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SYSTEMATIC REVIEW

Increased Prevalence of Periapical Lesions in Osteoporosis Patients: A Systematic Review

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ABSTRACT

Assessing scientific literature about prevalence of periapical lesions in individuals with osteoporosis in comparison to those without osteoporosis. Systematic searches were conducted up to November 24, 2023 in Cochrane Library, EMBASE, MEDLINE/PubMed, SCOPUS, Web of Science and Grey Literature Reports databases. Only observational studies were included. The ROBINS-E tool, a revised Cochrane instrument for assessing bias in nonrandomized exposure studies, was employed. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was utilized to evaluate the certainty of the evidence. From 484 studies, three were included. One of them was categorized as having a very high risk of bias, while two were deemed to have certain concerns. Two studies reported that osteoporotic patients have an increased risk to present a periapical lesion compared to non-osteoporotic patients. One study reported no differences between groups. The GRADE analysis indicated a markedly low level of certainty in the evidence. The present review indicates that osteoporotic patients may present more periapical lesions compared to non-osteoporotic patients. This statement should be cautiously interpreted and further well-designed studies are needed.

Keywords: Endodontics, osteoporosis, periapical lesion, systematic review

HIGHLIGHTS

- Osteoporotic patients may have higher chances of presenting periapical lesions.
- Evidences are limited and controversial.
- Well-designed researches are necessary to confirm the trends of this review.

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INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterized by decreased bone mass and deterioration of bone microstructure (1). When osteoclastic activity surpasses osteoblastic activity, the bone remodelling process becomes unbalanced, leading to increased bone mass reduction (2). Consequently, the bone becomes more fragile and susceptible to fractures (3). This disease may affect both sexes, every race, and the prevalence increases with age (4). Estimates suggest that around 200 million individuals across the globe could be impacted by this condition, with a higher prevalence in the population over 65 years old (3, 5, 6) and postmenopausal women (7).

Osteoporosis can be associated with oral health implications. Individuals affected by this disease can have higher levels of pro-inflammatory cytokines (8), resulting in decreased bone mineral density and trabecular

bone alterations, which can favor increased bone resorption and facilitate microbial infiltration (9, 10). Hence, bone repair in osteoporotic patients may be slower and with lower quality of the newly formed bone (11). Currently, there are some studies regarding the association between osteoporosis and periodontitis (12, 13). However, there is a lack of studies regarding osteoporosis and apical periodontitis.

Most of the knowledge available on the subject is from preclinical studies, which were encompassed and appraised in a previous systematic review. This systematic review concluded that a hypoestrogenic condition can promote an accelerated progression of apical periodontitis (14). As with periodontal diseases, bacterial infection plays a fundamental role in developing and maintaining apical periodontitis, which promotes alveolar and periapical bone resorption (15–17). These events are also related to the immunological and inflammatory host response (18).

Based on the above-mentioned information, it can be expected that osteoporosis may interfere with the development and repair of periapical lesions.. This systematic review aims to evaluate the available literature to answer the question: Is there a greater prevalence of periapical lesions in osteoporotic patients compared to non-osteoporotic patients?

MATERIALS AND METHODS

This review followed the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (19) and was registered in the database of the International Prospective Register of Systematic Reviews in Health and Social Care (PROSPERO) by the National Institute for Health Research in the UK, with the registration number CRD42021267558.

Search Strategy

Two authors (G.R.F. and B.L.C.) independently conducted a comprehensive search strategy across Cochrane Library, EMBASE, MEDLINE/PubMed, SCOPUS, Web of Science, and Grey Literature Reports databases. This search encompassed studies published up to November 24, 2023, without imposing any language or year restrictions. Systematically predetermined Medical Subject Heading (MeSH) terms and terms employed by previous studies on this subject were combined through the Boolean operators (OR, AND). For each database, the terms combined were: "Periapical Diseases", "Periodontitis, Apical", "Apical periodontitis", "Periapical lesion", "Periapical Periodontitis", "Pathologic Bone Demineralization", "Bone Demineralization, Pathologic", "Bone Diseases, Metabolic", "Metabolic Bone Diseases", "Bone Loss, Age-Related", "Biphosphonate", "Age-Related Osteoporosis", "Senile Osteoporosis", "Osteoporosis, Involutional", "Osteoporosis, Senile", "Osteoporosis, Post-Traumatic", "Osteoporosis, Age-Related" and "Osteoporosis". Table 1 provides the search strategies summary employed for each database studies that emerged from it. Additionally, manual searches were performed on the reference lists of the chosen studies. To facilitate article management, all selected papers were brought into the Mendeley© reference manager, a product of Mendeley Ltd.

Criteria for Eligibility

For this study, selection criteria for eligibility were based on PECOS strategy (20–22), as described below:

- P (population): Adult patients;
- E (exposure): Osteoporotic patients;
- C (comparison): Non-osteoporotic patients;
- O (outcome): Presence of periapical lesions;
- S (study design): Observational studies.

Only observational studies assessing the likelihood of osteoporotic patients to develop periapical lesions when compared to patients without osteoporosis. were considered for inclusion. This analysis excluded studies conducted in animals, histological studies, also systematic reviews, whether they included meta-analyses or not, along with case series or case reports, reviews, letters, opinion articles and conference abstracts.

Studies Selection

The process of selecting studies was independently conducted by two authors (G.R.F. and B.L.C.). Duplicate entries were identified and deleted. Subsequently, titles and abstracts were scrutinized, and articles meeting the eligibility criteria underwent thorough full-text evaluation to determine their inclusion status. Any discrepancies in selection were resolved through consultation with another author (M.V.R.S.), who provided a final decision.

