Review Article

Association between Systemic Diseases and Apical Periodontitis

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Abstract

Introduction: To date, the relationships between systemic diseases and periapical microbial infection remain unknown. Thus the purpose of this systematic review was to evaluate the relationship between host modifying factors and their association with endodontic pathosis. **Methods:** Two reviewers independently conducted a comprehensive literature search. The MEDLINE, Embase, Cochrane, and PubMed databases were searched. In addition, the bibliographies of all relevant articles and textbooks were manually searched. There was no disagreement between the 2 reviewers. **Results:** Sixteen articles were identified and included. The overall quality of the studies and the risk of bias were rated to be moderate. Only 3 studies demonstrated a low level of bias. **Conclusions:** The results of this review suggest that there may be a moderate risk and correlation between some systemic diseases and endodontic pathosis. More prospective and longitudinal research in this area is warranted to determine greater specificity in these possible interactions to potentially decrease or minimize the effects of systemic disease on the formation of apical periodontitis. *(J Endod 2016;■:1–8)*

Key Words

Correlation, endodontic pathosis, pathogenesis, systematic review, systemic diseases

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Significance

One of the current clinical healthcare challenges is to lower costs by controlling factors that may lead to systemic disease. If a definite cause-effect relation is confirmed between endodontic pathosis and systemic diseases, oral healthcare providers might be able to help lower the cost of treating such disease by prevention of chronic oral infections. The current systematic review reported that there may be moderate risk and correlation between systemic diseases and endodontics.

Many associated risk factors are shared by systemic diseases and oral infections that could confound a relationship between them (1–3). As these studies have noted, periodontal disease has received considerable interest when these relationships were studied. Endodontic infections have received much less attention, despite the fact that many of microbial pathogens are common in those 2 diseases.

Khader (4) conducted a study to investigate factors that were associated with periodontal patients. The author reported that increased age, low level of education, increased plaque index score, not routinely brushing their teeth, smoking more than 15 pack-years, and having diabetes were significantly associated with increased severity of periodontal disease. These are all clearly risk factors for cardiovascular disease as well, and the degree to which they have been controlled for in the aforementioned studies has been mixed.

Several systemic diseases were found to affect the outcome of endodontic treatment. Diabetes mellitus was found to be associated with significantly reduced endodontic treatment outcome of teeth with preoperative infections, suggesting that diabetes may serve as a disease modifier (5, 6). Also, both diabetes and hypertension were found to be associated with reduced survival of endodontically treated teeth (7). Therefore, at this time, systemic conditions and disorders can be considered modulating factors affecting oral infection progression rather than acting as the causative etiologic factor (1, 8, 9).

A number of observational studies (8, 10–12) and a longitudinal cohort study (13) have described, at least in part, a possible association between systemic involvement and endodontic periapical infection. However, one case-control study did not identify a correlation between periapical infection and atherosclerotic disease. Those authors also reported that calcified carotid artery atheromas observed in radiographs had a greater burden of chronic dental infection specifically with advanced mesial and distal periodontal bony defects $\geq$4 mm (14).

To date, the role of systemic medical conditions as a modulating factor in the development of endodontic periapical infection has been a subject of controversy with authors who found a strong association (15–17) and those who found weak to no association (8, 14, 18). A recent systematic review reported that although the evidence is limited, endodontic periapical infection and certain molecular markers of systemic inflammation could be closely related (19). Another systematic review examining the relationship between polymorphism and apical pathosis also suggested a plausible relationship between genetic polymorphism and apical pathosis (20).

Therefore, the purpose of this systematic review was to evaluate the pathogenesis and scientific evidence reporting any relationships between lesion of endodontic origin and risk of systemic diseases.

Materials and Methods

The protocol for this systematic review was developed following established guidelines (21). The protocol was prepared and registered on PROSPERO (registration no. CRD42016034111). Also, a well-defined review question was developed by using the patient population, intervention, comparison, and outcome (PICO) framework.

The AMSTAR checklist, the Oxford Systematic Review Appraisal Sheet, Critical Appraisal Skills Programme, and the Grading of Recommendations Assessment, Development and Evaluation system for grading evidence were used to ensure the accuracy of this data analysis in this systematic review (21–24).

