Association between diabetes and the outcome of root canal treatment in adults: An umbrella review

V Nagendrababu[1], JJ Segura-Egea[2,] AF Fouad[3], SJ Pulikkotil[1], PMH Dummer[5]

[1] Division of Clinical Dentistry, School of Dentistry, International Medical University, Kuala Lumpur, Malaysia; [2]Department of Endodontics, School of Dentistry, University of Sevilla, Sevilla, Spain, [3]Division of Comprehensive Oral Health, Adams School of Dentistry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA and [4]School of Dentistry, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK.

Corresponding author

V Nagendrababu BDS, MFDS RCPS (Glasg), MDS, PhD.

Division of Clinical Dentistry,

School of Dentistry, International Medical University

Bukit Jalil – 57000, Kuala Lumpur, Malaysia.

E mail: venkateshbabu@imu.edu.my

Keywords: Diabetes, outcomes, meta-analysis, Persistent apical periodontitis, umbrella review, systematic review

Running title: diabetes and the outcome of root canal treatment

The authors deny any conflicts of interest related to this study.

Association between diabetes and the outcome of root canal treatment in adults: An umbrella review

Abstract

Background: Diabetes mellitus is the most common metabolic disorder among dental patients. The association between diabetes and the outcome of root canal treatment is unclear.

Aim: To conduct an umbrella review to determine whether there is an association between diabetes and the outcome of root canal treatment.

Data source: The protocol of the review was developed and registered in the PROSPERO database (ID number: 141684). Four electronic databases (PubMed, EBSCHOhost, Cochrane and Scopus databases) were used to perform a literature search until July 2019.

Study eligibility criteria, participants, and interventions: Systematic reviews with or without meta-analyses published in English assessing any outcomes of root canal treatment comparing diabetic and nondiabetic patients were included. Two reviewers were involved independently in study selection, data extraction and appraising the reviews that were included. Disagreements were resolved with the help of a third reviewer.

Study appraisal and synthesis methods: The quality of the reviews was assessed using the AMSTAR tool (A measurement tool to assess systematic reviews), with 11 items. Each AMSTAR item was given a score of 1 if the criterion was met, or 0 if the criterion was not met or the information was unclear.

Results: Four systematic reviews were included. The AMSTAR score for the reviews ranged from 5-7, out of a maximum score of 11 and all the systematic reviews were classified as "medium" quality.

Limitations: Only two systematic reviews included a meta-analysis. Only systematic reviews published in English were included.

Conclusions and implications of key findings: Diabetes mellitus is associated with the outcome of root canal treatment and can be considered as a preoperative prognostic factor.

Declaration of interest: No funding was received to support this umbrella review. The authors declare no conflict of interest.

Keywords: Diabetes, outcomes, meta-analysis, persistent apical periodontitis, umbrella review, systematic review

Introduction

Diabetes mellitus is the most common chronic metabolic disorder worldwide (Guariguata *et al*. 2014). In 2017, it was estimated that 451 million individuals suffered from diabetes and this was predicted to increase to 693 million by 2045 (Cho *et al*. 2018). The prevalence of diabetes, the medical care provided and deaths attributable to the condition have substantial social, financial and health system implications. For example, the total global expenditure on diabetes was estimated to be approx. $US 850 billion in 2017 (Cho *et al*. 2018).

The common feature of diabetes mellitus is hyperglycaemia. Dysfunction of the beta cells in the pancreas results in insulin deficiency with or without insulin resistance (non-responsiveness) of peripheral tissues (Mealey & Oates 2006). There are several types of diabetes, including types 1 and 2, gestational and diabetes insipidus (Kharroubi & Darwish 2015, Robertson 2016). The data available in the endodontic literature is restricted to types 1 and 2. Given the changes in classification during the period of the available studies and the paucity of data, discussion of the relationship of both types of diabetes and endodontic disease is appropriate.

