Occurrence of bisphosphonate-associated osteonecrosis of the jaws in individuals with rheumatoid arthritis - a systematic review

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Abstract

Background: To access the occurrence of bisphosphonate-associated osteonecrosis of the jaw (BAONJ) in individuals with rheumatoid arthritis (RA).

Material and Methods: Observational studies that evaluated the occurrence of BAONJ in individuals with RA (BAONJ-RA) were considered for inclusion. Electronic searches were performed up to December 2022 in six databases and in the grey literature. The study selection, data extraction, and quality assessment of the included studies according to the Joanna Briggs Institute Critical Appraisal Checklists was performed. The certainty of evidence was evaluated using the GRADE approach.

Results: Five studies were included three cohort and two cross-sectional. The sample size of subjects with RA ranged from 16 to 3201. Together, the studies presented 36 cases of BAONJ-RA. Prevalence of BAONJ-RA ranged from 0.094% to 56.25%. The incidence ranged from 0.4% to 2.21. Women between the 6th and 8th decade of life were the most affected. Alendronate ($n=5$) and zoledronic acid ($n=9$), orally and intravenously, respectively, were the most used bisphosphonates. The duration of bisphosphonates use ranged from 2.7 to 8 years. The certainty of evidence was very low.

Conclusions: The occurrence of BAONJ-RA is low. However, the certainty of the evidence was very low for this outcome.

Key words: Bisphosphonate-associated osteonecrosis of the jaw, rheumatoid arthritis, diphosphonates.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects the joints (1). RA has an approximate global incidence of 0.5% to 1% (1). RA has complex etiopathogenesis and environmental, genetic and epigenetic factors contribute to synovial inflammation, cartilage destruction and bone erosion (2). The joint destruction characteristic of RA leads to chronic pain, disability, musculoskeletal deficits, decline in physical function and quality of life, and increases the cumulative risk of comorbidities (1,2). In addition to joint involvement, extra-articular manifestations such as cardiovascular, pulmonary, gastrointestinal, renal and neurological involvement reflect the multisystemic nature of the disease (3).

Once RA is diagnosed, the overall goal of treatment is to achieve total remission or at least significantly reduce disease activity, preventing joint damage, disability, and extra-articular manifestations (2). Pharmacological management of RA includes several classes of drugs, such as antimalarials, disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), tumor necrosis factor alpha (TNF-alpha) inhibitors, interleukin (IL) 6 inhibitors and glucocorticoids (1,2). The latter offer rapid symptomatic and disease-modifying effects, but are associated with serious long-term side effects, including osteopenia and osteoporosis (4). The American College of Rheumatology glucocorticoid-induced osteoporosis guidelines (2017) warn that patients with RA who use a dose greater than or equal to 2.5 mg of prednisone/day (or equivalent) for 03 months or more, are prone to have reduced bone mineral density and increased risk of fracture (5). Furthermore, alterations in calcium absorption and vitamin D metabolism that occur because of gastrointestinal and hepatic involvement also contribute to bone mineral impairment in these individuals (6).

In this context, bisphosphonates (BPs), drugs with antiresorptive properties, have been indicated for patients with RA who are at increased risk for fragility fractures (7). The use of these drugs has significantly reduced the incidence of vertebral and hip fractures (7). Nonetheless, an uncommon complication of the use of BPs is bisphosphonate-associated osteonecrosis of the jaws (BAONJ) (8). BAONJ is characterized by the presence of exposed bone, which is probed through an intraoral or extraoral fistula, for more than 8 weeks, in people with a history or current use of BPs (8). Individuals undergoing dentoalveolar surgeries are at increased risk for developing BAONJ (8).

Although it is a subject that has been extensively studied in oral medicine, to date, an evidence-based synthesis regarding the estimation of the global prevalence or incidence of BAONJ in individuals with RA, has not been reported yet. Thus, the aim of this study was to carry out a systematic review to answer the following focused question: What is the occurrence of bisphosphonate-associated osteonecrosis of the jaw in individuals with rheumatoid arthritis?

Material and Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (http://prisma-statement.org.br) and registered on the PROSPERO database (CRD42022360369).