Formulating the Review Question

The following PICO framework was developed for a systematic review of the existing literature regarding apical pathosis and systemic diseases. When compared with medically healthy individuals, can systemic diseases modify and/or influence apical pathosis?

Inclusion and Exclusion Criteria

The following types of studies were considered: clinical trials, case-control studies, cross-sectional studies, or cohort studies published in English language peer-reviewed scientific journals from 1997 to April 2016. The study had to have a control group. Studies assessed symptomatic or asymptomatic apical pathosis during nonsurgical endodontic treatment. Studies were included in which the periapical condition was established and/or quantified.

Exclusion criteria included the following: type of study: case series, cell culture laboratory studies, or animal studies.

Search Methodology

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

To answer the clinically relevant question, a 4-step method of evidence-based analysis was applied. Step 1 was a search for the clinical evidence regarding the systemic diseases and biological markers in electronic databases, and bibliographies of all relevant articles and review articles were both electronically and hand searched. Step 2 consisted of appraisal and selection of articles according to study validity and clinical importance. Step 3 consisted of collection and analysis of the published evidence. Step 4 determined the clinical applicability of the results.

By using the PICO formatted question, methodological MeSH (medical subject heading) terms were generated to make the search strategy more sensitive in identification of studies. These terms included endodontics, systemic disease and apical periodontitis, biological markers, and apical periodontitis. Studies that met the above inclusion criteria underwent critical analysis.

Extracted data included the size of the population in the group; the number of dropouts or withdrawals, if reported; a description of the materials and methods with a detailed assessment of systemic diseases; and the outcome variables used to measure the effect of biological markers on apical periodontitis.

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

Outcome Variables and Statistical Analysis

Because of the heterogeneity among the different studies and data from different inflammatory markers, it was not possible to perform meta-analysis.

Results

Because of the heterogeneity among the different studies, it was not possible to perform meta-analysis. Figure 1 presents a flowchart of the systematic review process according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Sixteen articles met the inclusion criteria.

In the present review, 8 of the included studies assessed the association between endodontic pathosis and cardiovascular disease (CVD), 5 studies focused on the association between endodontic pathosis and diabetes mellitus (DM), 1 study assessed the association with liver disease, 1 study assessed the association of blood disorder and endodontic pathosis, and 1 study evaluated any relationship between bone mineral density and endodontic pathosis.

The risk of bias assessment of the included studies is presented in Tables 1–3. Overall, the included studies showed a moderate risk of bias. Of all included studies there were 3 studies with low level of bias (11, 25, 27).

Discussion

Our review focused on any associations between endodontic pathosis and 5 primary systemic diseases: CVD, DM, liver, hematology disorder(s), and bone mineral density.

CVD

In the present systematic review, 8 articles regarding CVD were included. Seven of the included studies confirmed an association between endodontic pathosis and CVD. There was only 1 study (29) that rejected any association, which incidentally was the only article in this section with a high level of bias. In this study, hypertension was the systemic disease of interest. There are wide ranges of hypertensive states among patients and a multitude of treatment modalities for them, which may necessitate a larger sample size for examining this condition. Moreover, it should be mentioned that 2 groups were not matched regarding their smoking and DM statuses, which could have potentially affected the results of the study. Also investigators were not blinded regarding the status of CVD (Table 1). As a result, the study demonstrated a high risk of bias. In a recent pair-matched, cross-sectional study An et al (25) reported a significant association between apical periodontitis and CVD (odds ratio [OR], 5.3). The study demonstrated a low level of bias.

Gomes et al (13) explored the association between CVD and endodontic pathosis in a retrospective cohort study and reported that endodontic pathosis can act as an independent predictor of an incident of CVD (OR, 1.77). In a case-control study, Costa et al (26) explored the prevalence of endodontic pathosis in patients who were diagnosed with CVD. They reported that the prevalence of endodontic pathosis in a group of patients with CVD is twice that observed in the group without CVD (OR, 2.79). In a low-biased study by Caplan et al (11), they reported that there is an association between endodontic pathosis and CVD among those $\leq$40 years old (OR, 1.4). Also Pasqualini et al (27) reported that endodontic pathosis may be a risk factor for CVD (OR, 4.37).

On the basis of the current best available evidence, it can be postulated that there might be an association between endodontic pathosis and CVD. However, the results of the included studies