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Association between Apical Periodontitis and Chronic Diseases: An Umbrella Review

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Introduction: To assess the methodological quality of systematic reviews (SRs) that evaluated the association between apical periodontitis (AP) and chronic diseases. **Materials and Methods:** A systematic search was performed in the databases PubMed, Virtual Health Library, Scopus, Cochrane Library, Embase, Web of Science and Open Grey. SRs that evaluated the association between any chronic disease and AP, and that had performed a valid risk of bias assessment were included. The AMSTAR-2 tool was used for quality assessment and each included systematic review received a final categorization as having "high", "moderate", "low", or "critically low" quality. **Results:** Nine studies that met the eligibility criteria were included. The diseases investigated were cardiovascular diseases, diabetes mellitus, HIV, osteoporosis, chronic liver disease, blood disorders and autoimmune diseases. The systematic reviews included in this umbrella review showed a 'low' to 'high' quality of evidence. **Conclusion:** There are substantial heterogeneity and several methodological concerns in the included studies. It was observed a positive association between diabetes mellitus and apical periodontitis with limited evidence, no association between HIV and apical periodontitis and a positive association between apical periodontitis and cardiovascular disease, blood disorders, chronic liver disease, osteoporosis and autoimmune diseases with moderate evidence.

Keywords: Apical Periodontitis; Endodontics; Chronic Disease; Systematic Review; Umbrella Review

Introduction

On the last few years, the term endodontic medicine has emerged to define the study of the association between periapical lesions and systemic diseases [1]. The bidirectional relationship among the development of apical periodontitis and some common diseases such as cardiovascular alterations and diabetes is already well established [2-4]. These associations opened new avenues to the investigation of the relationship between other systemic conditions and endodontic infection. In this sense, other disorders like chronic renal disease, liver cirrhosis, pre-eclampsia, hypoestrogenism, osteoporosis and coagulation disorders were also suggested to be related to apical periodontitis although these associations still not so clear [5-10].

Apical periodontitis is an inflammatory local event that occurs as a response to endodontic infection [11]. This stimulates the production of pro-inflammatory mediators that penetrate blood vessels and attract defense cells to the local of injury [12]. Thereby, the spread of these inflammatory modulators can start the immunological response and influence the systemic condition of the patient [1, 2, 13]. In the opposite way, systemic diseases can also modulate the inflammatory response on the localized lesion exacerbating the destruction of the periapical tissues [1, 4]. Some systemic conditions may predispose a more intense inflammation which results in increased bone loss and delay of the healing process on apical periodontitis [1, 14, 15].

Several review studies have been conducted to analyze which are the main diseases related to the endodontic lesion and if there is scientific evidence that supports this association [1, 4, 16-19]. In general, the reviews show controversial and inconclusive results, and most of them are not systematic reviews and/or do not evaluate the quality and risk of bias of the included studies.

Table 1 Search strategy in the databases.