In diabetes, chronic inflammation and reduced tissue repair may occur due to impaired leucocyte function, increased proinflammatory cytokines and reduced macrophage growth factors (Iacopino 2001). Elevation of the levels of advanced glycation end-products (AGEs) upregulates oxidative stress and inflammatory responses. This is more pronounced in poorly controlled diabetes where the immune response is diminished with delayed wound healing (Salvi *et al*. 2008, Cabanillas-Balsera *et al*. 2019).

The outcome of root canal treatment is assessed using clinical signs and symptoms, radiographic/CBCT imaging and histopathological evaluation (Lazarski *et al*. 2001, Ng *et al.* 2011, Al-Nuaimi *et al.* 2018). Many preoperative, intra-operative and post-operative factors impact on the outcome of root canal treatment (Cabanillas-Balsera *et al*. 2019) with diabetes mellitus being a systemic condition that has been implicated in a greater incidence of post-treatment endodontic disease, delayed healing and an increased prevalence of tooth extractions (Segura-Egea *et al*. 2016). Clearly, clinicians and patients should be aware of the

potential relationship between diabetes and the outcome of root canal treatment and the impact that may have on the prognosis of root filled teeth.

Several systematic reviews and meta-analyses have attempted to determine whether there is an association between diabetes and the outcome of root canal treatment. These reviews have analysed epidemiological studies comparing the prevalence of periapical lesions in root filled teeth and the retention of root filled teeth in diabetic and non-diabetic subjects (Segura-Egea *et al*. 2019). Aminoshariae *et al*. (2017) reported there was no overall effect of diabetes on outcomes, but there was evidence for the association of diabetes with worse longitudinal outcomes in cases with pre-operative lesions. Tiburcio-Machado *et al.* (2017) concluded that the published clinical studies suggested a positive association between diabetes and a larger number of periapical lesions; however, due to the small number of studies they included, the authors concluded the association was not proven. Segura-Egea *et al*. (2016) reported that diabetic patients had a higher prevalence of periapical radiolucencies associated with root filled teeth, whilst Cabanillas-Balsera *et al*. (2019) concluded that diabetics had a significantly higher prevalence of extracted root filled teeth compared with healthy subjects. Many other risk parameters are unclear. For example, it is well-known that diabetic patients have a higher incidence of periodontal disease and tooth loss due to periodontal disease (Preshaw *et al.* 2012). Therefore, it is not clear from the available evidence if the risk of tooth loss related to endodontic disease is independent of periodontal disease risk. As a consequence of the inconsistencies within the existing systematic reviews in respect of the association between diabetes and endodontic outcomes there was a need to synthesize the evidence from the individual reviews by undertaking an umbrella review.

When a large number of systematic reviews and meta-analyses are published on one topic, they can reveal certain trends and help clinicians in their treatment planning and discussions with patients. However, when the systematic reviews have ambiguous conclusions it creates uncertainty and confusion (Aromataris *et al*. 2017). To overcome this situation, “Umbrella Reviews” have been introduced within the biomedical field (Fusar-Poli & Radua 2018). Umbrella reviews synthesise the results of systematic reviews on a specific topic and are the highest level in the hierarchy of evidence (Fusar-Poli & Radua 2018). Such

reviews can critically analyse each individual systematic review, collate evidence from them, identify consistent and/or contradictory findings and attempt to determine the truth (Botero *et al.* 2016).

The influence of diabetes on the outcome of root canal treatment remains unclear because the results obtained from systematic reviews to date are inconsistent or inconclusive. This umbrella review aims to analyse all systematic reviews on the association between diabetes and the outcome of root canal treatment in adults to determine whether there is an association.

Methods

The protocol of this umbrella review was developed and registered in the PROSPERO database (ID number: 141684). The umbrella review was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.* 2019).

Review questions

Is diabetes mellitus associated with the outcome of root canal treatment in adults?

Inclusion and exclusion criteria

Systematic reviews with or without meta-analysis published in English evaluating any root canal treatment outcomes comparing diabetic and nondiabetic patients were included. Case reports, clinical studies, laboratory studies, animal studies and narrative reviews were excluded.

