The Impact of Endodontic Infections on the Pathogenesis of Cardiovascular Disease(s): A Systematic Review with Meta-analysis Using GRADE

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Abstract

Introduction: The purpose of this systematic review was to determine whether endodontic infections had an impact on the pathogenesis of systemic disease. **Methods:** Two reviewers independently conducted a comprehensive literature search. The MEDLINE, Embase, Cochrane, and PubMed databases were searched. In addition, the bibliographies, gray literature of all relevant articles, and textbooks were manually searched. There was no disagreement between the 2 reviewers. **Results:** Four articles met the inclusion criteria with a high risk of bias. Three articles were analyzed for qualitative synthesis. All these articles were regarding cardiovascular disease (CVD). There was low-certainty evidence that a lesion of endodontic origin can contribute to systemic disease, 95% confidence interval, risk ratio 1.2 (0.079–1.83). Therefore, the authors have limited confidence in the effect estimate, which indicates that the true effect may be substantially different from the estimate of the effect. **Conclusions:** Whether the presence of a lesion of endodontic origin may or may not have some impact on cardiovascular disease, the level of evidence is low, and our confidence in the assessment is low. This systematic review raised questions in the designs and analysis of the data, and further well-conducted longitudinal researches would be required to make this causality claim. *(J Endod 2018;■:1–6)*

Key Words

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Significance

Lesions of endodontic origin may contribute to cardiovascular disease under unknown circumstances that warrant well-designed longitudinal clinical trials. Evidence for this appears to be limited and low at this time.

In a previous systematic review, the authors reported that there may be a correlation between some systemic diseases and the pathogenesis of endodontic diseases (1). The authors then performed another systematic review to address the relationship of systemic diseases and endodontic treatment outcomes (2). The results reported that some systemic diseases may negatively influence endodontic healing outcomes. To complement these analyses, a systematic review investigating the correlation between a lesion of endodontic origin (LEO) and the pathogenesis of systemic inflammation and/or disease was needed.

Gomes et al (3) reported that apical periodontitis was associated with increased levels of inflammatory markers contributing to a systemic immune response and potentially leading to increased systemic inflammation. A recent systematic review (4) and 2 narrative reviews (5, 6) investigating the influence of a LEO on cardiovascular disease (CVD) reported a plausible positive association between apical periodontitis and CVD.

In epidemiologic studies, the longitudinal cohort studies are considered superior to cross-sectional studies or case-controlled studies because the temporal association that implies causality would be suggested (7). In other words, the cross-sectional studies, case series, and case-controlled studies propose association and relationship. Randomized controlled trials and longitudinal cohort studies imply cause-effect relationship. There is a need for a systematic review of peer-reviewed literature focusing on the current evidence regarding LEO and systemic diseases. Therefore, the purpose of this systematic review was to evaluate the possible contribution of a LEO to the pathogenesis of systemic disease(s), focusing on longitudinal cohort studies.

Materials and Methods

The protocol for this systematic review was developed following established guidelines (8). The protocol was prepared and registered on PROSPERO (registration number: CRD42016034111). Also, a well-defined review question was developed by using the patient population, intervention, comparison, and outcome (PICO) framework.

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Assessing the Quality of the Evidence

The Cochrane Collaboration's tool for assessing risk of bias, the Oxford Systematic Review Appraisal Sheet, Critical Appraisal Skills Programme, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence were used to ensure the accuracy of these data analysis in this systematic review (8–11). Because judgement about evidence and recommendation are complex, the GRADE describes the process of rating the quality of the best available evidence and rates the certainty of evidence (11). GRADE enables the readers to know how much confidence they can place in evidence and recommendation (www.GradeWorkingGroup.org).

Formulating the Review Question

The following PICO framework was developed for a systematic review of the existing literature regarding a LEO and systemic disease:

Population: Patients receiving endodontic treatment
Intervention/exposure: Periapical lesion
Comparison: No periapical lesion
Outcome: Systemic disease.

Can a LEO, compared with absence of endodontic disease, impact the advent of systemic disease?

In this context, advent primarily refers to incident systemic disease, although it may also refer to course and duration of the systemic disease if the temporality of LEO precedes the systemic disease.