Database	Search strategy	Findings
Pubmed	**#1** (Systemic diseases [tiab] or Systemic condition [tiab] or Systemic disorders [tiab] or Metabolic diseases [mesh] or Diabetes Mellitus [mesh] or Diabetes [tiab] or Cardiovascular diseases [mesh] or Liver cirrhosis [mesh] or Chronic liver disease [tiab] or Osteoporosis [mesh] or Immune system diseases [mesh] or Blood coagulation disorders [mesh] or Chronic inflammatory diseases [tiab] or Inflammatory bowel diseases [mesh] or Hypertension [mesh] or Pre-eclampsia [mesh] or Chronic renal insufficiency [mesh] or Chronic obstructive pulmonary disease [mesh] or Metabolic syndrome [mesh] or AIDS [tiab] or Medicine [mesh] or Arthritis, Rheumatoid [mesh]) **#2** (Periapical periodontitis [mesh] or Periapical periodontitis [tiab] or Apical periodontitis [tiab] or Periapical condition [tiab] or Periapical inflammation [tiab] or Periapical lesions [tiab] or Periapical radiolucency [tiab] or Periapical patology [tiab] or Endodontic patology [tiab] or Periapical pathosis [tiab] or Periradicular lesions [tiab] or Endodontics [mesh] or Endodontics [tiab]) **#3** (Review[tiab]) OR Meta-analysis[tiab]) **#1** and **#2** and **#3**	6032181 34490 1725345 134
VHL	**#1** (tw:("Systemic diseases")) OR (tw:("Systemic condition")) OR (tw:("Systemic disorders")) OR (mh:("Metabolic diseases")) OR (mh:("Diabetes Mellitus")) OR (tw:(Diabetes)) OR (mh:("Cardiovascular diseases")) OR (mh:("Liver cirrhosis")) OR (tw:("Chronic liver disease")) OR (mh:(Osteoporosis)) OR (mh:("Immune system diseases")) OR (mh:("Blood coagulation disorders")) OR (tw:("Chronic inflammatory diseases")) OR (mh:("Inflammatory bowel diseases")) OR (mh:(Hypertension)) OR (mh:(Pre-eclampsia)) OR (mh:("Chronic renal insufficiency")) OR (mh:("Chronic obstructive pulmonary disease")) OR (mh:("Metabolic syndrome")) OR (tw:(AIDS)) OR (mh:(Medicine)) OR (tw:("Rheumatoid Arthritis")) **#2** (mh:("Periapical periodontitis")) OR (tw:("Apical periodontitis")) OR (tw:("Periapical condition")) OR (tw:("Periapical inflammation")) OR (tw:("Periapical lesions")) OR (tw:("Periapical radiolucency")) OR (tw:("Periapical patology")) OR (tw:("Endodontic patology")) OR (tw:("Periapical pathosis")) OR (tw:("Periradicular lesions")) OR (mh:(Endodontics)) OR (tw:(Endodontics)) **#3** (tw:Review OR Meta-analysis) **#1** and **#2** and **#3**	1725955 16237 3556810 82
Scopus	**#1** TITLE-ABS-KEY (“Systemic diseases” OR “Systemic condition” OR “Systemic disorders” OR “Metabolic diseases” OR “Diabetes Mellitus” OR Diabetes OR “Cardiovascular diseases” OR “Liver cirrhosis” OR “Chronic liver disease” OR Osteoporosis OR “Immune system diseases” OR “Blood coagulation disorders” OR “Chronic inflammatory diseases” OR “Inflammatory bowel diseases” OR Hypertension OR “Pre-eclampsia” OR “Chronic renal insufficiency” OR “Chronic obstructive pulmonary disease” OR “Metabolic syndrome” OR AIDS OR Medicine OR “Rheumatoid Arthritis”) **#2** TITLE-ABS-KEY (“Periapical periodontitis” OR “Apical periodontitis” OR “Periapical condition” OR “Periapical inflammation” OR “Periapical lesions” OR “Periapical radiolucency” OR “Periapical pathology” OR “Endodontic pathology” OR “Periapical pathosis” OR “Periradicular lesions” OR “Endodontics”) **#3** TITLE-ABS (Review OR Meta-analysis) **#1** and **#2** and **#3**	4332900 5533 5003997 337
Cochrane Library: Cochrane Reviews	**#1** systemic diseases OR systemic condition OR systemic disorders OR metabolic diseases OR diabetes mellitus OR diabetes OR cardiovascular diseases OR liver cirrhosis OR chronic liver disease OR osteoporosis OR immune system diseases OR blood coagulation disorders OR chronic inflammatory diseases OR inflammatory bowel diseases OR hypertension OR pre-eclampsia OR chronic renal insufficiency OR chronic obstructive pulmonary disease OR metabolic syndrome OR AIDS OR rheumatoid arthritis **#2** periapical periodontitis OR apical periodontitis OR endodontic OR apical periodontitis OR periapical condition OR periapical inflammation OR periapical lesions OR periapical radiolucency OR periapical patology OR endodontic patology OR periapical pathosis OR periradicular lesions **#1** and **#2**	2824 9 2
Embase	**#1** ‘Systemic diseases’:ab,ti OR ‘Systemic condition’:ab,ti OR ‘Systemic disorders’:ab,ti OR ‘Metabolic diseases’/exp OR ‘Diabetes Mellitus’/exp OR Diabetes:ab,ti OR ‘Cardiovascular diseases’/exp OR ‘Liver cirrhosis’/exp OR ‘Chronic liver disease’:ab,ti OR Osteoporosis/exp OR ‘Immune system diseases’/exp OR ‘Blood coagulation disorders’/exp OR ‘Chronic inflammatory diseases’:ab,ti OR ‘Inflammatory bowel diseases’/exp OR Hypertension/exp OR ‘Pre-eclampsia’/exp OR ‘Chronic renal insufficiency’/exp OR ‘Chronic obstructive pulmonary disease’/exp OR ‘Metabolic syndrome’/exp OR AIDS:ab,ti OR Medicine/exp OR ‘Rheumatoid Arthritis’/exp **#2** ‘Periapical periodontitis’/exp OR ‘Apical periodontitis’:ab, ti OR ‘Periapical condition’: ab,ti OR ‘Periapical inflammation’:ab,ti OR ‘Periapical lesions’:ab,ti OR ‘Periapical radiolucency’:ab,ti OR ‘Periapical pathology’: ab,ti OR ‘Endodontic pathology’:ab,ti OR ‘Periapical pathosis’:ab,ti OR ‘Periradicular lesions’:ab,ti OR Endodontics/exp **#3** ‘meta-analysis’/exp OR ‘systematic review’/exp **#1** and **#2** and **#3**	10958861 33726 2790498 214
Web of Science	**#1** TS=(“Systemic diseases” OR “Systemic condition” OR “Systemic disorders” OR “Metabolic diseases” OR “Diabetes Mellitus” OR Diabetes OR “Cardiovascular diseases” OR “Liver cirrhosis” OR “Chronic liver disease” OR Osteoporosis OR “Immune system diseases” OR “Blood coagulation disorders” OR “Chronic inflammatory diseases” OR	2567676