Literature search

The literature search was carried out in three electronic databases (PubMed, EBSCOhost, Cochrane and Scopus electronic databases) from inception to July 2019. The following search strategy: (((((diabetes) OR diabetic) OR hyperglycaemia)) AND (((((((root canal) OR endod*) OR periapical periodontitis) OR periapical diseases) OR periapical lesion) OR periradicular lesion) OR apical periodontitis)) AND ((systematic review) OR meta-analysis) were used to identify the relevant systematic reviews. Additional searches were performed

in reference lists of the included reviews. Two independent reviewers (VN, SP) were involved in the first stage (screening the titles and abstracts) and second stage (reading full text) to identify the relevant reviews. Disagreement and doubts regarding inclusion of the reviews was resolved by discussing with third reviewer (PD). The authors of the included reviews were contacted to provide missing data and/or clarify information that was unclear.

Data extraction

Data extraction sheets were developed and included: name and country of the first author, year published, name of the journal, number of databases used to search, search period, type of study design included, quality assessment tool used, outcomes assessed, number of studies included, number of subjects included, meta-analysis model, specific relative risk estimates with confidence interval, I2 statistic (to assess heterogeneity) and publication bias.

Primary outcome

Prevalence of persistent apical periodontitis associated with root filled teeth.

Secondary outcomes

1. Extraction of root filled teeth following root canal treatment;
2. Rate of healing following root canal treatment as assessed radiographically;
3. Post-treatment clinical signs and symptoms following root canal treatment;
4. Survival of root filled teeth;
5. Persistence of apical periodontitis associated with root filled teeth independent of marginal periodontitis;
6. Relationship between persistent apical periodontitis associated with root filled teeth and the level of glycaemia of the patient.

Methodological quality assessment using AMSTAR tool

The methodological quality of included systematic reviews was appraised using the AMSTAR tool (a measurement tool to assess systematic reviews), which consists of 11 items. (Shea *et al.* 2007). Two reviewers (VN, SP), assessed the quality of included reviews independently and in case of disagreement, it was resolved by the third reviewer (PD). The items within

each included systematic review that satisfied the specific criterion was given a score of "1". If the items were not clear or no information was provided in the systematic review, a score of "0" was given. Authors were contacted to obtain missing information. After scoring, each review was classified into high, medium and low quality if it obtained a score between 8 to 11, 4 to 7 and 0 to 3, respectively (Rangel-Rincón *et al*. 2018). The agreement between the two reviewers (VN and SP) and intra-examiner agreement in appraising the quality of included reviews was calculated by Cohen's kappa analysis.

Results

Search results

The literature search process used to identify the systematic reviews is shown in Figure 1. The total number of articles identified from the four electronic bases were 2975 and studies identified for the initial phase (title/abstract screening) were 2747. After excluding studies during the initial phase 11 reviews were included for full text assessment. A further seven reviews were excluded during the second phase (full text reading) because they were narrative reviews, not systematic (Fouad 2003, Segura-Egea *et al*. 2012, 2015, 2019, Lima *et al*. 2013, Sasaki *et al*. 2016, Holland *et al.* 2017). Finally, four systematic reviews were included (Segura-Egea *et al*. 2016, Aminoshariae *et al*. 2017, Tiburcio-Machado *et al.* 2017, Cabanillas-Balsera *et al*. 2019).

Characteristics of included reviews

The characteristics of the included systematic reviews were showed in Table 1. The systematics reviews were published in the years between 2016 to 2019 and published in *Clinical Oral Investigations* (n=1), *Journal of Endodontics* (n=2), *International Endodontic Journal* (n=1). The systematic reviews used the following electronic database MEDLINE/PubMed, Embase, Cochrane, Wiley Online, Web of Science, Scopus, LILACS and Scientific Electronic Library Online, to identify relevant studies in their review. The search period within the reviews ranged between 1980 to 2018. The number of studies included in each systematic review ranged from 3 to 11. Among the four reviews, only two conducted a meta-analysis (Segura-Egea *et al.* 2016, Cabanillas-Balsera *et al.* 2019). Two reviews (Segura-Egea *et al*. 2016, Cabanillas-Balsera *et al*. 2019) used the Centre for Evidence-Based

Medicine guidelines to assess the quality of included studies, whereas one review (Aminoshariae *et al.* 2017) used a specific quality assessment scale, based on three domains (selection bias, detection bias and reporting bias). The systematic review by Tiburcio-Machado *et al.* (2017) used the STROBE statement for observational studies and basic principles of research for clinical studies.

