characteristics			Sample			Intervention characteristics			Findings	
Author, year, country	Study design	Size (N)	Age, mean range (years)	Gender	BRONJ site and trigger factors	Underlying disease	Antiresorptive therapy type and time exposure	Imaging type	Radiographic findings	
Chianidussi et al. 2006–Italy	Descriptive Observational	10 BRONJ	72 (61–84)	M 3 F 8	Mand 7 Max 3 Bone biopsy 1 Periimplantitis 1 Preprosthetic surgery 1 Tooth extraction 4	Breast Ca 5 Lung Ca 2 Multiple myeloma 3	Zo i.v. 10	Pano CT MRI	Pano: Osteolysis 10 CT: Cortical bone erosion 10 Mixed lytic-sclerotic areas 10	
Cho et al., 2012 South Korea	Descriptive Observational	11 BRONJ	68 (49–79)	F 11	NR	Breast Ca 1 Osteoporosis 10	Zo i.v. 1 Al 9	Pano CT	Fracture 2 Osteolysis 11 Periosteal reaction 10	
Demir et al. 2017–Turkey	Retrospective Descriptive Observational	27 BRONJ	64 (37–83)	M 8 F 19	Tooth extraction 15 Pulpal periodontal infection 5 Irritation of prosthesis 7	Osteoporosis 7 Breast Ca 7 Prostate Ca 5 Renal Ca 2 Thyroid Ca 1 Multiple myeloma 4	iBPs 20 oBPs 5 unknown 2 Ca ly–10y	Periapical CBCT	Osteosclerosis 23 Persisting alveolar socket 16 Cortical bone erosion 22 Periosteal reaction 8 Sequestrum 12 Osteolysis 23	
Dore et al. 2009–Italy	Descriptive Observational	15 BRONJ	70 (54–86)	M 3 F 12	Mand 11 Max 6 Bone biopsy 1 Periimplantitis 1 Preprosthetic surgery 1 Tooth extraction 5 Traumatic lesion 1 Unknown 6	Breast Ca 9 Lung Ca 2 Multiple myeloma 4	Zo i.v. (15) 2 y (1–3 y)	Pano CT	Pano: Osteolysis 15 CT: Cortical bone erosion 4	
Elad et al. 2010 Israel	Descriptive Observational	30 BRONJ	67 (53–83)	M 48 F 19	Mand 19 Max 10 Tooth extraction and Dental implant 57%	Multiple myeloma 11 Non-hodgkin lymphoma 2 Waldenstrom macroglobulinemia 1 Chronic lymphocytic leukemia (n = 1) Solid Ca (n = 11)	Zo 14 Pa 11 Al 4 3.5 y (8 mo–9 y)	CT	Cortical bone erosion 24 Mixed lytic-sclerotic areas 16 Osteosclerosis 4 Osteolysis 30 Perforation to nearby anatomical cavities 6 Periosteal reaction 6 Sequestrum 7 The canal cortex was preserved and continuous but with localized areas of lower density 1	
Fleisher et al. 2010–USA	Analytical cross-sectional	68 BRONJ and controls	U	M F	Tooth extraction	U	U	Periapical Pano CT	PDL widening 24	
Fleisher et al. 2014–USA	Descriptive Observational	23 BRONJ	65	M 8 F 15	Mand 25 Tooth extraction 14 Spontaneous 11	Breast Ca 14 Myeloma 6 Other Ca 3	Zo 16 De 2 5	Periapical Pano 22	Pano: Lamina dura thickening 2	
Gill et al. 2009 USA	Retrospective Descriptive Observational	19 BRONJ	64 (48–80)	M 5 F 14	Mand 16 Max 5 Resection of a mandibular torus 1 Tooth extraction 14	Breast Ca 11 Lymphoma 1 Multiple myeloma 4 Osteoporosis 4 Prostate Ca 2	Zo or Pa 17 Al 2 (2–5y)	Pano 7 CT 13	Fractures 5 Mixed lytic-sclerotic areas 11 Osteosclerosis 4 Osteolysis 3 Sequestrum 4	