	"Inflammatory bowel diseases" OR Hypertension OR "Pre-eclampsia" OR "Chronic renal insufficiency" OR "Chronic obstructive pulmonary disease" OR "Metabolic syndrome" OR AIDS OR Medicine OR "Rheumatoid Arthritis") **#2** TS=("Periapical periodontitis" OR "Apical periodontitis" OR "Periapical condition" OR "Periapical inflammation" OR "Periapical lesions" OR "Periapical radiolucency" OR "Periapical pathology" OR "Endodontic pathology" OR "Periapical pathosis" OR "Periradicular lesions" OR "Endodontics") **#3** TS=(Review OR Meta-analysis) **#1** and **#2** and **#3**	7695 2700758 164
Open Grey	#1 systemic diseases OR systemic condition OR systemic disorders OR metabolic diseases OR diabetes mellitus OR diabetes OR cardiovascular diseases OR liver cirrhosis OR chronic liver disease OR osteoporosis OR immune system diseases OR blood coagulation disorders OR chronic inflammatory diseases OR inflammatory bowel diseases OR hypertension OR pre-eclampsia OR chronic renal insufficiency OR chronic obstructive pulmonary disease OR metabolic syndrome OR AIDS OR rheumatoid arthritis **#2** periapical periodontitis OR apical periodontitis OR endodontic OR apical periodontitis OR periapical condition OR periapical inflammation OR periapical lesions OR periapical radiolucency OR periapical patology OR endodontic patology OR periapical pathosis OR periradicular lesions **#3** Review OR meta-analysis **#1** and **#2** and **#3**	8117 85 13872 0

Systematic reviews using proper quality assessment tools provide the best evidence and unbiased information [20]. With the crescent number of systematic reviews assessing the relationship between systemic diseases and apical periodontitis, the evaluation of the quality of evidence of these studies using a systematic approach become essential to ensure that they provide the correct summary of results, allowing the most adequate decision on the clinical setting [21]

The overview of systematic reviews (*i.e.* 'umbrella' review) summarizes the evidence from multiple studies and highlights the inconsistency of their findings and gaps in the research area [22, 23]. Hence, the umbrella review provides a high-quality evidence and points to the weaknesses in the systematic reviews, in order to improve the methodological designs of future studies [24]. Therefore, an umbrella review was performed to (*i*) identify all the published systematic reviews that evaluated the association between periapical lesion and systemic diseases using a proper risk of bias assessment tools, (*ii*) assess the methodological quality of these studies and (*iii*) perform a critical evaluation of them to determine whether there is an association and to report the gaps in the research in this area.

Materials and Methods

The present umbrella review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. The protocol of the present review was registered in the PROSPERO database (http://www.crd.york.ac.uk) under registration number CRD42020189979.

Focused question

Is there evidence to support the association between systemic diseases and apical periodontitis?

Search strategy

A systematic search was performed without any parameter restrictions up to September 2022 by two independent reviewers (K.P.P. and C.M.A.F.) using specific Medical Subject Heading (MeSH) terms and free descriptors (title/abstract) regarding apical periodontitis, systemic diseases and reviews in the following electronic databases: PubMed, Virtual Health Library (VHL), Scopus, Cochrane Library, Embase, Web of Science and Open Grey (Table 1).

A complementary screening on the references of the selected studies was also performed in attempt to include any additional relevant study that did not appear in the database search. Also, the PROSPERO database was consulted to assess if there were registered protocols of systematic reviews in this theme and its publication. Duplicate manuscripts have been removed through the Endnote web software (www.endnoteweb.com).

Study selection

After the removal of duplicates, the studies were selected by title and abstract reading and the eligible studies were read in full by two independent reviewers (K.P.P. and C.M.A.F.) for a final decision. In cases of discordance after a consensus meeting, a third review author with expertise in the area made a final decision (E.J.N.L.S.).