Data Extraction

Two authors carried out data extraction independently (G.R.F. and B.L.C.). For each study, the subsequent data points were gathered: author(s); publication year; study design, number of participants; participant's gender and age; method to diagnose osteoporosis; methods to diagnose periapical lesion presence; pharmacological therapeutic interventions; outcomes; main findings. Whenever disagreements occured, another author (M.V.R.S.) gave the ultimate decision.

Quality Assessment

Two authors independently carried out the assessment of bias risk (G.R.F. and B.L.C.). When there was discordance, another author (M.V.R.S.) was advised for resolution.

To assess the bias risk in each study, the Risk of Bias in nonrandomized Studies - of Exposures (ROBINS-E) tool was employed. (23). The following domains were considered for potential bias:

1. Bias due to confounding factors: systemic factors (smoking, alcoholism, cancer and diabetes). "Low" when all the confounding factors were controlled at methodology or statistical analysis; "Moderate" when confounding factors were partially controlled; "Serious" when none of the confounding factors were controlled; "Critical" when confounding factors were not even discussed.
2. Bias due to measurement of exposure: "Low" when the methods to diagnose osteoporosis was adequately described; "Moderate" when some information on the exams performed to determine the study's variables was missing, but was not relevant for the proper diagnosis; "Seri-

TABLE 1. Search strategy in each database

Database	Search strategy	Findings
MEDLINE/PubMed	#1: ((((((((((((Osteoporosis) OR (Osteoporosis, Age-Related)) OR (Osteoporosis, Post-Traumatic)) OR (Osteoporosis, Senile)) OR (Osteoporosis, Involutional)) OR (Senile Osteoporosis)) OR (Biphosphonate)) OR (Bone Loss, Age-Related)) OR (Age-Related Osteoporosis)) OR (Metabolic Bone Diseases)) OR (Bone Diseases, Metabolic)) OR (Bone Demineralization, Pathologic)) OR (Pathologic Bone Demineralization)	157.126
	#2: (((Apical Periodontitis) OR (Periapical Lesion)) OR (Periapical Periodontitis)) OR (Periapical Diseases)) OR (Periodontitis, Apical)	12.356
	#1 AND #2	151
Cochrane Library	#1: Osteoporosis OR Osteoporosis, Age-Related OR Osteoporosis, Post-Traumatic OR Osteoporosis, Senile OR Osteoporosis, Involutional OR Senile Osteoporosis OR Biphosphonate OR Bone Loss, Age-Related OR Age-Related Osteoporosis OR Metabolic Bone Diseases OR Bone Diseases, Metabolic OR Bone Demineralization, Pathologic OR Pathologic Bone Demineralization	22.259
	#2: Apical Periodontitis OR Periapical Lesion OR Periapical Periodontitis OR Periapical Diseases OR Periodontitis, Apical	1.552
	#1 AND #2	19
Scopus	#1: (TITLE-ABS-KEY (osteoporosis) OR TITLE-ABS-KEY (osteoporosis, AND age-related) OR TITLE-ABS-KEY (osteoporosis, AND post-traumatic) OR TITLE-ABS-KEY (osteoporosis, AND senile) OR TITLE-ABS-KEY (osteoporosis, AND involutional) OR TITLE-ABS-KEY (senile AND osteoporosis) OR TITLE-ABS-KEY (biphosphonate) OR TITLE-ABS-KEY (bone AND loss, AND age-related) OR TITLE-ABS-KEY (age-related AND osteoporosis) OR TITLE-ABS-KEY (metabolic AND bone AND diseases) OR TITLE-ABS-KEY (bone AND diseases, AND metabolic) OR TITLE-ABS-KEY (bone AND demineralization, AND pathologic) OR TITLE-ABS-KEY (pathologic AND bone AND demineralization))	189.293
	#2: (TITLE-ABS-KEY (apical AND periodontitis) OR TITLE-ABS-KEY (periapical AND lesion) OR TITLE-ABS-KEY (periapical AND periodontitis) OR TITLE-ABS-KEY (periapical AND diseases) OR TITLE-ABS-KEY (periodontitis, AND apical))	12.755
	#1 AND #2	130
Web of Science	#1: TS=(Osteoporosis OR Osteoporosis, Age-Related OR Osteoporosis, Post-Traumatic OR Osteoporosis, Senile OR Osteoporosis, Involutional OR Senile Osteoporosis OR Biphosphonate OR Bone Loss, Age-Related OR Age-Related Osteoporosis OR Metabolic Bone Diseases OR Bone Diseases, Metabolic OR Bone Demineralization, Pathologic OR Pathologic Bone Demineralization)	121.026
	#2: TS=(Apical Periodontitis OR Periapical Lesion OR Periapical Periodontitis OR Periapical Diseases OR Periodontitis, Apical)	7.380
	#1 AND #2	92
EMBASE	#1: 'osteoporosis'/exp OR osteoporosis OR (osteoporosis, AND 'age related') OR (osteoporosis, AND 'post traumatic') OR (osteoporosis, AND senile) OR (osteoporosis, AND involutional) OR (senile AND osteoporosis) OR biphosphonate OR (bone AND loss, AND 'age related') OR ('age related' AND osteoporosis) OR (metabolic AND bone AND diseases) OR (bone AND diseases, AND metabolic) OR (bone AND demineralization, AND pathologic) OR (pathologic AND bone AND demineralization)	215.662
	#2: 'apical periodontitis'/exp OR 'apical periodontitis' OR (apical AND ('periodontitis'/exp OR periodontitis)) OR (periapical AND lesion) OR (periapical AND periodontitis) OR (periapical AND diseases) OR (periodontitis, AND apical)	6.964
	#1 AND #2	92
Grey Literature Reports	#1: Osteoporosis OR Osteoporosis, Age-Related OR Osteoporosis, Post-Traumatic OR Osteoporosis, Senile OR Osteoporosis, Involutional OR Senile Osteoporosis OR Biphosphonate OR Bone Loss, Age-Related OR Age-Related Osteoporosis OR Metabolic Bone Diseases OR Bone Diseases, Metabolic OR Bone Demineralization, Pathologic OR Pathologic Bone Demineralization	0
	#2: Apical Periodontitis OR Periapical Lesion OR Periapical Periodontitis OR Periapical Diseases OR Periodontitis, Apical	0
	#1 AND #2	0

ous" when the exams performed were not adequately described; "Critical" when the exams performed to identify the variables were not described.