- Eligibility criteria

In this sense, studies in humans (P) with RA (E), and that developed BAONJ (O) were included. Thus, studies in humans with RA (or with other rheumatic diseases associated with the presence of RA, such as: Sjögren's syndrome, Caplan's syndrome, rheumatoid vasculitis, and Felty's syndrome) of any age, gender or ethnicity, who used BPs at any frequency, dose or route of administration were included. Observational studies with full-text available that reported the frequency of occurrence, prevalence, or incidence of BAONJ in patients with RA were also included. Conversely, studies that reported data on patients using RANKL inhibitors (E.g. denosumab), antiangiogenic medications (E.g. bevacizumab), TNF alpha inhibitors (E.g. etanercept, adalimumab, infliximab, certolizumab, golimumab) or with a history of radiotherapy in the head and neck were excluded. Literature reviews, case reports, case series, animal studies, laboratory studies, book chapters, letters to the editor and conference/congress abstracts were also excluded.

- Search strategy and information sources

Controlled vocabulary (MeSH terms) and free key words were used in the search strategies, which were defined based on aim of this review. In July 2023 a systematic literature search in PubMed, Scopus, Embase, Web of Science, Cochrane Library, and LILACS via Virtual Health Library electronic databases was performed. In addition, the grey literature was also searched through Google Scholar and OpenGrey. A monthly search alert was created to notify new studies according to the outlined search strategy up to February 2023. The search strategy was performed independently by 2 reviewers (J.R.T and L.S.L.S.) using the terms related to "bisphosphonate-associated osteonecrosis of the jaw", and "rheumatoid arthritis" combined by the Boolean operators AND/OR, with no language or date restrictions (Table 1). A manual search on the included studies references lists was also performed to avoid missing any relevant publications. Similarly, experts in the field were contacted to retrieve possible relevant unpublished or ongoing studies data.

Table 1: Search strategies.

Database	Search strategy
PUBMED	(Arthritis, Rheumatoid[MeSH Terms] OR Rheumatoid Arthritis[Title/Abstract] OR Caplan Syndrome[MeSH Terms] OR Felty Syndrome[MeSH Terms] OR Rheumatoid Vasculitis[MeSH Terms] OR Sjogren's Syndrome[MeSH Terms] OR Sjogren's Syndrome[Title/Abstract]) AND (Osteonecrosis[MeSH Terms] OR Osteonecrosis[Title/Abstract] OR Bisphosphonate-Associated Osteonecrosis of the Jaw[MeSH Terms])
Web of Science	TS= ("Arthritis, Rheumatoid" OR "Rheumatoid Arthritis" OR "Caplan Syndrome" OR "Felty Syndrome" OR "Rheumatoid Vasculitis" OR "Sjogren's Syndrome")
	TS= (Osteonecrosis OR "Bisphosphonate-Associated Osteonecrosis of the Jaw")
SCOPUS	INDEXTERMS({Arthritis, Rheumatoid} OR {Caplan Syndrome} OR {Felty Syndrome} OR {Rheumatoid Vasculitis} OR {Sjogren's Syndrome}) OR TITLE-ABS-KEY({Rheumatoid Arthritis} OR {Sjogren's Syndrome}) AND INDEXTERMS(Osteonecrosis OR {Bisphosphonate-Associated Osteonecrosis of the Jaw}) OR TITLE-ABS-KEY(Osteonecrosis)
COCHRANE	ID Search Hits
	#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
	#2 MeSH descriptor: [Caplan Syndrome] explode all trees
	#3 MeSH descriptor: [Felty Syndrome] explode all trees
	#4 MeSH descriptor: [Rheumatoid Vasculitis] explode all trees
	#5 MeSH descriptor: [Sjogren's Syndrome] explode all trees
	#6 ("Rheumatoid Arthritis" OR "Sjogren's Syndrome"):ti,ab,kw
	#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
	#8 MeSH descriptor: [Osteonecrosis] explode all trees
	#9 MeSH descriptor: [Bisphosphonate-Associated Osteonecrosis of the Jaw] explode all trees
	#10 (Osteonecrosis):ti,ab,kw
	#11 #8 OR #9 OR #10
	#12 #7 AND #11
EMBASE	'rheumatoid arthritis'/exp OR 'rheumatoid arthritis' OR 'pneumoconiosis'/exp OR 'felty syndrome'/exp OR 'rheumatoid vasculitis'/exp OR 'sjoegren syndrome'/exp OR 'rheumatoid arthritis':ab,ti OR 'sjogrens syndrome':ab,ti
	'bone necrosis'/exp OR 'bone necrosis' OR 'bisphosphonate related osteonecrosis of the jaw'/exp OR osteonecrosis:ab,ti
BVS (LILACS)	((mh:("Arthritis, Rheumatoid")) OR (mh:("Caplan Syndrome")) OR (mh:("Felty Syndrome")) OR (mh:("Rheumatoid Vasculitis")) OR (mh:("Sjogren's Syndrome")) OR ("Rheumatoid Arthritis") OR ("Sjogren's Syndrome")) AND ((mh:(osteonecrosis)) OR (mh:("Bisphosphonate-Associated Osteonecrosis of the Jaw")) OR (osteonecrosis)) AND (db:("LILACS"))
Google Scholar	"rheumatoid arthritis" AND "Bisphosphonate-Associated Osteonecrosis of the Jaw"
OpenGrey	"rheumatoid arthritis" AND "Bisphosphonate-Associated Osteonecrosis of the Jaw"