Summary of meta-analysis

The summary of the meta-analysis included in this umbrella review were showed in Table 2. One review (Cabanillas-Balsera *et al.* 2019) reported heterogeneity to be high (70.8 %) among the outcome measures of the included studies (Higgins & Green 2011), whereas in the review by Segura-Egea *et al.* (2016) the heterogeneity was reported to be 0%. Both these reviews used the Breslow-Day test and I2 test to assess heterogeneity. To find the relationship between diabetes and nonretention of root filled teeth, one review used the DerSimonian–Laird method with random effects (Cabanillas-Balsera *et al.* 2019). To determine the relationship between diabetes and the presence of radiolucent periapical lesions (RPLs) in root filled teeth, one review used the Mantel-Haenszel with fixed effects model (Segura-Egea *et al.* 2016).

Methodological quality

The scores for the methodological quality of the systematic reviews included in this umbrella review are given in Supplementary Table 1. The AMSTAR score for the reviews ranged from 5 to 7 out of maximum score (11) and were therefore categorized as "medium". All the reviews scored 0 for two items ("scientific quality of the included studies used appropriately in formulating conclusions" and "status of publication used as an inclusion criterion"). A meta-analysis was not performed in two reviews (Aminoshariae *et al*. 2017, Tiburcio-Machado *et al*. 2017), therefore two items in the AMSTAR checklist ("Methods used to combine findings of studies appropriate" and Publication bias) were not applicable and were scored "0". The intra and inter-examiner reliability scores (VK and SP) for scoring the AMSTAR items of the included studies was 1 and 0.95 ($p<0.05$) respectively and equates to "almost perfect" agreement.

Discussion

Need for Umbrella Reviews

Endodontic medicine, which deals with the relationship between systemic disease and the prevalence and outcome of root canal treatment (Segura-Egea *et al*. 2019) has gained in importance in recent years. The focus on endodontic medicine has come about because it has been reported that various systemic diseases influence the outcome of root canal treatment (Segura-Egea *et al*. 2015). Among systemic diseases, diabetes mellitus is the most common metabolic disorder in dental patients, in which hyperglycaemia and delayed wound healing are the main clinical features (Segura-Egea *et al*. 2016). The association between diabetes, endodontic disease and the outcomes of root canal treatment is inconclusive and so the current umbrella review was undertaken to combine data from the highest level of evidence, systematic reviews and meta-analyses, in an attempt to define categorically whether there is an association between diabetes and outcome of root canal treatment. Additionally, the review identified methodological limitations in previous systematic reviews.

Outcomes assessed

A total of four systematic reviews were included that addressed the following outcomes:

- association between diabetes and endodontic outcome (Aminoshariae *et al*. 2017);
- apical periodontitis of endodontic origin (Tiburcio-Machado *et al*. 2017);
- diabetes and the presence of radiolucent periapical lesions in root filled teeth (Segura-Egea *et al* 2016); and
- occurrence of extracted root filled teeth (Cabanillas-Balsera *et al*. 2019).