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Table 1 (Continued)

Study characteristics			Sample			Intervention characteristics			Findings
Author, year, country	Study design	Size (N)	Age, mean range (years)	Gender	BRONJ site and trigger factors	Underlying disease	Antiresorptive therapy type and time exposure	Imaging type	Radiographic findings
Guggenberger et al. 2014 Switzerland	Analytical cross-sectional	22 BRONJ 22 controls	70 (46–85)	M 5 F 17	Explantation 2 Dental Implant 1 Poor fitting denture 1 Tooth extraction 12	Breast Ca 8 Osteoporosis 7 Ca 6	Zo 15 Pa 1 Al 3 Ib 2 De 1	CBCT	Necrosis 24 Osteosclerosis 23 Periapical reaction 23
Guo et al. 2016 China	Retrospective Descriptive Observational	44 BRONJ	65 (44–85)	M 18 F 22	Mand 24 Max 12 Tooth extraction 30	Breast Ca 14 Myeloma 10 Ca 8	Multiple Kidney Pa 9 Other 5	Zo 18 Pa 13 Zo + Pano CT	Osteosclerosis 28 Lamina dura thickening 25 IAC involvement 23 Periapical reaction 6 Cortical perforation 19 Fracture 5 Sequestrum 2
Hutchinson et al. 2010–USA	Prospective Descriptive Observational	30 Patients at risk for BRONJ	68	M 20 F 10	NR	Osteoporosis 10	Al 10 3y (2.4–4.7)	Pano CT CBCT	Osteosclerosis 10 Density confluence of cortical and cancellous bone 10 IAC involvement 10 Lamina dura thickening 20 Osteolysis 10 Cortical bone erosion 10 Persisting alveolar socket 20
Jadu et al. 2007 Canada	Retrospective Descriptive Observational	24 BRONJ 96 controls		F 120	Periodontal disease 19 Periapical disease 5 Pericoronitis 1	Multiple Myeloma	120 Pa 120	Periapical	Sequestrum 8 Osteolysis 3 Osteosclerosis 4 Necrosis
Klingelhofer et al. 2016 Germany	Case-control	36 BRONJ 24 controls	67	NR	NR	Malignant reasons 40 Benign reasons 18 Unknown 2	Zo 24 Al 13 Ri 3 Pa 4 Ib 2 Unknown 5 57 mo	Pano	*Sequestrum BRONJ 5, CG 1 *Osteosclerosis BRONJ 15, CG 6 *Persisting alveolar socket BRONJ 28, CG 5 *Lamina dura thickening BRONJ 5, CG 1 *IAC involvement BRONJ 7, CG 1 *Osteolysis BRONJ 1, CG 0 *Periapical reaction BRONJ 9, CG 1 *Density confluence of cortical and cancellous bone BRONJ 6, CG 2

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Table 1 (Continued)

