Association between Systemic Diseases and Endodontic Outcome: A Systematic Review

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Abstract

Introduction: To date, the relationships between systemic diseases and endodontic treatment outcomes remain poorly studied. Thus, the purpose of this systematic review was to evaluate the relationship between host-modifying factors and their association with endodontic outcomes. **Methods:** Two reviewers independently conducted a comprehensive literature search. The MEDLINE, Embase, Cochrane, and PubMed databases were searched. In addition, the bibliographies and gray literature of all relevant articles and textbooks were manually searched. There was no disagreement between the 2 reviewers. **Results:** Sixteen articles met the inclusion criteria with moderate to high risk of bias. There was no article with low risk of bias. Available scientific evidence remains inconclusive as to whether diabetes and/or cardiovascular disease(s) may be associated with endodontic outcomes. Human immunodeficiency virus and oral bisphosphonate did not appear to be associated with endodontic outcomes. **Conclusions:** Although additional well-designed longitudinal clinical studies are needed, the results of this systematic review suggest that some systemic diseases may be correlated with endodontic outcomes. *(J Endod 2017;43:514–519)*

Key Words

Cardiovascular disease, diabetes, endodontic outcome, human immunodeficiency virus, hypertension, medical conditions, systemic disease

Significance

Although additional well-designed clinical studies are needed, the results of this systematic review suggest that some systemic diseases may influence endodontic healing outcomes.

Systemic diseases and oral infections are closely related because they both share many associated risk factors (1–3). In a previous systematic review, our group reported that there may be a correlation between some systemic diseases and the pathogenesis of endodontic diseases (4). However, there is also a need to address the relationship of systemic diseases and endodontic treatment outcomes because this provides valuable information on the prognosis of endodontic treatment.

Several systemic diseases were found to be correlated with the outcome of endodontic treatment. Diabetes mellitus was reported to be significantly associated with reduced endodontic healing treatment outcomes 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 significantly associated with reduced survival of endodontically treated teeth (7). Therefore, systemic conditions and disorders may have an influence in the healing outcome of endodontically treated teeth rather than just acting as a causative etiologic factor in endodontic infections (1, 8, 9).

To date, the relationship of systemic medical conditions and outcomes of endodontic treatment remains poorly studied. Therefore, the purpose of this systematic review was to evaluate the relationship between systemic diseases and outcomes in endodontic treatment.

Materials and Methods

The protocol for this systematic review was developed following established guidelines (10). The protocol was prepared and registered on PROSPERO (registration number: CRD42016042711). Also, a well-defined review question was developed by using the patient population, intervention, comparison, and outcome (PICO) framework.

The Cochrane Collaboration's tool for assessing risk of bias, the Oxford Systematic Review Appraisal Sheet, and Critical Appraisal Skills Programme were used to ensure the accuracy of this data analysis in this systematic review (10–12).

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 influence endodontic clinical and radiographic healing outcomes?

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Inclusion and Exclusion Criteria

Inclusion criteria included the following:

1. 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 2016
2. The study must have had a control group
3. The effect of systemic diseases on healing outcomes was measured
4. Studies in which the healing outcome was defined in terms of clinical/radiographic healing and/or survival of the tooth

Exclusion criteria included the following types of studies:

1. Case series
2. Cell culture laboratory studies
3. 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 (A.A., J.K.) independently selected the relevant articles.

To answer the clinically relevant question, a 4-step method of evidence-based analysis was applied: step 1, 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, appraisal and selection of articles according to study validity and clinical importance; step 3, collection and analysis of the published evidence; and step 4, determining 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, diabetes, hypertension, cardiovascular disease, endodontic and medical condition, apical periodontitis, and endodontic outcome. Studies that met the above inclusion criteria underwent critical analysis.

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 the outcome variables used to measure the effect of biologic 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 study designs and data from different systemic conditions, it was not possible to perform a meta-analysis.

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 (10). Sixteen articles met the inclusion criteria for this systematic review. The overall quality of the included articles was moderate to high risk of bias. Three articles were identified to report on cardiovascular disease (CVD) (7, 13, 14). Eleven articles reported on diabetes mellitus (DM) (6, 7, 13–21). Three articles reported on human immunodeficiency virus (HIV) (22–24). One article reported on oral bisphosphonate and osteonecrosis of the jaw (25).

Discussion

This systematic review focused on any associations between endodontic outcome and 4 systemic diseases (CVD, DM, HIV, and oral bisphosphonate). The overall quality of the articles was determined to have moderate to high risk of bias, which indicates the true effect is likely to be close or substantially different from the estimate of the effect (26).