3. Bias in selection of participants: "Low" when all eligible participants were included in the study; "Moderate" when participant selection could be related to the outcome; "Serious" when participant selection was related to the outcome; "Critical" when the participant selection process was not described.
4. Bias due to post-exposure interventions: "Low" when exams conduction did not present differences among study participants; "Moderate" when the exams conduction presented some differences among the study participants, but which did not affect the outcome; "Serious" when exams conduction presented differences among the study participants and changes in the sample or interventions were necessary; "Critical" when exams' conduction presented several differences among the study participants.
5. Bias due to missing data: "Low" when the following data were well reported: time of evaluation, pharmacological therapeutic interventions; "Moderate" when some data were missing but they were not relevant for the study outcome; "Severe" when some relevant data for the study outcome were missing; "Critical" when many relevant data for the study outcome were missing.
6. Bias arising from measurement of outcomes: "Low" when an adequate methodology was used to verify the presence of periapical lesion; "Moderate" when the most adequate methodology was not used to verify the presence of periapical lesion, but it was appropriately described; "Serious" when an adequate methodology was not used to verify the presence of periapical lesion and it was not appropriately described; "Critical" when the methodology used was not described.
7. Bias in selection of the reported results: "Low" when the presence of periapical lesion was adequately reported; "Moderate" when the presence of periapical lesion was adequately reported, but not described; "Serious" when there was much discrepancy in data description between the groups; "Critical" when there was lack of information regarding the presence of periapical lesion.

The categorization of risk assessment for each domain proceeded in the following manner: low, some concerns, high, very high, or no information available. Overall bias risk was ascertained by aggregating the levels of bias across all domains. Specifically, the comprehensive bias risk was considered low when each domain showed a minimal risk of bias, some concerns if at least one domain raised some concerns about bias, high if a minimum of one domain indicated a high risk of bias, and very high if one or more domain showed a very elevated bias risk.

Certainty of Evidence

The assessment of the certainty of evidence in the incorporated studies was performed with the use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (GRADEpro GDT: GRADEpro Guideline Development Tool [Software], McMaster University, 2015, developed by Evidence Prime, Inc.) (24). This assessment adhered to the guidelines designed for non-randomized studies of exposure (25).

This tool comprises five domains that have the potential to either reduce or enhance the quality of the evidence. The domains of bias risk, indirectness, imprecision, inconsistency, and other factors (such as reporting bias, significant intervention effects, potential residual confounding, and the presence of a dose-response gradient) were assessed to establish the overall confidence in the evidence.

RESULTS

Selection of Study

Figure 1 displays the search strategy's flowchart.

The databases yielded a combined total of 484 potentially relevant records. Duplicates, totaling 198 records, were excluded. Based on their titles and abstracts, an additional 286 records underwent further examination. From them, 275 studies were excluded as they did not meet the eligibility criteria. A sum of eleven studies was chosen for a comprehensive review of the full text (26–36).

The exclusion of eight studies was based on the following reasons: one of them was excluded as it was a literature review (35); five studies were excluded as they did not perform a comparative analysis with non-osteoporotic patients (29–32, 34); and two studies were excluded since they evaluated lesions of periodontal origin (33, 35). Finally, three studies made part of this systematic review (26–28). No extra studies were added following the manual search on the references of the included studies.

Study Characteristics

Table 2 shows the characteristics and the primary results from the studies which were included.

To diagnose the periapical lesions, all three studies used radiographic exams. One study performed digital panoramic radiographs (28); one did not specify which type of radiography (27); and another performed panoramic and periapical radiographs (26).

In one study, 75 postmenopausal women over 50 years old were recruited (28). Measurement of bone mineral density was conducted through DXA (dual-energy X-ray absorptiometry). Three categories were defined: normal bone, osteopenic and osteoporotic. Among osteopenic and osteoporotic women, a total of 25% displayed at least one periapical lesion, whereas only 7.4% of healthy women exhibited at least one periapical lesion. Even though the odds ratio (OR) showed that osteoporotic/osteopenic patients had 4.2 times more chance to present at least 1 periapical lesion, this was not significant (p=0.061). Multivariate analysis marginally correlated low bone mineral density with having a minimum of one periapical lesion (OR=1.9; CI 95%=1.0–3.8; p=0.05) (28).

Another study evaluated the data from osteoporosis diagnosis (not specified the diagnostic method) and periapical lesions retrieved from a health service database (27). Among 1,644,953 patients evaluated, 8715 were found to have periapical lesions.