Study characteristics			Sample			Intervention characteristics			Findings
Author, year, country	Study design	Size (N)	Age, mean range (years)	Gender	BRONJ site and trigger factors	Underlying disease	Antiresorptive therapy type and time exposure	Imaging type	Radiographic findings
Koth et al. 2017 - Brazil	Analytical cross-sectional	27 BRONJ 108 controls	NR	M 10 F 125	Tooth extraction 15 Dental Implant 3 Dental Prosthesis 6 Periodontitis 2	Osteoporosis 113 Metastasis 18 myeloma 4	Al 96 Ib 2 Ri 11 Zo 13 Pa 25 Clo 2 Pano	Periapical Pano	Sequestrum BRONJ 2, CG 1 Osteosclerosis BRONJ 14, CG 24 Persisting alveolar socket BRONJ 14, CG 13 Lamina dura thickening BRONJ 6, CG 24 IAC involvement BRONJ 13, CG 30 Osteolysis BRONJ 18, CG 10 PDL widening BRONJ 13, CG 34 Periradicular radiolucency BRONJ 8, CG 22 Osteolysis 2 IAC involvement 2
Melo & Obeid, 2005–USA	Retrospective Descriptive Observational	11 BRONJ	69 (59–83)	M 7 F 4	Mand 8 Max 2 Both 1	Breast Ca 3 Lung Ca 1 Multiple myeloma 7	Pa 7 Zo 7 34 mo	Pano	
Obinata et al. 2017–Japan	Descriptive Observational	34 BRONJ	68 (40–88)	M 9 F 25	Mand 20 Max 12 Both 2 Tooth extraction 20 Periodontitis 10 Spontaneous 2 Unknown 2	Oropharyngeal Ca 6 Tongue Ca 5 Parotid Ca 2 Others Ca 3	iBPs 20 oBPs 14	Pano CT	Osteolysis 29 Osteosclerosis 31 Sequestrum 25 Periosteal reaction 15 Fracture 5 Lamina dura thickening 2 Cortical bone erosion 4 Mixed lytic-sclerotic areas 18 Sequestrum 18 IAC involvement 4 Fracture 4 IAC involvement 3 Osteolysis 4 Osteosclerosis 16 PDL widening 4 Periapical radiolucency 5 Persisting alveolar socket 5 Lamina dura thickening 7 Sequestrum 3
Olutayo et al., 2010 - Nigeria	Descriptive Observational	22 BRONJ	54–82	M 17 F 5	None 1 Pain from bone or tooth 4 Spontaneously 8 Tooth extraction 9	Breast Ca 3 Multiple myeloma 9 Prostate Ca 5 Renal cell Ca 4	Zo i.v. 22	Periapical Pano CBCT	
Phal et al. 2007 USA	Retrospective Descriptive Observational	15 BRONJ	52–85	M 4 F 11		Metastatic Ca 8 Multiple myeloma 3 Osteoporosis 4	Zo 2 Pa 4 Al 6	CT	
Popovic et al. 2010 - Slovenia	Prospective Descriptive Observational	11	52 (41–76)	M 6 F 5	Mand 6 Max 2 Tooth extraction 8 Unknown 3	Breast Ca 3 Multiple myeloma 6 Prostate Ca 2	Zo 9 Zo + Pa 2 28CT mo (13–36)		IAC involvement 4 Osteosclerosis 11 Osteolysis 11 Periosteal bone proliferation 7 Sequestrum 1

(Continued)

Table 1 (Continued)

Study characteristics			Sample			Intervention characteristics			Findings
Author, year, country	Study design	Size (N)	Age, mean range (years)	Gender	BRONJ site and trigger factors	Underlying disease	Antiresorptive therapy type and time exposure	Imaging type	Radiographic findings
Rugani et al. 2013–Austria	Cohort 4 y 8 mo follow-up	48	(43–60)	F 48	Mand 8 Jaws 2 Tooth extraction 4 Dental Implant 1 Unknown 4	Breast Ca 48	Zo 48 3y	Pano CBCT	Osteosclerosis 3 Lamina dura thickening 1 Persisting alveolar socket 4 Osteolysis 3 Density confluence of cortical and cancellous bone 3
Treister et al. 2009–USA	Analytical cross-sectional	39 BRONJ 18 controls		M 24 F 15	Tooth extraction 25	Myeloma 25 Breast Ca 6 Prostate Ca 4 Osteoporosis 1 Other 3	iBPs 39	Pano	Osteosclerosis 32 Cortical bone erosion 20 Persisting alveolar socket 14 Sequestrum 4 Osteolysis 7
Wilde et al. 2012–Germany	Retrospective Descriptive Observational	20 BRONJ	NR	M 6 F 14	NR	Breast Ca 5 Multiple myeloma 8 Other 4 Prostate Ca 3	Zo 10 Zo + B 2 Zo + Pa 2 Zo + B + Pa 3 Other 3	CBCT	Osteolysis 15 Cortical bone erosion 13 Sequestrum 5 Osteosclerosis 1 Perosteal reaction 3
Wutzl et al. 2006–Austria	Descriptive Observational	17 BRONJ	65 (36–79)	M F	Tooth extraction 13 Unknown 4	Breast Ca 4 Histiocytosis X 1 Multiple myeloma 12	Pa 5 Zo 12	Pano CT	Pano;Persisting alveolar socket 13 CT; Osteosclerosis 17