CVD

Both CVD and endodontic infections share similar inflammatory mediators in the initiation and progression of the disease process (27–29). Three articles were identified to address a relationship between CVD and endodontic outcomes (7, 13, 14). Two had moderate risk of bias (13, 14), and one had high risk of bias (7). Two of these articles reported that there was a relationship, whereas Ng et al (13) reported that there was no relationship between CVD and outcomes of endodontic treatment.

DM

After an inflammatory reaction, elevated levels of circulating interleukin 6 and tumor necrosis factor-α may impair glycemic control (30). Six articles with moderate to high risk of bias reported that there was an association between DM and endodontic outcomes (7, 9, 13–15, 18). Most of these articles had high risk of bias except two (13, 18), which had moderate risk of bias.

Five articles with moderate to high risk of bias reported that there is no association between DM and endodontic outcome (16, 17, 19–21). All 5 articles demonstrated a high risk of bias except 1 article, which had a moderate risk of bias (21).

Oral Bisphosphonates

Bisphosphonates inhibit osteoclast formation and activity and shorten the life span of osteoclasts (31). However, current evidence suggests that the possibility of developing osteonecrosis of the jaw after oral bisphosphonate treatment is 1 in 23 patients or approximately 4% of the population (32). Bone remodeling is an integral part of the healing process. Only 1 article with 7-month follow-up was identified to address the effect of oral bisphosphonates and healing of nonsurgical root canal therapy with periapical lesions (25). The article suggested no association between oral bisphosphonate and endodontic outcomes. The quality of the evidence was determined to be moderate. Thus, more research is indicated in this area to clarify any current association.

HIV

Three parameters define the clinical staging for HIV: opportunistic infections, CD4+ count, and viral load (33). T cells play an important role in the development, progression, and resolution of endodontic infections (34). The results of the current investigation identified 3 articles. Two articles had high risk of bias (22, 23) and one with moderate risk of bias (24). All 3 articles suggested that there is no correlation between HIV and outcomes of endodontic healing.

The results of the current systematic review also agree with other studies, although they exhibit lower level evidence (33, 35, 36). Most of the available studies that explored the relationship between endodontic outcomes and systemic disease did not differentiate between cases with preoperative infections and those with vital pulp. Clearly, when it comes to endodontic prognosis, the single most important factor is the presence of a preoperative lesion, a finding that was also true in the studies reviewed here, which took this into consideration (6, 13). In cases with vital pulp, the prognosis of endodontic treatment is very good; therefore, the potential role of systemic disease may be