Among the four systematic reviews, a meta-analysis was performed for only two outcomes: relationship between diabetes and radiolucent periapical lesions in root filled teeth (Segura-Egea *et al*. 2016) and occurrence of extracted root filled teeth (Cabanillas-Balsera *et al*. 2019). For the pair-wise meta-analysis the two models used fixed effect and random effects models. Random effects models are preferred when there is heterogeneity among the studies included in a meta-analysis (Higgins & Green 2011). Cabanillas-Balsera *et al.* (2019) used a random effects model due to the substantial heterogeneity (I2=70.8%) in

their meta-analysis, whereas, Segura-Egea *et al.* (2016) used a fixed-effect model, probably due to the absence of heterogeneity (I2=0%). However, a random effects model is recommended as there is inevitably going to be between-study heterogeneity even if it is not detected statistically (Higgins & Green 2011). The two reviews which performed a meta-analysis did not assess and report on publication bias. The evaluation of publication bias is important to assess the effect of missing studies due to under- or non-reporting.

Principal findings and possible explanations

Segura-Egea *et al*. (2016), analyzing data from seven epidemiological studies, reported that diabetic patients have a greater prevalence of periapical radiolucencies associated with root filled teeth. On the other hand, Aminoshariae *et al*. (2017) concluded that there is no overall effect of diabetes on outcomes, but there was evidence for the association of diabetes with worse longitudinal outcomes in cases with pre-operative lesions. Tiburcio-Machado *et al*. (2017) reported that with the limited evidence available, there was a positive relationship between diabetes and a larger number of periapical lesions. Cabanillas-Balsera *et al*. (2019) concluded that there was a relationship between diabetes and increased frequency of loss of root filled teeth. From the above findings, it can be concluded that diabetes has an impact on the outcome of root canal treatment and must be considered as a major preoperative prognostic factor. The possible reasons attributed for the association between diabetes and outcome of root canal treatment are (Segura-Egea *et al*. 2016, Cabanillas-Balsera *et al*. 2019):

- diabetes predisposes to chronic inflammation;
- diabetes reduces tissue repair capacity;
- diabetes impairs the immune response enhancing susceptibility to infections;
- diabetes impairs bone deposition and delays wound healing; and
- diabetes has a strong association with periodontal disease, which itself has a strong association with apical periodontitis and with tooth loss.

In this umbrella review, it was not possible to consider two outcomes (persistence of apical periodontitis independent of marginal periodontitis and relationship between

persistent apical periodontitis and the level of glycaemia of the patient) because the systematic reviews did not address these issues:

i) *Persistence of apical periodontitis independent of marginal periodontitis:* It has long been established that diabetes and marginal periodontitis have a strong bidirectional association (Loe 1993, Sanz *et al.* 2018). At the same time, it is known that the presence of marginal periodontitis is associated with persistent apical periodontitis and is one of the most important factors in tooth loss (Rotstein 2000, Jannson 2015). In assessing the effect of diabetes on endodontic treatment outcomes, several longitudinal studies have controlled for marginal periodontitis by using the periodontal probing status of the endodontically treated tooth as a covariate (Fouad & Burleson 2003), or by excluding patients with advanced marginal periodontitis (Arya et al. 2017). However, previous systematic reviews have not addressed this important variable.

ii) *Relationship between persistent apical periodontitis and the level of glycaemia of the patient:* Glycated haemoglobin (HbA1c) is considered to be the gold standard for mean glycaemia and as a measure of risk for the development of complications associated with diabetes mellitus (Sánchez-Domínguez *et al.* 2015). In an animal model, oral infections influenced the glycaemic conditions and increased the HbA1c levels in diabetic rats (Cintra *et al.* 2014). Sánchez-Domínguez *et al*. (2015) reported that HbA1c levels of diabetic patients were associated with periapical conditions. In future, systematic review should be performed to confirm the association between persistent apical periodontitis and the level of glycaemia.

Quality of the individual systematic reviews

In the current umbrella review, methodological quality was appraised using "A MeaSurement Tool to Assess systematic Reviews" (AMSTAR) and has good agreement, reliability, and validity when used to appraise the quality of systematic reviews (Shea *et al*. 2009). This is the only tool currently available to evaluate the methodological quality of a systematic review. This tool is more objective and can be used independently (Sharif *et al*. 2013). The number of systematic reviews that are published has increased substantially in recent years and they are being used for clinical and policy decision-making. Hence, the ability to evaluate the quality and reliability of systematic reviews is important (Sharif *et al*.