Inclusion and Exclusion Criteria

1. The following types of studies were considered: cohort studies published in English language peer-reviewed scientific journals from 1997 to 2018.
2. The study must have had a control group.
3. The study must have a documented follow-up time.
4. The effect of the LEO on the advent of systemic diseases was discussed, and specifically, the LEO must have been temporally present before the advent of the systemic disease(s) in question.
5. Studies in which the medical outcome was defined in terms of lab results and/or clinical diagnosis

Exclusion criteria included the type of study: case-series, case-control studies, cross-sectional studies, cell culture laboratory studies, or animal studies.

Search Methodology

The electronic MEDLINE, Embase, Cochrane, and PubMed databases were searched. In addition, the bibliography of all relevant articles and textbooks were manually searched. On the basis of inclusion and exclusion criteria, 2 reviewers (A.A., J.K.) independently selected the relevant articles (Appendix 1).

Using the PICO formatted question, methodologic MeSH (medical subject heading) terms were generated to make the search strategy more sensitive in identification of studies. These terms included the following: endodontics; systemic disease and apical periodontitis; diabetes; hypertension; cardiovascular disease; endodontic and medical condition; apical periodontitis; and endodontic outcome. Studies that met the above inclusion criteria underwent critical analyses.

Extracted data included the size of the population in the group(s); the number of dropouts or withdrawals, if reported; a description of the materials and methods with a detailed assessment of systemic diseases and periapical lesion; and the outcome variables used to measure the effect of a LEO on systemic diseases.

The qualities of the included studies were evaluated according to a proposed specific quality assessment scale.

Outcome Variables and Statistical Analysis

The forest plot and meta-analysis were conducted by using RevMan 5 Cochrane Community (http://community.cochrane.org/tools/review-production-tools/revman-5/revman-5-download).

Results

Figure 1 presents a flowchart of the systematic review process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8). Four articles met the inclusion criteria for this systematic review (12–15). The articles that did not meet the inclusion criteria (excluded articles) are presented in Appendix 2. The overall quality of the included articles was assessed to have high risk of bias (Table 1). Three articles (12–14) underwent meta-analysis for qualitative synthesis (Table 2). The risk ratio (RR) was 1.20, 95% confidence interval (CI), 0.79–1.82, and there was very low certainty that a LEO can influence the development of systemic disease (forest plot, Figure 2). The reasons to downgrade the quality of evidence are detailed as follows:

1. high risk of bias among the articles (Table 1); and
2. inconsistency (Figure 2, top picture) (11).

Thus, subgroup analysis was warranted to address this inconsistency/heterogeneity among the articles, Figure 2, top picture (I^2 = 66% and *P* value is less than .05, suggesting the studies are heterogeneous and subgroup analysis is warranted). The article by Inchingolo et al (12) was reported to be the article contributing to the inconsistency because of the following reasons:

1. follow-up time was only 3 months, whereas the other studies had longer than 1 year of recall;
2. oxidative stress was stressed with no actual adverse effect; and

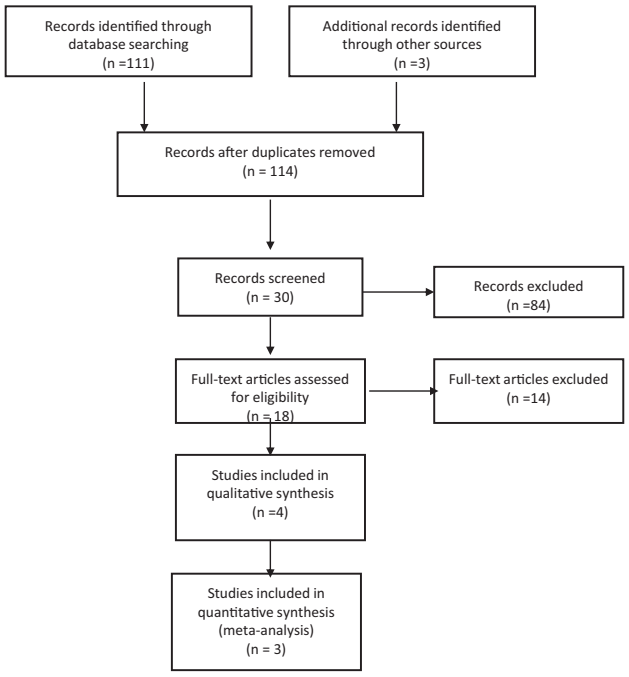

Figure 1. Prisma 2009 flow diagram.