1, one;Al: AlendronateBRONJ: bisphosphonate-related osteonecrosis of the jawsCBCT: cone beam computerized tomographyCG: control groupCa: cancerClo: ClodronateEti: EtidronateIAC: inferior alveolar canalb: ibandronateMi: MinodronateNR: not reportedPa: PamidronatePano: Panoramic radiographsRi: risedronateU: unclear informationZo: ZolendronateiBPs: intravenous bisphosphonatesi.v.: intravenousmo: monthsoBPs: oral bisphosphonatesy: years
a: data calculated by the authors.

Figure 2 Forest plot for all radiographic findings that occurred in patients that received antiresorptive therapy reported by observational descriptive studies (Group1). Sample = 609. (to be continued)

cancellous bone 16.61% (CI:0.06 to 52.88; $n = 60$). Also, two studies reported a prevalence of no signs of 26.35% (CI: 3.30 to 60.89; $n = 83$) (Figure 5).

Results from the meta-analysis in Group 2 (analytical cross sectional studies) showed RF prevalence as following: osteosclerosis 52.69%, (CI:26.66 to 59.55; $n = 265$); IAC involvement 35.15% (CI:27.96 to 42.10%; $n = 221$); PDL widening 35.12% (CI:28.74 to 41.77; $n = 203$); cortical bone erosion 26.41% (CI:12.24 to 43.67; $n = 143$); osteolysis 24.83% (CI:10.60 to 42.66; $n = 278$); persisting alveolar socket 21.60% (CI:16.11 to 27.66; n

= 192); and sequestrum 10.43% (CI:0.77 to 29.06; $n = 278$) (Figure 6).

Post hoc subgroup analyses were conducted with the following moderator variables: medication administration method (intravenous and/or oral), type of imaging examination (periapical, panoramic, CT, and/or CBCT), and number of specialized radiologists evaluating images. A minimum of 10 studies in meta-analyses was only available in Group 1 for osteosclerosis, osteolysis, cortical bone erosion, and sequestrum. No significant differences across effect sizes

MIXED LYTIC-SCLEROTIC AREAS

PERSISTING ALVEOLAR SOCKET

LAMINA DURA THICKENING

FRACTURES

PDL WIDENING

DENSITY CONFLUENCE OF CORTICAL AND CANCELLOUS BONE

Figure 3 (continuation) Forest plot for all radiographic findings that occurred in patients that received antiresorptive therapy reported by observational descriptive studies (Group I). Sample = 609.

were observed regarding medication administration methods, however, tests for heterogeneity were significant ($p < 0.05$) for both type of imaging examination and number of radiologists in all outcomes assessed, except for sequestrum.

Supplementary data from all meta-analyses and *post hoc* analyses can be found in Supplementary Material 3.

Quality assessment

For descriptive studies, three questions were considered “Not Applicable” and not considered in the final score: “If comparisons are being made, was there sufficient description of the groups?”, “Was the follow up carried out over a sufficient time period?”, and “Were the outcomes of people who withdrew described and included in the analysis?”. For analytical studies

Figure 4 Forest plot for all radiographic findings that occurred in patients that received antiresorptive therapy reported by analytical cross-sectional studies (Group2). Sample = 416.

all questions were considered applicable in both questionnaires.

As a result, two studies presented a high risk of bias, 16 had a moderate risk, and 11 had low risk scored by MASTARI checklists. The main topics that introduce bias were: no use of a random or pseudo random sample; no use of an appropriate statistical analysis; and no description of confounding factors and strategies to deal with them. Most studies recruited a group known to have BRONJ. Figure 7 and Supplementary Material 4 present detailed information on the risk of bias assessment.