2013). The quality assessment of the clinical studies included in a systematic review is also necessary to evaluate the quality of evidence that is produced by a subsequent meta-analysis.

The quality of each individual systematic review included in the current umbrella review was categorized as "medium". A high AMSTAR score for a review does not necessarily mean that the original clinical studies they included were of good quality. All the individual reviews scored "0" for two items (1. grey literature was not included in the literature search process and 2. the quality of the included studies was not used in formulating the conclusions). Grey literature is defined as: "that which is produced on all levels of government, academic, business and industry in print and electronic formats, but which is not controlled by commercial publishers" (Paez 2017). Thus, the grey literature includes conference abstracts, committee and government reports, unpublished data, dissertations, policy documents and personal correspondence (Sharif *et al*. 2013, Paez 2017). Searching the grey literature helps to reduce publication bias and increase the comprehensiveness of reviews, but may include unscientific or non-peer-reviewed material which may have considerable bias. On the other hand, excluding unpublished studies may reduce the specificity of systematic reviews and the validity and reliability of meta-analyses (McAuley *et al*. 2000, Paez 2017). Overall, it is recommended that the authors of systematic review should perform a literature search regardless of the publication status (i.e. grey literature).

Another item which is often neglected is "scientific quality of the included studies used appropriately in formulating conclusions". The methodological rigor and scientific quality of individual randomized clinical trials or other clinical studies should be considered in the analysis and the conclusions of a systematic review. It should be mentioned explicitly when formulating recommendations, which may subsequently be used to develop or change clinical practice guidelines (Sharif *et al*. 2013).

Three reviews (Segura-Egea *et al*. 2016, Tiburcio-Machado *et al*. 2017, Cabanillas-Balsera *et al*. 2019) were scored "0" for protocol registration. Developing a protocol for systematic review in advance helps the researchers to reflect prospectively on the proposed methodology, which reduces methodological flaws, bias and risk of duplication, and

increases transparency and visibility to potential researchers (de Vries *et al*. 2015, Straus & Moher 2010). Therefore, protocol development and registration is likely to benefit evidence-based practice.

Strengths

The present umbrella review has summarized systematically the current evidence on the association between diabetes and the outcome of root canal treatment. This review has consolidated the evidence and presents a highly evidenced-based result on the association between diabetes and root canal treatment outcome. The following parameters can be considered as a strength: i) an *a priori* protocol was developed and registered in the PROSPERO database, ii) a robust literature search was performed in four electronic databases in an attempt to avoid missing relevant reviews, iii) the literature search and data extraction were carried out by two independent reviewers and disagreements were resolved by third reviewer, iv) it followed standard approaches to appraise the quality of reviews using AMSTAR.

Limitations

The current umbrella review has several limitations: i) only two systematic reviews undertook a meta-analysis, ii) short publication time frame (2016-2019) of the included systematic reviews resulted in a small number of the same primary studies being included in more than one, iii) several systematic reviews had serious methodological inadequacies, iii) systematic reviews other than English were excluded.

Reporting deficiencies and gaps in knowledge/methodology

On reviewing the clinical studies and systematic reviews on the topic of the relationship between diabetes and endodontic disease and treatment several deficiencies in methodology and reporting were identified. To improve the quality of clinical studies and systematic reviews, the following recommendations on their conduct and reporting are proposed.

Future recommendation for clinical studies

1. *Sample size calculation*: Authors must define the number of cases that should be included by carrying out a sample size calculation based on the previous literature or a pilot study. A small sample size may not have sufficient power to identify statistically significant results.

2. *Type of diabetes (type 1 and type 2)*: Authors need to undertake a separate analysis for patients with type 1 and type 2 diabetes. Type 1 diabetes has a more severe effect on tissues (Tiburcio-Machado *et al.* 2017). Hence, spurious conclusion will be drawn if both types of diabetes are combined in the analysis.