- Study selection process

Articles identified in databases and by manual search were compiled into a bibliographic reference manager (Online version of EndNote, Version X7; Thomson Reuters, Philadelphia, PA). After automatic duplicated references removal, these records were exported to the Rayyan (https://www.rayyan.ai) software and underwent manual deletion of duplicates. Using Rayyan, two review authors (J.R.T. and L.S.L.S) performed the study selection, independently, through the evaluation of the titles and abstracts of all studies according to the eligibility criteria. Besides, when any title and abstract did not provide enough information for a definitive decision, the full text was retrieved and examined. Subsequently, all selected articles were read in full to confirm the eligibility. Any disagreements regarding the eligibility of studies for inclusion were resolved through consensus or with the help of a third author (L.C.M). Articles published in languages other than English and authors native idiom were translated using the Google® Translate tool (http://translate.google.com.br).

- Data collection process

The following data were collected: author, year, country, type of study, total sample size (n), RA sample size,

number of cases of BAONJ in individuals with RA (BA-ONJ-RA), prevalence/incidence of BAONJ (according to the type of study), participants age range and sex, type of BP used, route of administration (oral/intravenous), duration of use, and history of previous oral surgical procedure (when available). When data were not fully available, participants in this systematic review contacted the Correspondence of the article through weekly emails for four consecutive weeks.

- Study risk of bias and certainty of evidence assessment

The risk of bias in the included studies was assessed independently by two reviewers (D.E. and L.S.L.S) using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for Observational Studies (Cross-sectional and Cohort) (9). For cross-sectional studies, all 10 items were applied. For cohort studies, 10/11 questions were considered applicable. Item 10 of the JBI for cohort studies (related to strategies to deal with incomplete follow-up) was considered not applicable, since the data needed for the study do not require the evaluation of cases with incomplete follow-up. Disagreements between the reviewers about the quality assessment were solved by a third author (A.V.B.P.).

The certainty of evidence was evaluated using the GRADEpro tool (10). Risk of bias, inconsistency, indirectness, imprecision, suspicion of publication bias, presence of large effect, plausible confounders and dose response gradient were the items considered to rate the overall certainty of evidence (11,12). All the judgments were adapted to qualify the evidence synthesized in a narrative way (13).

- Synthesis methods

Initially, the characteristics of the included studies were summarized and tabulated using Excel spreadsheets (Excel®, Microsoft, USA). Studies were grouped for synthesis based on study design (cross-sectional or cohort), incidence/prevalence, route of administration (oral/intravenous) and duration of use (in years) of BPs.