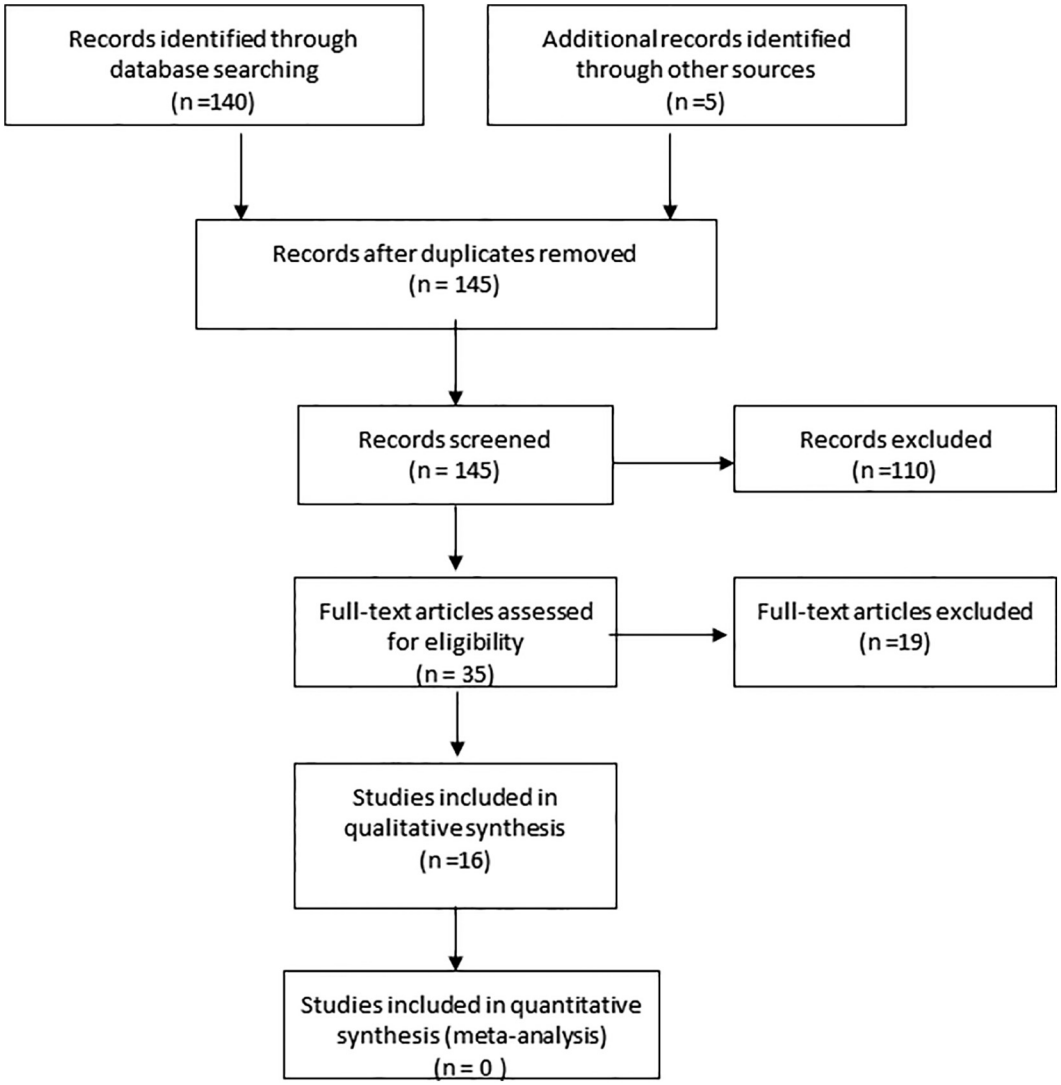

Figure 1. Prisma 2009 flow diagram.

marginal and one that requires adequate controls to assess accurately. However, cases with preoperative lesions have a significantly lower prognosis, and the role of the systemic disease may be more substantial. In this regard the study by Fouad and Burleson (6) found no effect for DM on the entire population of treated patients during their 6-year evaluation period. However, when only the cases with preoperative lesions were considered, a significant association was detected, which became even more significant after a number of confounding variables were controlled through a multivariate analysis. Future studies should explore the difference in the prognosis of vital cases and cases with infections separately, because infections remain the major clinical problem in endodontic treatment.

Controlling for confounding variables is another important requirement in studies evaluating oral and systemic diseases. Furthermore, because there is already a large body of evidence present on the relationship of periodontal disease and systemic disease and on the relationship of endodontic and periodontal prognosis, periodontal disease should be added to the list of variables to be controlled. Many of the reviewed studies controlled for these confounding variables (Table 1). This level of evidence allows the determination of whether the systemic disease exerts an independent effect on endodontic treatment outcomes.

A recent publication (37) reported that patients with medical conditions (clustering all medically compromised patients in one group) were not associated with poorer healing outcome after nonsurgical root canal therapy. It should be noted that all medical conditions are not the same. Also, in that study the severity of these medical conditions was not discussed. Last, the information regarding the glycemic control, complete blood count with differentials was not available to compare (between the patients or even within the same patient) and then to discern whether such association existed.

Thus, from this systematic review it remains inconclusive whether there is or is not a relationship between CVD, DM, and endodontic outcomes. Longitudinal investigations with well-designed research methodologies are needed to address this question.

Although additional well-designed clinical studies are needed, the results of this systematic review suggest that some systemic diseases may influence endodontic healing outcomes.

TABLE 1. Characteristics of Studies Assessing the Relationship between Systemic Diseases and Endodontic Outcome