RoB across studies

Within the studies with a low RoB ($n = 11$), the overall RF prevalence was slightly smaller than studies with a moderate RoB ($n = 16$) (Supplementary Material 5). Only one RF was reported by both studies to have a high RoB ($n = 2$), which was persisting alveolar socket that also presented higher prevalence (41.29%) than studies with low RoB (33.44%).

Level of evidence

The overall quality of evidence identified using GRADE's SoF table was very low due to the following reasons: (1) observational studies started GRADE analysis from a low score, (2) high or moderate risk of bias scored for some studies (Figure 5), and (3) high I^2

(inconsistency) scored by the meta-analysis for some studies (Supplementary Material 3); suggesting very low confidence in the estimated effect from the assessed outcomes (Table 2). Moreover, since effect estimates of this SR are prevalence rates, significance levels potentially causing publication bias were not a major concern. Explanations for non-publication of primary studies might be related to poor methods or small sample sizes. Nonetheless, included studies presented relatively small sample sizes and thus publication bias was not suspected.

Discussion

This systematic review investigated the available evidence on the prevalence of RF among patients that received antiresorptive bone therapy. No previous systematic review focused on this topic. Summarizing the available data is considered to be a useful exercise to provide the basis for early detection of associated bone structural alterations. Usually, clinicians pay attention to radiographic bone alterations after a medical history of chronic use of antiresorptive drugs. However, anamnesis processes do not always have specific questions related to antiresorptive medication and sometimes patients may omit valuable data regarding their current medication. Therefore, the results of this review may

Figure 5 Distribution of the prevalence of radiographic findings reported by observational descriptive studies (Group 1).

help clinicians consider the identified RF as potential adverse jaw bone signs of antiresorptive therapy. Such findings may also greatly assist clinicians with a patient at the start of therapy giving them advice on how to address future complications before the expected bone alterations.

Figure 6 Distribution of the prevalence of radiographic findings reported by analytical cross-sectional studies (Group 2).

Antiresorptive therapy consists of regular administration of antiresorptive medications, such as BP, which were commonly prescribed intravenously for oncological therapy, as well as, orally for treating diseases involving lytic bones, such as osteoporosis. These drugs are potent inhibitors of osteoclast-mediated bone resorption and are used for controlling skeletal-related events acting through the inhibition of bone remodeling capability.² Our finally selected sample consisted of 29 studies that recruited a total of 1133 patients that had been treated with antiresorptive bone therapy for either oncological or non-oncological reasons and also investigated the associated RF. The most used BP were nitrogen-containing injectables such as pamidronate^{3,9,19,25,27,30,33,34,38,42} and zoledronate.^{3,6,7,9,19,20,22,24–27,30,33–35,38,40,42} Whereas some cases reported the use of Alendronate, Ibandronate, and Risedronate. Due to heterogeneity in the reporting of therapy time exposure in the included studies, prevalence of RF based on specific time exposure groups was not possible.

From the studies included in the meta-analysis, the results showed that the most prevalent RF reported in patients under antiresorptive therapy was mixed lytic-sclerotic areas (73.88%), followed by osteolytic changes (66.18%), osteosclerosis (65.75%), cortical bone erosion (50.83%), persisting alveolar socket (45.77%), PDL widening (44.69%), IAC involvement

Figure 7 Risk of bias summarized assessment. (a) Analytical Cross Sectional Studies. (b) Analytical Cohort and Case-Control studies. (c) Descriptive studies.