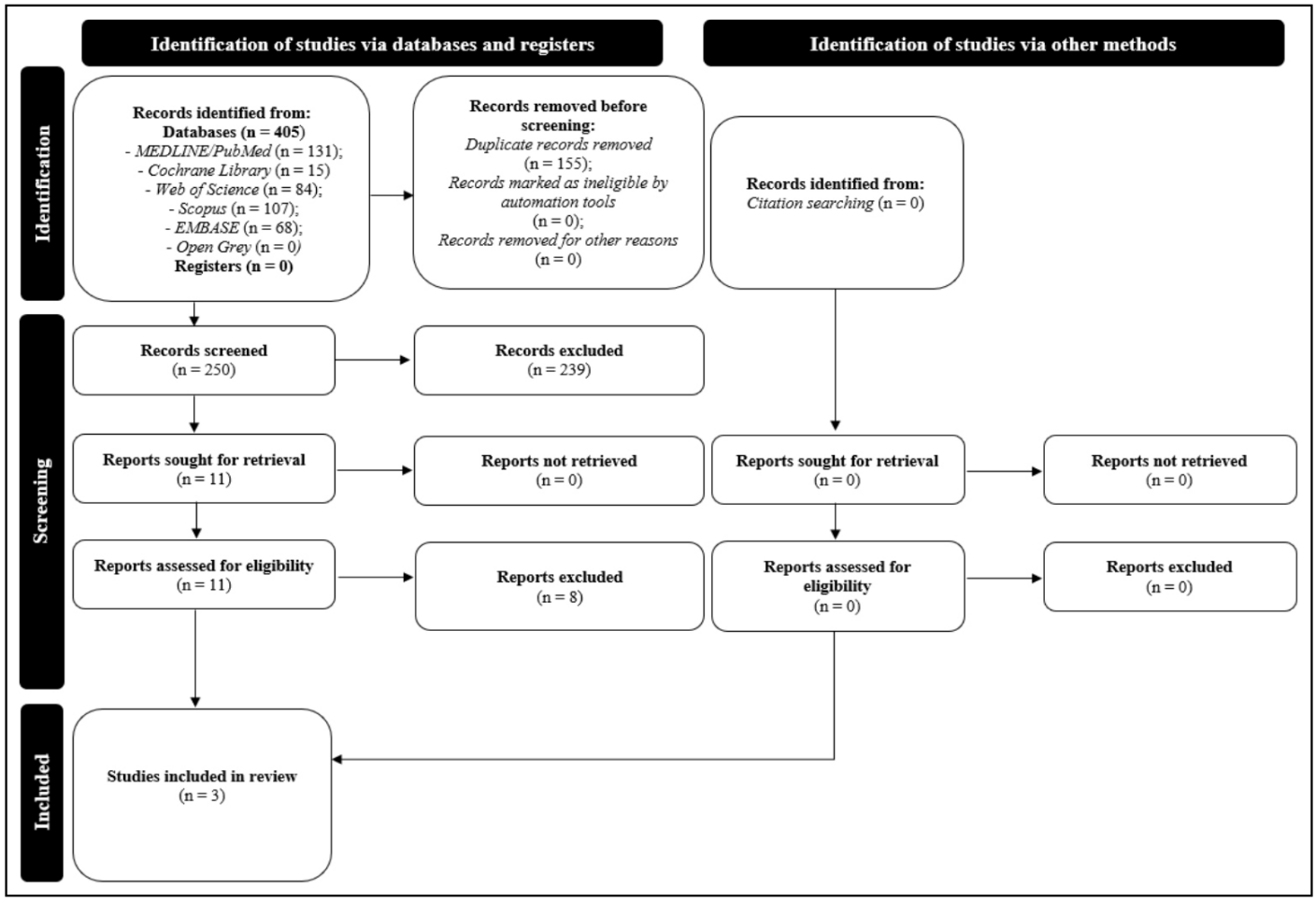

Figure 1. PRISMA flow diagram depicting the systematic search process

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

A total of 42,292 patients were diagnosed with osteoporosis, and 754 patients had both periapical lesions and osteoporosis. The occurrence of periapical lesions in individuals diagnosed with osteoporosis was 1.78%, and for non-osteoporotic patients was 0.52% (OR=3.36; CI 95%=3.12–3.62; p<0.0001). The results showed that the osteoporotic patients may have 3.36 times more chance to present a periapical lesion comparing to non-osteoporotic patients. Unlike the previous study, this result was statistically significant (p<0.0001) (27).

Another study investigated 152 patients (76 osteoporotic and 76 non-osteoporotic) (26). Dual-energy X-ray absorptiometry was utilized to assess bone mineral density. The occurrence rate of periapical lesions in both osteoporotic and non-osteoporotic individuals was 42.1% and 47.4%, respectively (p=0.62). Periapical lesions were higher in teeth that had undergone root canal treatment when compared to nontreated teeth in osteoporotic individuals (p=0.03); without differences in non-osteoporotic patients (p=0.03) (26).

In an additional analysis, one study concluded that osteoporotic patients treated with bisphosphonates presented less periapical lesions (p<0.0001), especially when risedronate is administrated (27). Additionally, another study concluded that there was no difference in periapical lesion presence in osteoporotic patients under pharmacological treatment (bisphosphonates – 32.3%; denosumab 63.6%; denosumab + bisphosphonates 63.6%) and not under pharmacological treatment (36%) (p=0.61) (26). And in a multivariate analysis, shown that patients treated with denosumab resulted in an increased risk for periapical lesion (OR=1.83; CI 95%=1.15–3.37; p=0.03), while no significant associations were observed among the variables (26).

Qualitative Assessment

Figure 2 displays a summary of bias risk of the selected studies (37).

Overall, two studies exhibited certain concerns regarding bias risk (26, 28), and one had a very high risk of bias (27). Both studies with an overall presence of certain concerns regarding the risk of bias (26, 28), had some concerns risk within the domain of bias due stemming from extraneous factors. The study that exhibited a highly elevated overall risk of bias also demonstrated a very high risk of bias within the domain related to third variables, and a elevated risk of bias in the area of bias arising from the outcome measurement (27).

Certainty of Evidence

Table 3 displays the results of GRADE assessment.