Results

- Study selection

The flowchart of the search selection procedures is shown in Fig. 1. Of the 4.361 articles retrieved through database searches, 1.636 duplicates were removed. A total of 2.701 records were excluded by reading titles and abstracts, remaining 24 articles that were sought for retrieval. Nineteen reports (Supplement 1) were excluded after full-text reading and 05 studies were finally included (14-18). Eight studies were identified via grey literature, but none met the eligibility criteria by reading titles and abstracts.
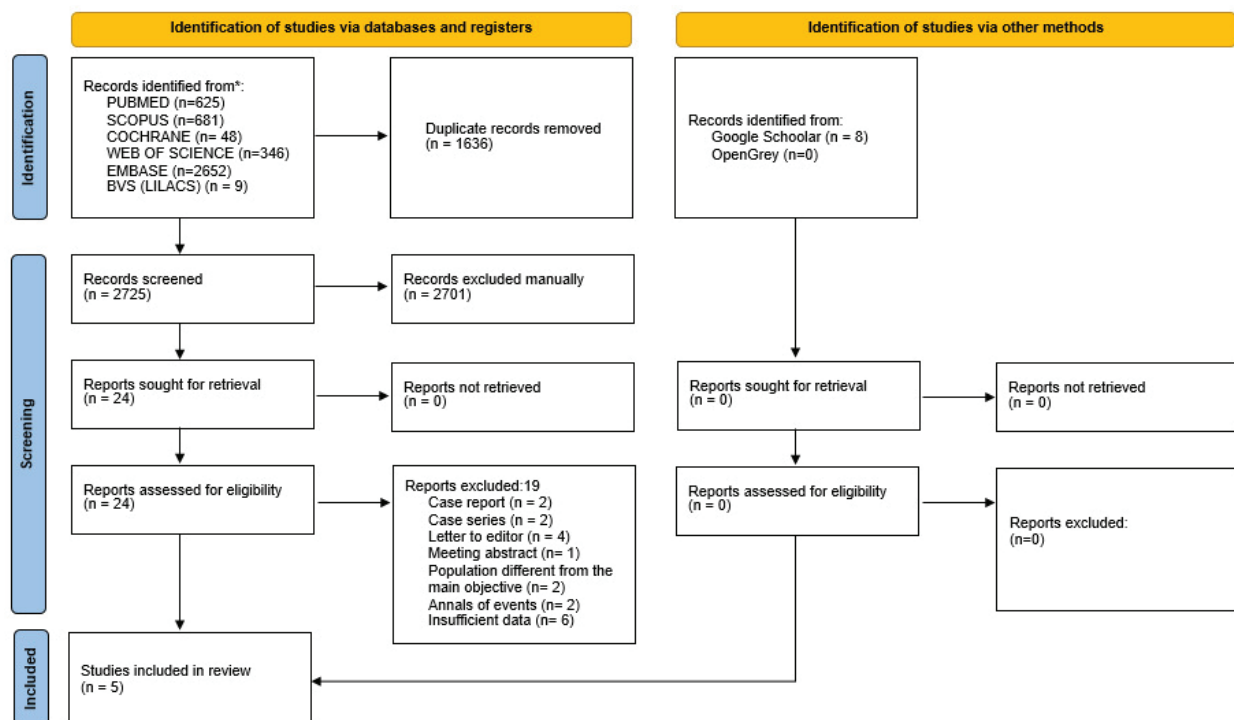

Fig. 1: PRISMA flowchart.