Articles that did not address the proposed theme, primary studies, laboratory studies, case reports with literature review and other types of reviews that did not follow systematic review guidelines were excluded. Studies published in an abstract form, meeting report or as protocols were not considered. Only systematic reviews that performed a valid risk of bias assessment of the studies were included. All included systematic reviews underwent data extraction and quality assessment.

Data extraction

Data extraction was performed by two independent reviewers (K.P.P. and C.M.A.F.) and any disagreement was solved by a third

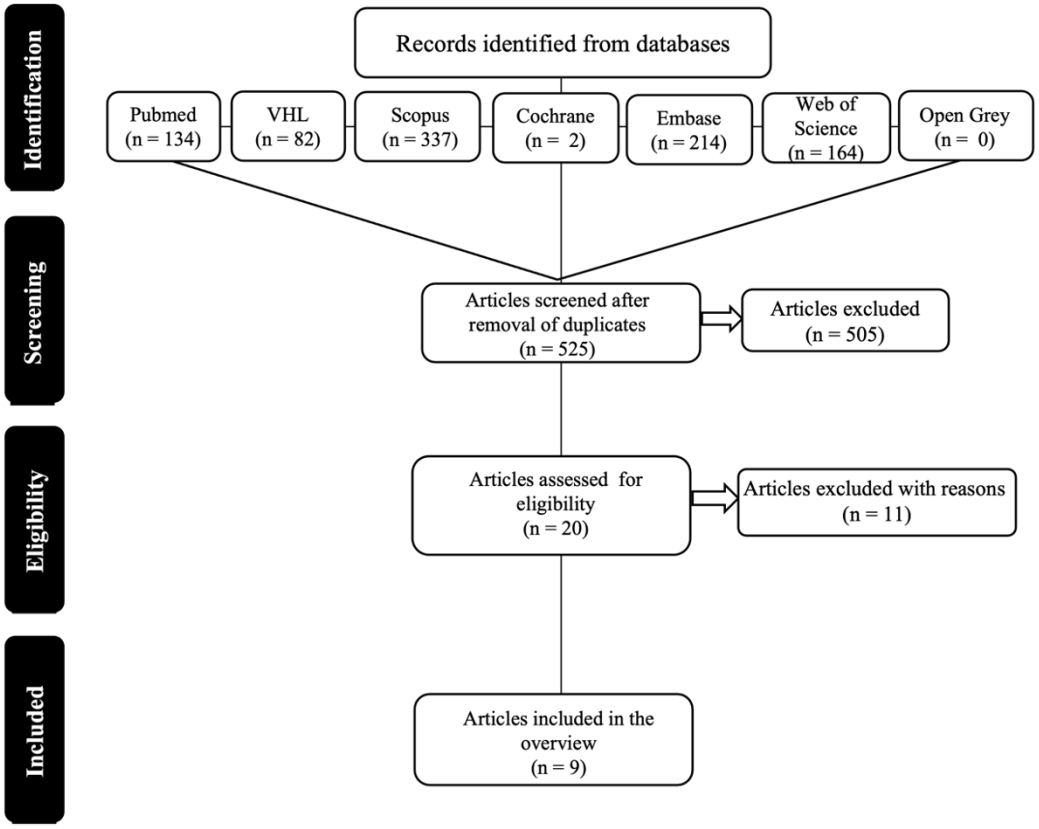

Figure 1. Flow diagram of literature search according to PRISMA guidelines

review author (E.J.N.L.S.). It was obtained the summary of findings from each included study, as follows: author, year and journal of publication, the systemic diseases evaluated, databases searched, study designs included, number of included studies, if it was performed a meta-analysis, and the quality assessment tool used.

Quality assessment

The quality of evidence of the included studies was assessed by two independent reviewers (K.P.P. and C.M.A.F.) using the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2) [26]. Whenever differences occurred between the two evaluators, a third reviewer was consulted (E.J.N.L.S.).

The AMSTAR-2 toll consists of a checklist with sixteen items that evaluate the methodological quality of the included studies, as follows: inclusion of the components of PICO, provision of an a priori design, selection of the design of included studies, comprehensive literature search, duplicate study selection, duplicate data extraction, listing of excluded studies, provision of characteristics of included studies, assessment of the risk of bias, report on the sources of funding of included studies, appropriate methods used to combine findings, assessment of the impact of the risk of bias on the results of included studies, take into account the risk of bias of included studies when discussing the results of the review, heterogeneity in the results of the review, assessment of publication bias, and stated conflict of interest [26]. The items are presented in the form of questions, with possible responses of "yes", "partial yes" or "no" [26]. The online checklists were answered on the AMSTAR website (https://amstar.ca/Amstar_Checklist.php). A final categorization of each systematic review was generated, and the studies were classified as having "high", "moderate", "low", or "critically low" quality.