Studies received "serious" categorization of bias risk, and for inconsistency received "not serious" classification, indirect

TABLE 2. Characteristics of the included studies

Authors (Year of publication)-study design	Number of participants (per group)	Participant's gender (%)	Method to diagnose osteoporosis	Method to diagnose periapical lesion presence	Pharmacological therapeutic intervention	Outcomes	Main findings
López-López et al. (28), 2015 – Cross-sectional study	N=75 (Osteoporotic: n=12; Osteopenic: n=36; Non-osteoporotic: n=27)	Female: 75 (100%)	Bone densitometry	Digital panoramic radiographs	NR	• 25% of osteopenic (n=9) and osteoporotic (n=3) women had at least one periapical lesion; while only 7.4% of non-osteoporotic (n=2) had at least one periapical lesion (OR=4.2; CI 95%=0.9–20.3; p=0.061); • Multivariate analysis marginally correlated low bone mineral density to the presence of at least one periapical lesion (OR=1.9; CI 95%=1.0–3.8; p=0.05).	• After multivariate analysis, low bone mineral density is marginally associated with a higher frequency of periapical lesions
Katz and Rotstein (27), 2021 – Case-control study	N=1.644.953 (Osteoporotic: n=42.292; Non-osteoporotic: n=1.602.661)	Male: 741.955 (45.1%); Female: 902.998 (54.9%)	NR	Radiographic examination (not specified)	Biphosphonates - BP (Alendronate; Risendronate)	• Periapical lesions prevalence was of 1.78% in osteoporotic patients; while was of 0.52% in non-osteoporotic patients (OR=3.36; CI 95%=3.12-3.62; p<0.0001); • Osteoporotic patients treated with BP had a prevalence of 1.25% of periapical lesion, compared to 0.52% in non-osteoporotic patients (p<0.0001); • OR for periapical lesion presence in osteoporotic patients treated with BP was 2.35 (1.91-2.90), compared with 3.52 (3.25-3.82) of osteoporotic patients not treated with BP (p<0.0001); • Osteoporotic patients treated with alendronate had an OR=1.6 (1.28-2.00) for periapical lesion prevalence (p<0.0001); • Osteoporotic patients treated with risendronate had an OR=1.34 (0.72-2.50) for periapical lesion prevalence (p=0.35).	• Presence of periapical lesion was significant higher in osteoporotic patients; • Osteoporotic patients treated with BP had a reduction in the presence of periapical lesions, especially with risendronate
Cadoni et al. (26), 2022 – Case-control study	N=152 (Osteoporotic: n=76; Non-osteoporotic: n=76)	Male: 25 (16.45%); Female: 127 (83.55%)	Bone densitometry	Panoramic and periapical radiographs	Denosumab; Biphosphonates (Alendronate; Risedronate; Ibandronate; Clodronate; Neridronate; Zoledronate)	• Osteoporotic patients had a periapical lesion prevalence of 42.1%; while non-osteoporotic patients had a periapical lesion prevalence of 47.4% (p=0.62); • There was no difference in periapical lesion prevalence in patients under pharmacological treatment and not under pharmacological treatment (p=0.61); • There were no differences in periapical lesion prevalence regarding the pharmacological treatment modality (p=0.11); • Multivariate analysis shown that patients treated with denosumab resulted in an increased risk for periapical lesion (OR=1.83; CI 95%=1.15–3.37; p=0.03). Other variables were not associated; • Periapical lesions were more prevalent in root canal treated teeth compared with nontreated teeth in osteoporotic patients (p=0.03); without differences in non-osteoporotic patients (p=0.03)	• Osteoporosis does not appear to be associated with the development of periapical lesion

SD: Standard deviation; NR: Not reported; BP: Bisphosphonates; OR: Odds ratio

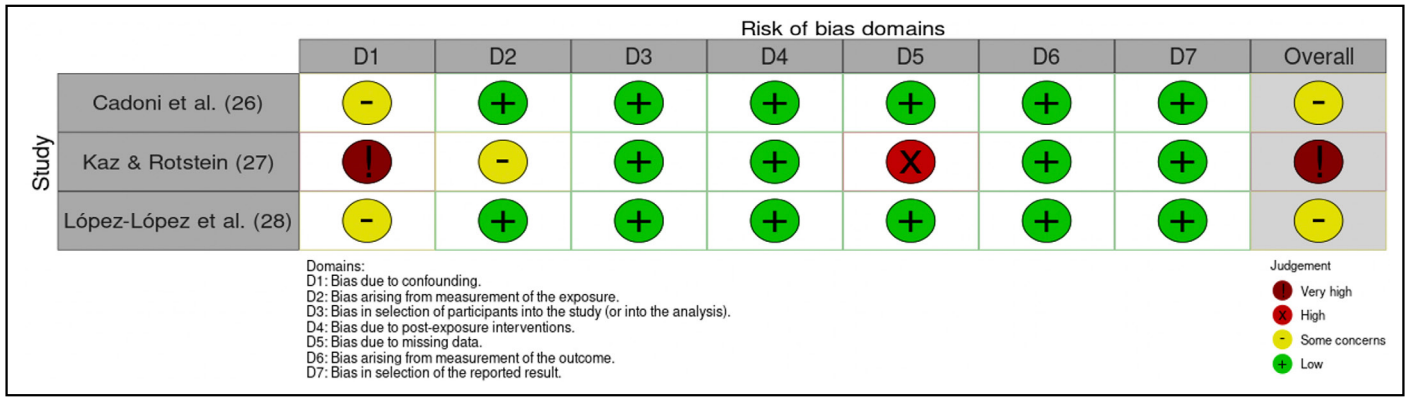

Figure 2. Quality assessment of the nonrandomized studies, according to the Cochrane Collaboration standard scheme for bias and ROBINS- E tool

ROBINS-E: Risk of Bias in nonrandomized Studies - of Exposures

evidence, also imprecision. No further aspects were verified. Therefore, research encompassed received classification as presenting an overall evidence certainty very low.