- Studies characteristics

Two cross-sectional studies (15,17) and 03 cohort studies (14,16,18) published between 2014 and 2021 were included in this systematic review. The studies were carried out in Taiwan (14,16), Japan (15), Spain (17) and South Korea (18) and a total of 5009 patients with RA were analyzed. The sample size of subjects with RA in the cross-sectional studies ranged from 16 (17) to 1236 (15) patients, and in cohort studies ranged from 226 to 3201 patients. The incidence of BAONJ-RA was low, ranging from 0.4% (18) to 2.21% (14). Prevalence ranged from 0.094% (15) to 56.25% (17). Age ranges in gross values for individuals with BAONJ-RA, when available, ranged from 65 (15) to 91.51 (16) years. The female gender was predominant in all studies for which this data was available (15,16,17). Alendronate (n=5) (15,16) and zoledronic acid (n=9) (17), orally and intravenously, respectively, were the most used BPs by the individuals with BAONJ-RA. In cross-sectional studies (15,17) the minimum time of use of BPs was 5 years. Only one cohort study (16) reported the duration of use of such drugs by the patients with BAONJ-RA, which ranged from 2.76 to 7.01 years. This same study showed that there was a higher proportion of occurrence of ONJ among individuals taking alendronate who had a history of tooth extractions in the year prior to the final date of data collection, with a crude odds ratio of 10.46. A cross-sectional study (17) showed that 10/16 patients with RA had a history of tooth extractions, of which 09 developed BAONJ. The detailed characteristics of the studies are presented in Table 2.

- Risk of bias/quality of studies

The cohort studies (14,16,18) showed clarity and methodological rigor, especially in terms of similarity and patient recruitment, exposure measures, identification of confounding factors, absence of the outcome at baseline, outcome measures, follow-up time and statistical analysis. However, for two of them (14,16) it does not seem clear whether there were strategies to deal with the confounding factors (presence of diabetes mellitus, smoking, among others) and the loss of some follow-ups.

The two cross-sectional studies apparently had problems with outcome measures, in one of the studies (15), the diagnosis of osteonecrosis of the jaws was conditioned to the answer to a questionnaire answered by the patient, and in the other, the diagnostic criteria employed were not detailed (17). The latter (17) also had some methodological flaws, including problems with inclusion criteria and sample characterization, exposure measures, strategies to deal with confounding factors, and statistical analysis. JBI's critical appraisal results according to the type of each study are listed in Supplement 2 and Supplement 3.

- Results of the studies

A narrative synthesis of the included studies was performed and the results of the individual studies are shown in Table 2.

Only one cohort study presented the variables studied for the group of individuals with RA who developed BAONJ (BAONJ-RA). However, in general, the incidence of BAONJ-RA was low, reaching a maximum of 2.21% (n=5), in a study (14) with a sample of 226 individuals with RA. Chiu et al. (2014) (14) showed that having RA increased the risk of developing BAONJ by 4.56 times. In the study by Kim et al. (2021) (18), this estimated risk was 7.39.

Furuya et al. (2018) (15) evaluated 1236 patients with AR, of which 5 developed BAONJ, resulting in a reduced prevalence of this condition. On the other hand, a cross-sectional (17) study showed a marked prevalence of BAONJ-RA, reaching 56.25%.

- Certainty of evidence

The certainty of evidence was rated as very low (Table 3). In cross-sectional studies some limitations related to imprecision (number of events - BAONJ cases), indirectness (outcomes were not similarly defined in these studies), which also reduced the certainty of evidence in terms of inconsistency. The included cross-sectional and cohort studies had methodological flaws that could alter the results, reducing the evidence due to the risk of bias.

Discussion

BAONJ is a bone disease that is continuously studied in oral medicine and, although uncommon, it can present with chronic exposure of necrotic bone in the oral cavity, pain, fistula, oroantral communication and pathological fracture (8). The occurrence of this condition within the context of the RA patient, who already has chronic joint pain, morning stiffness and a propensity for disability and deformity, may further reduce the quality of life of affected individuals (1,2). The focused question of this systematic review was aimed at clarifying the global prevalence and incidence of BAONJ in individuals with RA. The present review synthesized the evidence on this issue and found that most of the included studies have shown low prevalence and incidence of BAONJ in individuals with RA (14,15,16,18). Although the study by García-Quintana et al (2019) showed a discrepant prevalence (56.25%), this data needs to be carefully analyzed, since its methodology included a group of patients with osteonecrosis of the jaw (ONJ) (n=24) and another without this condition (n=280); within the sample of patients with ONJ, a small portion had RA as the main comorbidity (n=9).

The relationship between RA and BAONJ has already been shown in animal models and in human studies (19,20). Although it seems to be an uncommon condition, the dentist must be aware that individuals with RA

Table 2: Characteristics of the included studies.