(43.40%), periosteal reaction (34.27%) and lamina dura thickening (32.97%). Less frequently, but equally important, sequestrum (29.94%), pathologic fractures

(20.90%), and density confluence of cortical and cancellous bone (16.61%) were reported. We found different study designs, which reflect differences in sample origin and have clear implications on the clinical applicability of the results. The prevalence found in observational descriptive studies (Group 1) was relatively higher than the results of analytical cross-sectional studies (Group 2). These groups reflect different clinical scenarios; in Group 1, included individuals were selected based on their BRONJ diagnoses, in other words, only symptomatic patients were evaluated without a broader control population, which prevented the ability to address causality. In Group 2 data were collected at a defined time including BRONJ and non-BRONJ. The presence of seven RF was described by both observational descriptive studies (Group 1) and analytical cross-sectional studies (Group 2), which were osteosclerosis, IAC involvement, PDL widening, cortical bone erosion, osteolysis, persisting alveolar socket and sequestrum. All of them had lower frequency reported in studies from Group 2. This fact confirmed that a controlled study may report a lower prevalence than a descriptive non-controlled study, and the presence of a broader control population in the sample may represent a better clinical scenario.

The RF reported by just one study were considered as insufficient data for being included in the meta-analysis, and did not account for the pooled frequency, which were the worm-eaten appearance (16 cases),²³ perforation to nearby anatomical cavities (6 cases),²⁷ and periapical radiolucency (30 cases).³⁸ Just one case of canal cortex with areas of lower density was reported.²⁷ Additionally, no radiographic signs were detected on 20 patients. Only one analytical case-control and one analytical cohort study were found, therefore there was insufficient data to conduct a meta-analysis of these designs. The latter can be considered to be a better representation of the general population, representing the most realistic incidence among the general population, which usually lowers the results of the condition. As expected, Rugani et al⁴⁰ found an overall RF incidence of 43%.

It is noteworthy that the focus of this systematic review was patients under antiresorptive bone therapy and not patients with confirmed diagnosis of BRONJ. However, with the exception of Rugani et al⁴⁰ and Popovic et al³³ for all included studies that investigated patients under antiresorptive bone therapy, the sample comprised of patients with a confirmed diagnosis of BRONJ according to AAOMS criteria. More specifically, in 27 studies the authors identified and selected BRONJ patients and investigated their radiographic features; whereas only Rugani et al⁴⁰ and Popovic et al³³ studied a group of patients under antiresorptive bone therapy and actually investigated the RF.

BRONJ is defined as the presence of persisting exposed bone, in the maxilla or mandible, for more than 8 weeks, including a history of BP use and absence of radiotherapy to the head/neck region. Bone exposure

Table 2 GRADE's Summary of findings

<i>Among patients receiving antiresorptive bone therapy, what is the prevalence of radiographic findings on jaws?</i>		
<i>Outcomes</i>	<i>No of participants (studies)</i>	<i>Quality of the evidence (GRADE)</i>
Overall prevalence of radiographic findings assessed by descriptive observational studies	609 (21 studies)	^c ⊕○○○ ^d VERY LOW ¹⁻³
Overall prevalence of radiographic findings assessed by analytical cross sectional studies	416 (6 studies)	^b ⊕○○○ ^{2,3} ^c VERY LOW
Overall prevalence of radiographic findings assessed by cohort studies	48 (1 study)	^b ⊕○○○ ² VERY LOW
Overall prevalence of radiographic findings assessed by case-control studies	60 (1 study)	^b ⊕○○○ ² ^d VERY LOW

CI, Confidence interval;
^aobservational studies starts GRADE analysis from score LOW.
^bhigh or moderate risk of bias scored for some studies (Figure 5).
^cHigh I2 (inconsistency) scored by the meta-analysis;
^dWe have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

can occurred spontaneously^{6,9,19,26} or have trigger factors such as tooth extractions,^{3,6,7,9,10,19,24–27,33,35,37,38,40} oral trauma by prosthesis,^{7,19,24,35,38} or implants.^{7,9,19,24,25,35,38,40} The progression of bone exposure can follow sequestrum.^{6,10,19,25,27,33–35,42} AAOMS staged BRONJ patients from at-risk category (no evidence of necrotic bone in patients with a history of bisphosphonate use) to Stage 0 to 3.⁴ However, the BRONJ diagnosis remains a challenge and usually is made at the last stages, when there is bone exposure to the oral cavity (Stages 1 to 3). The clinical and radiographic features that precede Stages 1 to 3 BRONJ (clinical symptoms without exposed necrotic bone) remain largely unknown, and less is known in patients under antiresorptive bone therapy without BRONJ (no clinical signs and symptoms without exposed necrotic bone).⁵ From the included studies, only eight studies staged the BRONJ cases and reported RF accordingly, the others reported RF altogether; which did not allow for a meta-analysis on BRONJ stages subgroups.