Results

Search results

The initial search retrieved 933 manuscripts. After the removal of duplicates, 525 manuscripts had their titles and abstracts screened and 505 studies were excluded. Twenty articles had their full text assessed but 11 studies were not included in this review because they were not systematic reviews or did not address the aim of the present umbrella review or did not performed risk of bias assessment of the included studies. The reasons for exclusion of these articles are detailed in Table 2. Nine studies [16, 18, 19, 27-32] that met the eligibility criteria were included in the present review (Figure 1). Three concluded

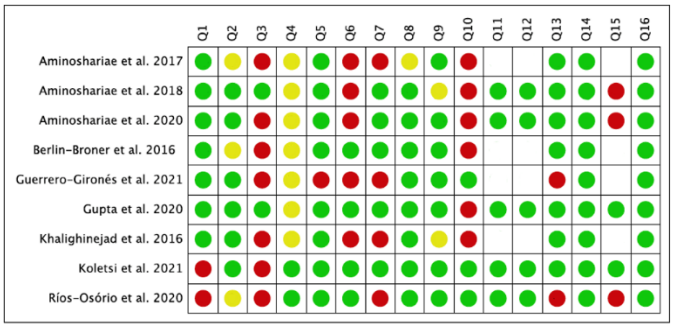

Figure 2. Quality assessment of the included studies according to AMSTAR-2. Blank space means the question is not applicable for the study (i.e. study without meta-analysis) (Green symbol means "yes", yellow symbol means "partial yes" and red symbol means "no")

systematic reviews were identified in the PROSPERO database and all of them had already been recovered in the initial search. It was also identified nine protocols of ongoing systematic reviews about this theme.

Characteristics of the included systematic reviews

The characteristics of the included systematic reviews are presented in Table 3. The publication years ranged from 2016 to 2021, and the studies were published in the Journal of Endodontics (*n*=3), International Endodontic Journal (*n*=2), Clinical Oral Investigations (*n*=1), Quintessence International (*n*=1), International Journal of Environmental Research and Public Health (*n*=1) and Journal of Clinical Medicine (*n*=1). The diseases more investigated were cardiovascular diseases (CVD) (*n*=6) and diabetes mellitus (DM) (*n*=4), and it was also assessed HIV, osteoporosis, chronic liver disease, blood disorders and autoimmune diseases (*n*=1). The number of databases used in the reviews ranged from 3 to 6 and included the MEDLINE, Embase, Cochrane, PubMed, Google Scholar, Scopus, Web of Science and EBSCO host. The number of studies included in each systematic review ranged from 3 to 21. Out of the nine included studies, five [18, 19, 29-31] conducted meta-analyses. Three reviews [18, 28, 30] used the Newcastle-Ottawa scale to assess the risk of bias of the included studies, one review used the Joanna Briggs Institute critical appraisal tool [19], one review used the ROBINS-I tool [31], three reviews used a proposed specific quality assessment tool using a combination of several tools such as The Cochrane Collaboration's tool for assessing the risk of bias, the Oxford Systematic Review Appraisal Sheet and the Critical Appraisal Skills Programme tool [16, 27, 29], and one review used a proposed specific quality assessment tool adapted from STROBE guidelines [32].

Methodological quality assessment

The methodological quality of the included systematic reviews is shown in Figure 2. One study [19] was graded as "high" quality and did not address only the question 10 of the AMSTAR-2 checklist (Did the review authors report on the sources of funding for the studies included in the review?), six studies [16, 18, 27-29, 31] were graded as "moderate" quality due to different reasons, and two studies [30, 32] were graded as "low" quality, as they did not address several questions of the AMSTAR-2 checklist.

Main findings

The systematic review of Aminoshariae *et al.* [27] evaluated the influence of different systemic diseases on the periapical healing or survival of root canal treated teeth. From the included studies in the above-mentioned systematic review, three evaluated CVD (two of them reported a positive significant association and one study did not find association), eleven studies evaluated DM (six of them reported association and 5 did not found significant association), and three studies assessed HIV (none of them found association). The meta-analysis was not performed due to the heterogeneity among the different study designs and different systemic conditions. The overall quality of the included studies was considered to have a moderate to high risk of bias. The result of the review was inconclusive regarding the association between CVD or DM and root canal treatment outcome due to the few studies reporting a positive association and their high risk of bias.