Study	Type of disease	Study design	Endodontic outcome	Sample size	Matching	Main result	Selection bias	Detection bias	Reporting bias	Bias risk
Mindiola et al, 2006 (7)	Diabetes, hypertension, CVD	Observational cohort	Survival	5460 cases	No	DM, hypertension, and CVD were significant risk for tooth extraction	High	High (unclear if teeth were fractured, or how instrumented and/or other reasons that could contribute to treatment failure)	High (multivariate analysis was not performed to adjust for age, tooth type, final restoration for final analysis because they were both reported to be risk factors)	High
Wang et al, 2011 (14)	DM, CVD	Cross-sectional	Survival	49,334 patients, 1592 teeth extracted during 2 y	No	Increased risk of tooth extraction for NSRCT with DM, hypertension, CVD	Low (random)	Low (all extracted teeth were retrieved by databank for specific treatment codes and analyzed; technical failures were excluded)	Low (multivariate analysis adjusted for age, tooth type for final analysis because they were both reported to be risk factors)	Moderate
Britto et al, 2003 (15)	DM	Cross-sectional	Radiographic	30 DM/23 control	Yes	Men with type 2 diabetes who had NSRCT were more likely to have residual lesion	High	High (cross-sectional and radiographic evaluation only)	High (radiographic only)	High
Fouad and Burleson, 2003 (6)	DM	Retrospective cohort 2 y and longer	Radiographic	72 DM/459 control	No	Patients with DM have reduced likelihood of endodontic success in cases with preoperative lesions	High (information on patients' degree of glycemic control not available)	Low (radiographic and clinical exam)	High (multivariate analysis was not performed). Pulpal diagnosis, severity of DM not discussed	High
Segura-Egea et al, 2005 (17)	DM	Cross-sectional	Radiographic	32 DM/38 control	No	DM and endodontically treated teeth were not associated ($P = .17$)	Low	High (radiographic only)	High (radiographic only and cross-sectional study)	High
Doyle et al, 2007 (16)	DM and smokers	Retrospective observational cohort	Radiographic and clinical data	196 implant/ 196 NSRCT	Yes	DM and NSRCT were not associated. Smoking was associated with poorer outcome for both implants and NSRCT	High (information on patients' degree of glycemic control or what is defined by smoking not available)	Low	High (multivariate analysis was not performed). Pulpal diagnosis, severity of DM not discussed	High
Lopez-Lopez et al, 2011 (18)	DM	Cross-sectional case-controlled	Radiographic using periapical index score	50 DM/50 control	Yes	Periapical status and number of NSRCT were significantly associated with diabetic status	Low (patients were randomly selected; DM classification was defined)	High (radiographic only and cross-sectional)	Low (multivariate analysis adjusted for confounding variables)	Moderate
Ng et al, 2011 (13)	DM and steroids and CVD	Prospective longitudinal study (4 y)	Survival	572 patients (22 teeth DM/737 normal teeth; 11 teeth steroids/ 748 teeth normal; 58 teeth CVD; 701 normal teeth)	No	DM and steroids significantly influenced tooth survival for primary and secondary NSRCT. CVD was not found to influence NSRCT outcome	Low	Low	High (multivariate analysis adjusted for confounding variables), but had low sample size and evaluated teeth not patients; multiple teeth were used from the same patient(s), which in this sample size would affect the outcome	Moderate

(*continued*)

TABLE 1. (*continued*)

Study	Type of disease	Study design	Endodontic outcome	Sample size	Matching	Main result	Selection bias	Detection bias	Reporting bias	Bias risk
Marotta et al, 2012 (19)	DM	Cross-sectional case-controlled	Radiographic using full-mouth periapical and panoramic radiographs	30 DM/60 control	Yes	No statistically significant difference between NSRCT of control and DM	High (non-random, DM not described)	High (radiographic only and cross-sectional)	High (did not adjust for confounding variables)	High
Marques-Ferreira et al, 2014 (20)	DM	Case-controlled	Periapical and panoramic r adiographs	23 DM/23 control	No	No statistically significant difference ($P = .06$) between NSRCT of control and DM	High (non-random, DM not described)	High (radiographic only and cross-sectional)	High (did not adjust for confounding variables)	High
Sanchez-Dominguez et al, 2015 (21)	DM	Cross-sectional case-controlled	Radiographic	59 DM > 6.5 hemoglobin A1c/24 DM < 6.5 hemoglobin A1c	Yes	No statistically significant difference and glycemic control, CVD, smoking, number of teeth, and outcome of root-filled teeth	Low	High (radiographic only and cross-sectional)	Low (multivariate analysis adjusted for confounding variables)	Moderate
Quesnell et al, 2005 (22)	HIV	Cohort (1 y)	Radiographic using periapical index	33 HIV/33 healthy	No	There were no statistically significant differences between the 2 with respect to degree of periradicular healing.	High (patients were not matched for tooth type, preoperative diagnosis, age, gender, steroids, antibiotics, smoking, CVD, etc)	High (radiographic evaluation only)	High (did not adjust for confounding variables)	High
Alley et al, 2008 (23)	HIV	Cohort study (3 y)	Radiographic chart review	31 patients (50 teeth) HIV/ 46 patients (50 teeth) control	Yes	No statistically significant difference between groups.	High (non-random)	High (radiographic evaluation only and evaluators were not blinded)	Low	High
Tootla and Owen, 2012 (24)	HIV	Cohort study (6, 12, 18, 24 mo)	Radiographic and clinical	46 HIV/59 control	Yes	No statistically significant difference between groups.	High (non-random)	Low	Low	Moderate
Hsiao et al, 2009 (25)	Bisphosphonate	Retrospective cohort (7-mo follow-up)	Radiographic and clinical	34 oral bisphosphonate/ 38 control	Yes	No statistically significant difference between groups.	Low	Low	High (short follow-up)	Moderate

NSRCT, nonsurgical root canal treatment; PAI, periapical index score.

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