DISCUSSION

Osteoporosis and apical periodontitis are defined by the presence of osteolysis that result from inflammation (33). Moreover, a systematic review that encompassed preclinical studies pointed that a hypoestrogenic condition may worsen the progression of apical periodontitis (14). Therefore, one can reasonably deduce that osteoporosis might have some influence on periapical lesions, by favouring the development/progression and/or jeopardizing the repair. Therefore, the objective of this systematic review was to investigate whether individuals with osteoporosis are more likely to exhibit periapical lesions when compared to non-osteoporotic patients.

So far, there is limited and controversial evidence to point a possible relation between an osteoporotic condition and a higher prevalence of periapical lesions. Two studies reported no differences for presence of periapical lesions both in osteoporotic and non-osteoporotic patients (26, 28). Only one study reported a higher prevalence in osteoporotic patients (27). However, it is important to emphasize that this study had the larger sample size (n=1.644.953) and this must be taken in consideration when evaluating the findings. It can be hypothesized that the studies that did not find any differences among groups (26, 28) do not have a sufficient larger sample size (n=75; n=152, respectively) to estimate whether there was a significant difference or not (38). In addition, one study reported the use of panoramic radiographs (28) and another panoramic and periapical radiographs usage (26) to assess occurrences of periapical lesions. While one study only stated the use of radiographs, without specifying which type of radiography (27). Periapical and panoramic radiographs are known to be less accurate compared to cone-beam computed tomography (39, 40). Therefore, it is feasible to hypothesize that some periapical lesions could have been missed, which could present some influence in the results of the above-mentioned studies.

Risk of bias assessment aids in enhancing the transparency of evidence synthesis outcomes and conclusions, through the evaluation of limitations in the design and execution of individual studies. In the present review, ROBINS-E tool was used to assess risk of bias. The use of ROBINS-E initiates with delineating the ideal randomized trial, encompassing the precise characterization of the study population, the exposure variables of interest, the comparative exposures, and the designated outcomes for assessment. The ideal randomized trial is used as the comparison due to its position at the top of an evidence hierarchy organised by increasing protection against bias. Subsequently, each domain will undergo evaluation and classification as presenting low, moderate, high, or very high risk of bias, guided by parameters predefined by the evaluators.

In this review, one study presented an overall very high risk of bias, mainly because of a high risk resulting from the "confounding factors" (27). For this study, authors did not address for any possible confounding factors. Several factors can influence the occurrence of apical periodontitis, such as alcohol and tobacco use (41, 42), history of dental trauma (43), endodontic filling extension and presence of satisfactory crown rehabilitation (44), and systemic diseases (e.g., diabetes) (45). Also, since no information was provided in relation to how the

TABLE 3. Certainty of the evidence from the included studies according to the GRADE approach for preclinical animal studies

Certainty assessment						
Number of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Overall certainty of evidence**
3 observational studies	Serious[a]	Not serious	Not serious	Not serious	None	⊕◯◯◯ VERY LOW

[a]: 1/3 study was classified as presenting a very high risk of bias, and 2/3 as presenting some concerns risk of bias. GRADE: The Grading of Recommendations Assessment, Development, and Evaluation.

investigated outcomes were measured (e.g., measurement methods of osteoporosis and periapical lesions), a high risk of bias was attributed to "measurement outcomes".

Two studies presented an overall some concerns bias (26, 28). This classification was presented due to some concerns bias in "confounding factors". Despite controlling for some possible confounding factors both studies fail in control for important confounders. For example, one study did not report controlling for systemic diseases (28) Additionally, both studies did not report controlling for history of dental trauma, which can be associated to the occurrence of necrosis (43), and factors regarding the technical quality of endodontic therapy (e.g. filling of root canal extension and coronal restoration), which can influence on root canal treatment outcome (44).

The comprehensive certainty of evidence was classified by the GRADE assessment as very low. The 'serious' categorization was assigned within the risk of bias domain (46), since one study had a high risk of bias, and the other some concerns risk of bias. Domain inconsistency concerns an unexpected variety in findings (47), and it was categorized as 'non serious'. The domain indirectness assesses whether the studies evaluated similar populations, treatments, measures of results and indirect contrasts, and it was also assessed as 'non serious' (48). Domain imprecision was evaluated as recommended by Murad et al. (49), since conducting a meta-analysis was not feasible. It is advised to take into account the overall participant count (i.e., at least 400 in the pooled sample size) of the encompassed research and the confidence interval (CI) of largest studies (49). A combined sample size below 400 is concerning for inaccuracy, as well as results might be inaccurate when 95% CIs of largest studies encompass no effect of significant benefits or side effects (49). Consequently, domain imprecision was categorized as "non serious". Domain other consideration encompassed an evaluation of publication bias, plausible confounding, large effect, also dose–response gradient, and not a single of them were verified in the included studies (50).

In an additional analysis, data on the use of medications to treat osteoporosis and its influence on the development of periapical lesion was extracted. Once again, controversial results were found. One study reported that individuals with osteoporosis treated by using bisphosphonates presented less chances of periapical lesions (27). Meanwhile, another study concluded that there was no difference in periapical lesion presence in osteoporotic patients under pharmacological treatment and not under pharmacological treatment, although individuals treated with bisphosphonates presented lowest chance to have periapical lesions (26). This can probably be explained by the antiresorptive properties of these medications (51–53), and it is corroborated by a previous study that reported similar results on periapical repair in patients taking oral bisphosphonates compared to controls (not taking bisphosphonates) (54). As for the results on the use of denosumab, the researchers discussed that findings may be on account of the small sample size (26). Since there are no further clinical studies evaluating the use of this medication on the chances of osteoporotic patients to present periapical lesions, further discussion is not possible.