Table 2 Reasons for exclusion of each full-text read article

Author	Reason for exclusion
Aminoshariae *et al.*	The study did not address the aim of the present umbrella review
Abraham *et al.*	This systematic review included studies assessing teeth with pulp necrosis or apical periodontitis
Botero *et al.* 2020	The study did not address the aim of the present umbrella review
Cabanillas-Balsera *et al.*	The study did not address the aim of the present umbrella review
Cintra *et al.*	The study is a narrative review
González Navarro *et al.*	It was not performed a quality assessment
Mauri Obradors *et al.*	It was not evaluated the risk of bias of the included studies
Pérez-Losada *et al.*	It was not evaluated the risk of bias of the included studies
Segura-Egea *et al.*	The study is a narrative review
Segura-Egea *et al.*	It was not evaluated the risk of bias of the included studies
Tibúrcio-Machado *et al.*	The study is a critical review

Table 3. Characteristics of the included studies.

Author	Name of the journal published	Systemic diseases evaluated	Outcomes evaluated	Databases searched	Study designs included	Number of included studies	Meta-analysis	Quality assessment tool
Aminoshariae *et al.* [27]	Journal of Endodontics	CVD, DM, HIV	Healing of periapical lesions and tooth survival after root canal treatment	MEDLINE, Embase, Cochrane, and PubMed	Clinical trial, case-control, cross-sectional, and cohort	16	No	Proposed specific quality assessment scale
Aminoshariae *et al.* [29]	Journal of Endodontics	CVD	Influence of periapical lesion on the development of CVD	MEDLINE, Embase, Cochrane, and PubMed	Cohort	4	Yes	Proposed specific quality assessment scale
Aminoshariae *et al.* [18]	Clinical Oral Investigations	CVD	Healing of periapical lesions and tooth survival after root canal treatment	Cochrane, Scopus, MEDLINE, Google Scholar, Embase and PubMed	Cohort	3	Yes	Newcastle-Ottawa scale
Berlin-Broner *et al.* [28]	International Endodontic Journal	CVD	Association between periapical lesion and CVD, in both pathways	MEDLINE, PubMed and Embase	Case-control, cross-sectional, and cohort	19	No	Newcastle-Ottawa scale
Guerrero-Gironés *et al.* [32]	Journal of Clinical Medicine	Autoimmune diseases	Association between pulpal-periapical pathology and autoimmune disease	MEDLINE, SciELO, Web of Science, Cochrane Library, and Scopus	Case-control and cross-sectional,	7	No	Proposed specific quality assessment scale adapted from STROBE guidelines
Gupta *et al.* [19]	International Endodontic Journal	DM	Healing of periapical lesions in root filled teeth	MEDLINE (Pubmed), Scopus, Ebsco host	Clinical trial, case-control, cross-sectional, and cohort	10	Yes	The Joanna Briggs Institute Critical Appraisal Tool
Khalighinejad *et al.* [16]	Journal of Endodontics	CVD, DM, CLD, Blood disorders and Osteoporosis	Association between systemic diseases and periapical lesions	MEDLINE, Embase, Cochrane, and PubMed	Clinical trial, case-control, cross-sectional, and cohort	16	No	Proposed specific quality assessment scale
Koletsi *et al.* [31]	International Journal of Environmental Research and Public Health	CVD	Association between CVD and chronic endodontic infection	MEDLINE (Pubmed), Scopus, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviwes	Observational studies (retrospective cohort, prospective cohort, case-control, cross-sectional)	21	Yes	ROBINS-I
Ríos-Osório *et al.* [30]	Quintessence International	DM	Prevalence, development and periapical healing	MEDLINE (Pubmed), Web of Science, Scopus	Cross-sectional, and cohort	10	Yes	Newcastle-Ottawa scale

CLD, Chronic Liver Disease; CVD, Cardiovascular Disease; DM, Diabetes Mellitus

The systematic review of Aminoshariae *et al.* [18] performed a similar evaluation but only related to CVD. The overall certainty of evidence was moderate with low risk of bias, and the meta-analyses indicated 67% higher risk for a negative outcome after root canal treatment in patients with CVD compared with healthy patients. The systematic review of Aminoshariae *et al.* [29] also evaluated CVD, but in the opposite pathway: it was evaluated the impact of the periapical lesion on the development of CVD. It was observed a small significant effect with this relative risk (RR) and confidence interval (CI): RR=1.20, (95% CI, 0.079–1.82), but the overall certainty of evidence was low, and the overall risk of bias was high.