Author (year), country	Type of study	Total sample (RA sample)	Number of cases of BA-ONJ-RA	P or I	Age range in BA-ONJ-RA	Sex in BAON-J-RA	Type of BP in BA-ONJ-RA	Route of admin-istra-tion in BAONJ-RA	Dura-tion of use of BP	History of previ-ous oral surgical procedure	Additional results of interest	Con-flicts of inte-rest	Funding
Chiu et al. (2014) - Taiwan	Cohort	7332 (226)	5	I: 2,21 %	NR	NR	NR	NR	NR	NR	Preexisting RA increas-es the risk of developing BAONJ (OR 4.56; 95% CI 1.726-12070).	No	Not repor-ted
Furuya et al. (2017) - Japan	Cross--sectio-nal	5695 (1236)	5	P: 0,094 %	**Min:** 65 **Max:** 79 **Me-dian:** 77	**Fema-le:** 05 (100%)	Mino-dronate: 02 (40%) Rise-dronate: 01 (20%) Alen-dronate: 01 (20%) Unk-nown: 01 (20%)	**Oral:** 04 (80%) **Unk-nown:** 01 (20%)	**Min:** 5 years **Max:** 8 years **Me-dian:** 6 years	Of the 378 RA patients who underwent tooth extractions during the prior 6 months, 83 patients (22.0 %) reported receiv-ing oral BPs dur-ing that period.	Four subjects with BA-ONJ-RA (80 %) were receiving oral glucocor-ticoids, and most tended to have other complica-tions such as diabetes (n=2/40%). Advanced age was signifcantly associated with both dental treatments and tooth extractions dur-ing the prior 6 months, and ever smoking was signifcantly correlated with history of tooth extractions during the prior 6-month period.	Yes	Not repor-ted
Chiu et al. (2018) - Taiwan	Cohort	7625 (330)	4	I: 1,33 %	**Min:** 66,45 **Max:** 91,51 **Me-dian:** 75,51	**Fema-le:** 04 (100%)	Alen-dronate: 04 (100%)	**Oral:** 04 (100%)	**Min:** 2,76 years **Max:** 7,01 years **Medi-an:** 5,31 years	There was a significantly greater propor-tion of ONJ oc-currence among subjects taking alendronate with versus without antecedent tooth extraction in the prior year of end dates (2.16% versus 0.21%, $p < 0.001$), with a crude odds ratio of 10.46 (95% CI, 4.32±24.50, $p < 0.001$).	Tooth extraction is significantly associated with increased risk for BAONJ among osteo-porotic patients taking alendronate for 3 years or more ($p = 0.012$) and in those with less than 3 years of use ($p <0.001$), independent of drug duration. In addi-tion, there is a greater proportion of BAONJ among patients with BP duration of 3 years or more versus less than 3 years of use (0.92% versus 0.24%, $p = 0.002$), sup-porting the influence of BP duration on BAONJ occurrence.	No	This work was sup-ported by the osteo-porosis and meta-bolic bone diseases research fund and research grants from the depart-ment of medical research.
García--Quin-tana et al. (2019) - Spain	Cross--sectio-nal	304 (16)	9	P: 56,25 %	**Mean:** 59,5	**Fema-le:** 09 (100%)	Zole-dronic acid: 09 (100%)	**IV:** 9 (100%)	> 5 years for all patients	Ten RA patients had history of previous tooth extractions.	-	No	Not repor-ted
Kim et al. (2021) - South Korea	Cohort	329.852 (3201)	13	I: 0,40 %	NR	NR	NR	NR	NR	NR	Individuals with RA are at significantly higher risk for BAONJ with an AHR of 7.39 (95% CI, 3.90-14.00; $p < 0.001$)	No	No

RA: rheumatoid arthritis; BAONJ: bisphosphonate associated osteonecrosis of the jaws in patients with RA; P: prevalence; I: incidence; NR: not reported to RA group; BP: bisphosphonates; ONJ: osteonecrosis of the jaws; AHR: adjusted hazard ratio; CI: confidence interval; OR: odds ratio.