The present systematic review has some limitations. Methodological heterogeneity challenges more accurate comparisons or meta-analysis. Although the control for confounding factors that may influence apical periodontitis are difficult in observational studies, these must be cautiously evaluated in order to provide reliable results on the investigated subject. Additionally, based solely on these three observational studies and due to the high heterogeneity of results, it is not possible to establish a clear association between osteoporosis and apical periodontitis. Therefore, this study suggests that osteoporotic patients could exhibit a greater occurrence of periapical lesions when compared to non-osteoporotic patients, however more well-conducted clinical studies are still necessary to provide more robust scientific evidence.

CONCLUSION

In summary, the present review argued that osteoporotic patients might show a more pronounced presence of periapical lesions when compared with non-osteoporotic individuals. However, it is important to exercise caution when interpreting this statement since the available evidence is controversial and limited. The current body of evidence is still unsubstantial considering the extremely limited confidence in the evidence. Further well-designed investigations addressing the discussed limitations are essential to establish the trends presented by this review.

Disclosures

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REFERENCES

1. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014; 25:2359–81. [CrossRef]
2. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. Lancet 2011; 377:1276–87. [CrossRef]
3. Kanis JA, Cooper C, Rizzoli R, Reginster JY; Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2019; 30(1):3–44. Erratum in: Osteoporos Int 2020; 31(1):209. Erratum in: Osteoporos Int 2020; 31(4):801. [CrossRef]
4. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res 2014; 29:2520–6. [CrossRef]
5. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. Bone 2006; 38:S4–9. [CrossRef]
6. Richards JB, Leslie WD, Joseph L, Siminoski K, Hanley DA, Adachi JD, et al. Changes to osteoporosis prevalence according to method of risk assessment. J Bone Miner Res 2007; 22:228–34. [CrossRef]