The studies of Berlin-Broner *et al.* [28] and Koletsi *et al.* [31] also evaluated the relationship between periapical lesion and CVD. In the systematic review of Berlin-Broner *et al.* [28], thirteen included studies found a positive association (in two of them the positive association lost significance after multivariable analysis), five studies did not report a significant association and one study found a negative association. No meta-analysis was conducted due to the heterogeneity among the included studies, especially related to the study design and outcomes of interest, and the quality of evidence of the included studies varied from moderate to low. In the systematic review of Koletsi *et al.* [31], the meta-analysis showed that patients with chronic endodontic infection had 1.38 times risk of CVD diagnosis compared to those without infection (RR=1.38; 95% CIs: 1.06, 1.80; *P*=0.008). However, most of the included studies were graded as having serious risk of bias and the overall quality of evidence was graded as very low.

The systematic review of Khalighinejad *et al.* [16] evaluated the association between different systemic diseases and periapical lesion. Eight included studies assessed CVD (seven of them showed a positive association, with low to moderate risks of bias), five studies assessed DM (three of them found a positive association, with moderate to high risk of bias), one study assessed chronic liver disease (CLD), one study assessed blood disorder and one study assessed osteoporosis (each study showed positive associations but presented high risk of bias). Because of the heterogeneity among the studies design and data, it was not performed a meta-analysis. The overall risk of bias of the included studies was moderate and the results were inconclusive.

The systematic review of Guerrero-Gironés *et al.* [32] assessed the relationship between periapical pathology and autoimmune diseases and showed that periapical lesions were associated with three autoimmune diseases (diabetes mellitus I, rheumatoid arthritis, and inflammatory bowel disease), although most studies report statistically non-significant associations. Among the seven included studies, four showed low risk of bias, while three presented moderate risk of bias.

The systematic reviews of Gupta *et al.* [19] and Ríos-Osório et al. [30] evaluated the association of DM and the prevalence and healing of periapical lesions. In the study of Gupta *et al.* [19], out of the ten included studies, seven found a positive association. The results of the meta-analysis indicated a higher prevalence of root filled teeth with radiolucent periapical lesions in diabetics patients, compared to healthy patients. However, an association with delayed periapical healing could not be established. In the study of Ríos-Osório *et al.* [30], all of the ten included studies showed a positive association, however, nine studies were considered as having high risk of bias, which led to inconclusive results and just a suggestion that the DM could act as a risk factor for apical periodontitis.

Discussion

This umbrella review was performed to assess the methodological quality of systematic reviews and meta-analyses evaluating the association between systemic diseases and apical periodontitis, and to report the methodological flaws and gaps in the research to improve future studies. It was included only systematic reviews that performed risk of bias assessment of the primary studies, to enhance the reliability of the findings. For this reason, five systematic reviews were excluded: one systematic review that evaluated the association between CVD and apical periodontitis, but did not perform quality assessment [33], and four systematic reviews that evaluated the association between DM and apical periodontitis [34-37], which reported having performed quality assessment using the evidence levels of the guidelines of the "Oxford Centre for Evidence-Based Medicine (OCEBM) [38]. The OCEBM guidelines are used to grade the levels of evidence according to the study design [38, 39], but it is not a tool to evaluate the risk of bias of included studies. When performing a systematic review, the risk of bias of individual studies must be appraised and should be considered in the analysis of the results and used to develop the conclusions and future recommendations [25, 26].

Two previous umbrella reviews on this theme were performed, evaluating specifically the association between CVD and apical periodontitis [40] and the association between DM and the outcome of root canal treatment [41]. However, these studies included systematic reviews that did not perform a valid risk of bias assessment [34, 36] and new systematic reviews were published regarding the association between these conditions and apical periodontitis [19, 30-32].

In the present umbrella review, the systematic reviews that assessed CVD showed 'low' to 'moderate' quality of evidence, while the systematic reviews that assessed DM were graded as

having 'low' to 'high' quality of evidence and, although the results suggest a positive association between these chronic disease and apical periodontitis, the evidence remains inconclusive. Regarding the other evaluated systemic diseases (HIV, CLD, blood disorders, osteoporosis and autoimmune diseases), the systematic reviews presented 'moderate' quality. No association was observed between HIV and apical periodontitis and a positive association was observed regarding blood disorders, CLD, osteoporosis and autoimmune diseases.

All the included systematic reviews concluded that there is a need for more well-designed clinical studies testing the underlining mechanisms to address the cause-effect relationship between apical periodontitis and systemic diseases, since the majority of the primary studies on this matter are observational studies. With this purpose, it is indicated the assessment of biomarkers of inflammation in clinical studies [42]. In cases that clinical trials should not be conducted for ethical reasons, animal studies and larger cohorts with adequate follow-ups should take place [43].