Table 3: Certainty of evidence.

Certainty assessment								
Number of studies	Study design	Risk of bias	Incon-sistency	Indirect evidence	Imprecision	Other con-siderations	BAONJ-RA	Certainty
INCIDENCE								
3	Observational (cohort)	Not serious	Not serious	Not serious	Very serious[a]	None	22	⊕◯◯◯ Very low
PREVALENCE								
2	Observational (cross-sectional)	Very serious[b]	Very serious[c]	Serious[d]	Very serious[a]	None	14	⊕◯◯◯ Very low

[a, d] The number of cases of BAONJ-RA were lower than 300.; [b] Methodological flaws including: sample selection, statistical analysis and outcome measures; [c] Prevalence effects between studies were distant; [d] Lack of homogeneity in the characterization of the sample and outcomes were not similarly defined.

can experience worse oral health conditions due to factors related to the underlying disease (21) and, in addition, present foci of oral infection that act as a trigger for the development of BAONJ in patients using BP.

In general, the included studies showed some methodological limitations, many of them related to the nature of observational studies. However, given the multifactorial characteristic of BAONJ, all studies (14-18) pointed to confounding factors that may influence the development of BAONJ, including: diabetes mellitus and smoking. However, two studies (14,16) did not show strategies to deal with the presence of these factors. It is possible that these conditions influenced the results found.

The demographic profile of patients with BAONJ-RA consisted predominantly of women between the 6th and 8th decade of life. This was an expected finding, since both RA and osteoporosis are more common in post-menopausal women (22). However, this data deserves to be carefully analyzed, given the reduced number of events found (i.e. number of cases of BAONJ).

Dentoalveolar surgeries are the main local factors associated with the development of BAONJ (8). Unfortunately, most of the studies included were not clear about the prior performance of oral procedures specifically in individuals with RA using BPs. Furthermore, other local factors that are commonly associated with an increased risk for developing BAONJ (anatomical factors and concomitant oral disease) (8) were also not addressed. Another issue that needs to be mentioned is the quality of the outcome measures, that is, how the diagnosis of BAONJ was performed. The cross-sectional studies included showed a lack of clarity in this regard (15,17). It is important to emphasize that the diagnosis of BAONJ is based on well-established clinical criteria and that radiographic imaging is an auxiliary resource, especially in more advanced cases, to define the extent of bone involvement (8).

In this sense, given the low level of evidence, the authors suggest that studies with the following criteria can be carried out: 1) specifically select samples from patients with RA as the main systemic disease; 2) clearly show the diagnostic criteria for BAONJ; 3) describe local risk factors for BAONJ; 4) report in detail the type of BPs used, as well as dose, route of administration and duration of use; 4) describe in detail the confounding factors and show robust strategies to deal with them.

It's important to note that certain antirheumatic medications, such as TNF-alpha inhibitors, have also been associated with osteonecrosis of the jaw (23). There is also a potential risk of osteonecrosis of the jaw with other antiresorptive and antiangiogenic medications. This led the American Association of Oral and Maxillofacial Surgeons to define the term 'medication-associated osteonecrosis of the jaw' (8). Therefore, in this study, we specifically used the term BAONJ to focus exclusively on patients using BPs. Additionally, it's worth mentioning that the study sample likely included individuals who initially appeared to be stable but may have experienced relapses, necessitating the use of steroids for an extended period, warranting additional bone protection therapy. For those individuals who do not respond to first-line treatment, biologic medications may become a necessary option.

This systematic review has some limitations that need to be addressed, among them is the lack of some data specifically related to individuals with RA. Furthermore, the five studies (14-18) included were methodological heterogeneous in some aspects, such as: study design, type and route of administration of BPs used. Thus, it was not possible to carry out a quantitative synthesis through meta-analysis.

Conclusions

In summary, the occurrence of BAONJ in individuals

with RA is low. However, this data needs to be analyzed carefully, since the certainty of the evidence was very low for this outcome. We recommend conducting studies with high methodological quality to improve the evidence.

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Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics
Not applicable as this is a systematic review research.

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