7. Kanis JA, Melton LJ 3rd, Christiansen C, Johnston C, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994; 9(8):1137–41. [CrossRef]
8. Wang CJ, McCauley LK. Osteoporosis and periodontitis. Curr Osteoporos Rep 2016; 14:284–91. [CrossRef]
9. Bando K, NItta H, Matsubara M, Ishikawa I. Bone mineral density in periodontally healthy and edentulous postmenopausal women. Annals Periodontol 1998; 3:322–6. [CrossRef]
10. Weyant RJ, Pearlstein M, Churak A, Forrest K, Famili P, Cauley J. The association between osteopenia and periodontal attachment loss in older women. J Periodontol 1999; 70:982–91. [CrossRef]
11. Hollinger JO, Onikepe AO, MacKrell J, Einhorn T, Bradica G, Lynch S, et al. Accelerated fracture healing in the geriatric, osteoporotic rat with recombinant human platelet-derived growth factor-BB and an injectable beta-tricalcium phosphate/collagen matrix. J Orthop Res 2008; 26:83–90. [CrossRef]
12. Duarte P, de Assis D, Casati M, Sallum A, Sallum E, Nociti F Jr. Alendronate may protect against increased periodontitis-related bone loss in estrogen-deficient rats. J Periodontol 2004; 75:1192–202. [CrossRef]
13. Liu Z, Liu L, Kang C, Xie Q, Zhang B, Li Y. Effects of estrogen deficiency on microstructural changes in rat alveolar bone proper and periodontal ligament. Mol Med Rep 2015; 12:3508–14. [CrossRef]
14. Rossetti BR, Lemos AF, So BB, Weissheimer T, Martins MD, So MVR. Effects of estrogen deficiency on the progression of apical periodontitis. A systematic review of preclinical studies. Arch Oral Biol 2022; 142:105496. [CrossRef]
15. Siddiqui YD, Omori K, Ito T, Yamashiro K, Nakamura S, Okamoto K, et al. Resolvin D2 induces resolution of periapical inflammation and promotes healing of periapical lesions in rat periapical periodontitis. Front Immunol 2019; 10:307. [CrossRef]
16. Kakehashi S, Stanley H, Fitzgerald R. The effects of surgical exposures of dental pulps in germ-free and conventional laboratory rats. Oral Surg Oral Med Oral Pathol 1965; 20:340–9. [CrossRef]
17. Qian H, Guan X, Bian Z. FSH aggravates bone loss in ovariectomised rats with experimental periapical periodontitis. Mol Med Rep 2016; 14:2997–3006. [CrossRef]
18. Siqueira JF Jr, Rocas IN, Provenzano JC, Guilherme BP. Polymorphism of the FcgammaRIIIa gene and post-treatment apical periodontitis. J Endod 2011; 37:1345–8. [CrossRef]
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. [CrossRef]
20. Maia L, Antonio A. Systematic reviews in dental research. A guideline. J Clin Pediatr Dent 2012; 37:114–24. [CrossRef]
21. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews 2015; 4:1–9. [CrossRef]
22. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann T, Mulrow CD, et al. Mapping of reporting guidance for systematic reviews and meta-analyses generated a comprehensive item bank for future reporting guidelines. J Clin Epidemiol 2020; 118:60–8. [CrossRef]
23. Bero L, Chartres N, Diong J, Fabbri A, Ghersi D, Lam J, et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. Syst Rev 2018; 7:242. [CrossRef]
24. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011; 64:383–94. [CrossRef]
25. Morgan RL, Thayer KA, Santesso N, Holloway AC, Blain R, Eftim SE, et al. A risk of bias instrument for non-randomized studies of exposures: A users' guide to its application in the context of GRADE. Environ Int 2019; 122:168–84. [CrossRef]
26. Cadoni E, Ideo F, Marongiu G, Mezzena S, Frigau L, Mela Q, et al. Periapical status in patients affected by osteoporosis: a retrospective clinical study. Clin Exp Dent Res 2022; 8:1068–75. [CrossRef]
27. Katz J, Rotstein I. Prevalence of periapical lesions in patients with osteoporosis. J Endod 2021; 47:234–8. [CrossRef]
28. Lopez-Lopez J, Castellanos-Cosano L, Estrugo-Devesa A, Gomez-Vaquero C, Velasco-Ortega E, Segura-Egea JJ. Radiolucent periapical lesions and bone mineral density in post-menopausal women. Gerodontology 2015; 32:195–201. [CrossRef]
29. Alam T, AlShahrani I, Assiri KI, Almoammar S, Togoo RA, Luqman M. Evaluation of clinical and radiographic parameters as dental indicators for postmenopausal osteoporosis. Oral Health Prev Dent 2020; 18:499–504.
30. Lopez-Lopez J, Estrugo-Devesa A, Jane-Salas E, Ayuso-Montero R, Gomez-Vaquero C. Early diagnosis of osteoporosis by means of orthopantomograms and oral x-rays: a systematic review. Med Oral Patol Oral Cir Bucal 2011; 16:e905–13. [CrossRef]
31. Erdogan O, Incki KK, Benlidayi ME, Seydaoglu G, Kelekci S. Dental and radiographic findings as predictors of osteoporosis in postmenopausal women. Geriatr Gerontol Int 2009; 9:155–64. [CrossRef]
32. Licks R, Licks V, Ourique F, Radke Bittencourt H, Fontanella V. Development of a prediction tool for low bone mass based on clinical data and periapical radiography. Dentomaxillofac Radiol 2010; 39:224–30. [CrossRef]
33. Pizzo G, Guiglia R, Lo Russo L, Campisi G. Dentistry and internal medicine: from the focal infection theory to the periodontal medicine concept. Eur J Intern Med 2010; 21:496–502. [CrossRef]
34. Sasaki H, Hirai K, Martins CM, Furusho H, Battaglino R, Hashimoto K. Interrelationship between periapical lesion and systemic metabolic disorders. Curr Pharm Des 2016; 22:2204–15. [CrossRef]
35. Khalighinejad N, Aminoshariae MR, Aminoshariae A, Kulild JC, Mickel A, Fouad AF. Association between systemic diseases and apical periodontitis. J Endod 2016; 42:1427–34. [CrossRef]
36. Sultan N, Rao J. Association between periodontal disease and bone mineral density in postmenopausal women: a cross sectional study. Med Oral Patol Oral Cir Bucal 2011; 16:e440–7. [CrossRef]
37. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods 2021; 12:55–61. [CrossRef]
38. Serdar CC, Cihan M, Yucel D, Serdar MA. Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies. Biochem Med (Zagreb) 2021; 31:010502. [CrossRef]
39. Antony DP, Thomas T, Nivedhitha MS. Two-dimensional periapical, panoramic radiography versus three-dimensional cone-beam computed tomography in the detection of periapical lesion after endodontic treatment: a systematic review. Cureus 2020; 12:e7736. [CrossRef]
40. Leonardi Dutra K, Haas L, Porporatti AL, Flores-Mir C, Nascimento Santos J, Mezzomo LA, et al. Diagnostic accuracy of cone-beam computed tomography and conventional radiography on apical periodontitis: a systematic review and meta-analysis. J Endod 2016; 42:356–64. [CrossRef]
41. Tiburcio-Machado CS, Michelon C, Zanatta FB, Gomes MS, Marin JA, Bier CA. The global prevalence of apical periodontitis: a systematic review and meta-analysis. Int Endod J 2021; 54:712–35. [CrossRef]
42. Segura-Egea JJ, Martin-Gonzalez J, Castellanos-Cosano L. Endodontic medicine: connections between apical periodontitis and systemic diseases. Int Endod J 2015; 48:933–51. [CrossRef]
43. Zaleckiene V, Peciuliene V, Brukiene V, Drukteinis S. Traumatic dental injuries: etiology, prevalence and possible outcomes. Stomatologija 2014; 16(1):7–14.
44. Ng YL, Mann V, Gulabivala K. A prospective study of the factors affecting outcomes of nonsurgical root canal treatment: part 1: periapical health. Int Endod J 2011; 44:583–609. [CrossRef]
45. Yip N, Liu C, Wu D, Fouad AF. The association of apical periodontitis and type 2 diabetes mellitus: A large hospital network cross-sectional case-controlled study. J Am Dent Assoc 2021; 152:434–43. [CrossRef]
46. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol 2011; 64:407–15. [CrossRef]
47. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011; 64:1294–302. [CrossRef]
48. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011; 64:1303–10. [CrossRef]
49. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evidence-based Medicine 2017; 22:85–7. [CrossRef]
50. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011; 64:1311–6. [CrossRef]

51. Silva RAB, Sousa-Pereira AP, Lucisano MP, Romualdo PC, Paula-Silva FWG, Consolaro A, et al. Alendronate inhibits osteocyte apoptosis and inflammation via IL-6, inhibiting bone resorption in periapical lesions of ovariectomized rats. Int Endod J 2020; 53:84–96. [CrossRef]
52. Rao NJ, Wang JY, Yu RQ, Leung YY, Zheng LW. Role of periapical diseases in medication-related osteonecrosis of the jaws. Biomed Res Int 2017; 2017:1560175. [CrossRef]
53. Song M, Alshaikh A, Kim T, Kim S, Dang M, Mehrazarin S, et al. Preexisting periapical inflammatory condition exacerbates tooth extraction-induced bisphosphonate-related osteonecrosis of the jaw lesions in mice. J Endod 2016; 42:1641–6. [CrossRef]
54. Hsiao A, Glickman G, He J. A retrospective clinical and radiographic study on healing of periradicular lesions in patients taking oral bisphosphonates. J Endod 2009; 35:1525–8. [CrossRef]