Furthermore, several confounders must be carefully addressed in the primary studies. One of the most important factors when it comes to root canal treatment prognosis is the presence of preoperative periapical lesion [44, 45]. Thus, future primary studies evaluating the outcome of root canal therapy should consider the presence or not of preoperative apical periodontitis and make distinct evaluations. Similarly, the severity of the systemic conditions should be considered when performing a primary study (*i.e.* glycemic control, blood counts, bone markers). The hyperglycemia in diabetic patients can be associated with a higher prevalence of apical periodontitis [46] and it is the most important feature that impairs the healing process [34, 47-50]. In this way, it is essential to measure the glycemic levels of the patients and make a distinct evaluation between controlled diabetic patients and non-controlled diabetic patients when relating the DM to an increased prevalence, exacerbation or impair healing of periapical lesions. In the same manner, the response to a localized infection in HIV-positive patients is regulated by their CD4+ and viral counts [51], the immunological response of patients with CLD is impaired by their increased levels of many intrinsic factors such as endotoxins, nitric oxide and cytokines [52], and the inflammatory and healing process in patients with blood disorders involve alterations in the quantification of specific vascular cells [53]. Therefore, future studies should measure these factors when addressing the relationship between the systemic disease and the development and healing of apical periodontitis.

It is important to emphasize that some systemic diseases are representative of several systemic conditions. For example, CVD is a representative of many conditions such as hypertension, angina, atherosclerosis, and myocardial infarction [54], as well as blood disorders involves anemia, hemophilia, and autoimmune diseases [55]. The heterogeneity among these outcomes and the methodologies used to evaluate each of them make it difficult to combine results. Future studies should also address the association between apical periodontitis and specific conditions in separate.

The included systematic reviews that evaluated CVD highlighted the importance of the evaluation of periodontitis as a risk factor, since most of the primary studies did not take this into consideration. The presence of periodontitis is a potential confounder that may be responsible for a positive association between apical periodontitis and CVD [43, 56]. Also, periodontitis is the most important confounding variable associated with DM [57], and it is also a risk factor for CLD [58]. In the same way, tobacco smoking can be a potential risk factor for apical periodontitis, CVD, DM and osteoporosis [59-61], as well as alcohol consumption can be a risk factor for CLD and osteoporosis [62-64]. In addition, genetic predisposition has been associated with both apical periodontitis and systemic diseases including DM [65, 66]. It is almost impossible to control for all confounders, but it is essential to evaluate and control the most important risk factors that can interfere in the accuracy of the findings.

There is also a need to improve the methodological flaws in future systematic reviews on this theme. When evaluating the systematic reviews included in this umbrella review, it was observed that except for two studies, the Item 4 of the AMSTAR checklist (Did the review authors use a comprehensive search strategy?) was not fully accomplished by the studies. Most of them did not search for grey literature and study registers. The grey literature includes unpublished papers, such as conference papers, dissertations and thesis, and its inclusion in the systematic search reduces the publication bias [67, 68]. Moreover, most of the systematic reviews did not justify the selection of the included study designs (Item 3 of the AMSTAR checklist). Study designs included in a systematic review should be well selected to provide the right answer to the question of interest and to reduce biases [69, 70]. Another point to be considered is that except for one study, the included systematic reviews did not report on the funding sources of the primary studies (Item 10 of the AMSTAR checklist). It is well known that studies funded by private sectors can present biases, and moreover, it was showed that they are less likely to have all results published compared to studies that is independently funded [26, 71].

The present umbrella review has the limitation that it was not possible to perform a summary of the meta-analyses of the included systematic reviews due to the high heterogeneity

among their methodological design and outcomes of interest. It is encouraged the conduction of new systematic reviews with well-designed methodologies assessing the relationship between apical periodontitis and other chronic diseases that are widely being studied.

Both patient and clinician should be aware of the possible relationship between chronic systemic diseases and apical periodontitis. These diseases can impact the development and healing process of periapical lesions and therefore, can interfere in the prognosis of the root canal treatment. On the other way, the recognition of periapical lesions as a risk factor for some chronic inflammatory diseases can highlight the importance of a quality public oral healthcare access, which is essential to provide an adequate prevention and early intervention to improve health outcomes.

Conclusion

There is a positive association between CVD and apical periodontitis and between DM and apical periodontitis with limited quality of evidence, no association between HIV and apical periodontitis and positive association between apical periodontitis and blood disorders, CLD, osteoporosis and autoimmune diseases with moderate quality of evidence. There are several methodological flaws in the primary studies and systematic reviews and there is a need for future well-designed clinical studies following the recommendations of this umbrella review.

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