From the studies that staged BRONJ cases, the RF reported of BRONJ Stages 1 to 3 from panoramic radiography, CT, and CBCT included sclerosis, cortical surface irregularities, persistent extraction sockets, bone fragmentation (sequestrum), and lytic or radiolucent changes.^{7–11,43,44} RF for the BRONJ stage 0 has been pointed as alveolar bone loss (not associated to chronic periodontal disease), trabecular bone alterations, persistent alveolar sockets, sclerotic changes of the lamina dura, and inferior alveolar canal narrowing.⁵ From this point, the destructive bone changes have been often depicted as progressive, starting from the lamina dura and cortical plate, involving the alveolar bone and then progressing to the medullar bone, and finally affecting the entire cross-sectional area of the jaw bone.⁶ A clearer understanding of the significance of RF on the jaws among patients receiving antiresorptive bone therapy may assist in identifying patients at increased risk for BRONJ.⁵ Early diagnosis can make a significant difference in the outcome of the disease enabling better

treatment and prevention of new potential cases.⁵ At the last stages, the most common clinical finding of BRONJ is an area of ulcerated mucosa with exposed devitalized bone. However, the patients with exposed necrotic bone, often clinically present a smaller area of ulceration with a wider area of underlying bone necrosis.^{6,45} This makes imaging mandatory, even in advanced cases, for assessing the real extent of the lesion. Moreover, high-resolution imaging could be helpful to compare the affected areas to the non-affected areas while asymptomatic areas can also be detected.⁶

Most of the included studies did not cluster the RF by the imaging technique. The pooled data were stemming from periapical and panoramic radiographs as well as CT and CBCT. More useful information and a more accurate evaluation of the patient's condition can be obtained with CT and CBCT.²⁸ However, the lack of data related to a specific imaging technique was a limitation preventing analysis of the correlation between the RF and each imaging technique. In absence of this correlation, it was not feasible to compute adjusted confidence intervals based on imaging technique.

It should be mentioned that substantial heterogeneity across studies was observed and that effect estimates varied greatly. Whilst some would criticize conducting a meta-analysis in such circumstances, others suggest that it may be better to examine sources of heterogeneity rather than use them as a reason for not conducting one.⁴⁶ Since limited information was available regarding moderator variables and also because relevant data were often clustered, a meta-regression was considered not appropriate.⁴⁷ Nonetheless, *post hoc* subgroup analyses were carried out, suggesting that variability in type of imaging examinations and number of specialized radiologists might be potential sources heterogeneity across studies.

Finally, it is important to point out that most of the imaging features are relatively nonspecific and should always be cross-referenced to the clinical context. All these reported manifestations may simply be due to

physiologic changes in bone architecture induced by BP. Among the essential factors in dealing with patients who are at risk for developing bone alterations due to antiresorptive therapy is mandatory education for the dental practitioners in the diagnosis of possible early radiological signs of necrosis as well as in the related preventive measures.

The RF prevalence values calculated in our meta-analysis showcased RF related to patients undergoing antiresorptive medications. This information impacts the diagnosis and the decision-making process of practitioners facing those patients, especially in those cases whether the anamnesis is insufficient. Also, identifying these radiographic changes earlier may be useful for the prevention of osteonecrosis.

Limitations

This systematic review has several potential limitations. First, the lack of a control group as most of the included studies enrolled patients who received BP therapy without a broader control population, thus, causality could not be suggested. Second, the fact that only patients with specific symptoms received additional clinical evaluation may have introduced bias in our meta-analysis.

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