3. *Methods used to assess diabetic status*: In this umbrella review, the methods used to assess the status of diabetic patients in the individual reviews were self-reporting, laboratory blood tests and medical records. It is essential that each clinical study reports the method(s) used to assess the condition. Information from laboratory tests or medical records containing data based on diagnostic tests provide more reliable information than self-reporting, which may not be sufficiently accurate. It is also important to use haemoglobin A1c as the preferred glycaemia measure, and to document changes in glycaemia throughout the observation period.

4. *Quality of the outcome assessor/examiner*: The examiners involved in the assessment of clinical and radiographic or other findings must to be trained and calibrated. Authors of clinical studies should report both inter-examiner and intra-examiner agreements, to demonstrate they have attempted to reduce measurement bias and increase the reproducibility of the results. Blinding of examiner to the diabetic status of patients is required to avoid further bias.

5. *Coexistence of other systemic diseases and smoking habits*: Various factors and systemic conditions, such as smoking habits, obesity, high blood pressure, low level of HDL cholesterol, high level of triglycerides, history of gestational diabetes, sedentary lifestyle, and history of heart disease or stroke, are well-defined risk factors for type 2 diabetes. These same factors could also be risk factors for endodontic disease. The control of these factors is difficult but would allow a most accurate estimation of the odds ratio.

6. *Other potential confounders*: The most important confounding variable is periodontal disease which has been shown to be significantly associated with diabetes (Nascimento *et al.* 2018, Madianos & Koromantzos 2018) and with endodontic disease (de Lima *et al.* 2017). Other potential confounders include patient-related factors such as age, gender, genomic polymorphisms and teeth with/without a permanent restoration. At the time of follow-up, the type of root canal treatment (primary vs retreatment), socioeconomic status and the level of training of the operator who performed the treatment should be controlled at the design stage or during analysis by matching the groups for such confounding factors or by adjusting for these factors in the statistical analysis. However, some factors are very difficult or almost impossible to control. Individuals with specific genotypes could be more susceptible to disease or could have an increase in disease severity. The same genetic polymorphism which increases the predisposition to a systemic disease could increase the susceptibility to apical periodontitis, or delay periapical repair, causing persistent apical periodontitis. For example, genetic polymorphisms of the receptor activator of nuclear factor kappa B (RANK) and the receptor activator of nuclear factor kappa B ligand (RANKL) genes are associated with persistent apical periodontitis (Petean *et al.* 2019), but also with type 2 diabetes (Duan *et al.* 2016).

7. *Endodontic diagnosis*: Since few of the studies included in the reviews have taken into account whether or not the endodontically treated tooth had a previous periapical radiolucent lesion, the influence of this possible confounding factor cannot be excluded. In future studies, authors should distinguish between cases with vital pulps, non-vital pulps and those with preoperative apical periodontitis as it appears there are differences in longitudinal outcome studies where this distinction has been made. It would also be useful to conduct studies including only root canal treatments in patients with irreversible pulpitis, without periapical lesions.

8. *Role of glycaemia on periapical healing*: The outcome of root canal treatment should be compared in relation to the glycaemia of the patients, regardless of their diabetic status. Cheraskin & Ringsdorf (1968) studied the radiographic healing of periradicular lesions after

root canal treatment, in 12 patients with low-plasma glucose (70-89 mg/mL), and 13 patients with high-plasma glucose (90-110 mg/mL). After 30 weeks, the periradicular radiolucencies in the patients of the low-glucose group were reduced by an average of 74%, compared with a reduction of only 48% in the patients in the high-glucose group.

9. *Role of root canal treatment on glycaemia*: Given the bidirectionality of the relationship of diabetes and periodontal disease, authors should consider whether root canal treatment affects the level of glycaemia. Although root canal treatment did not improve HbA1c levels in patients with type 2 diabetes (Arya *et al*. 2017), it has been reported that HbA1c levels in diabetic patients are associated with periapical status. It has been reported that a worse periapical status correlated significantly with HbA1c levels ≥ 6.5% in type 2 diabetic patients (Sánchez-Domínguez *et al*. 2015).

10. *Systemic medications*: Systemic medications that diabetic patients are likely to be taking and that affect bone deposition should be considered in clinical trials. For example, *Metformin* has been shown to reduce apical periodontitis in animal models (Liu *et al*. 2012, Lai *et al.* 2018), possibly due to its antimicrobial effects (Malik *et al.* 2018) or because it attenuates the oxidative and cytotoxic action of hypoxia. Statins have been shown to be associated with improved endodontic outcomes (Alghofaily *et al.* 2018), but may increase glycemia (Maki *et al*. 2016).

Future recommendation for systematic reviews and meta-analyses

Those conducting and reporting systematic reviews and meta-analyses should consider the following criteria:

i. *Protocol:* The protocol of systematic reviews must be prepared and registered in advance. The protocol guides the authors to carry out the review in a defined way, which improves its quality;

ii. *Grey literature*: The authors of systematic reviews must include the grey literature in the search process, so they include dissertations, committee reports, government reports, newspaper, and conference abstracts;

iii. *Quality assessment*: The results of the quality assessment (risk of bias) of the individual trials that were included in a review should be used to formulate the conclusion(s) of the review;

ii. *Sub-group analysis*: It is a good practice to perform subgroup meta-analysis in order to consider the following: Type of diabetes, methods used to assess diabetic status, coexistence of other oral or systemic diseases, metabolic syndrome, systemic medications and smoking habits.

Conclusion

Diabetes is associated with the outcome of root canal treatment and should be considered as an important preoperative prognostic factor. In future, high quality clinical studies with long-term follow-up and more control of confounding variables are required.

References

Aminoshariae A, Kulild JC, Mickel A, Fouad AF (2017) Association between Systemic Diseases and Endodontic Outcome: A Systematic Review. *Journal of Endodontics* **43**, 514-9.

Alghofaily M, Tordik P, Romberg E, Martinho F, Fouad AF (2018) Healing of Apical Periodontitis after Nonsurgical Root Canal Treatment: The Role of Statin Intake. *Journal of Endodontics* **44**, 1355-60.

Al-Nuaimi N, Patel S, Davies A, Bakhsh A, Foschi F, Mannocci F (2018) Pooled analysis of 1-year recall data from three root canal treatment outcome studies undertaken using cone beam computed tomography. *International Endodontic Journal* **51**, e216-e226.

Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P (2017) Chapter 10: Umbrella Reviews. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute,. Available from https://reviewersmanual.joannabriggs.org/.

Arya S, Duhan J, Tewari S, Sangwan P, Ghalaut V, Aggarwal S (2017) Healing of Apical Periodontitis after Nonsurgical Treatment in Patients with Type 2 Diabetes. *Journal of Endodontics* **43**, 1623–7.

Botero JE, Rodríguez C, Agudelo-Suarez AA (2016) Periodontal treatment and glycaemic control in patients with diabetes and periodontitis: an umbrella review. *Australian Dental Journal* **61**, 134-48.

Cabanillas-Balsera D, Martín-González J, Montero-Miralles P, Sánchez-Domínguez B, Jiménez-Sánchez MC, Segura-Egea JJ (2019) Association between diabetes and nonretention of root filled teeth: a systematic review and meta-analysis *International Endodontic Journal* **52**, 297-306.

Cheraskin E, Ringsdorf WM Jr (1968) The biology of the endodontic patient, 3: variability in periapical healing and blood glucose. *Journal of Oral Medicine* **23**, 87-90.

Cho NH, Shaw JE, Karuranga S, *et al*. (2018) IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice* **138**, 271-81.

Cintra LT, Samuel RO, Facundo AC, *et al*. (2014) Relationships between oral infections and blood glucose concentrations or HbA1c levels in normal and diabetic rats. *International Endodontic Journal* **47**, 228–37.

de Lima CO, Devito KL, Baraky Vasconcelos LR, Prado MD, Campos CN (2017) Correlation between endodontic infection and periodontal disease and their association with chronic sinusitis: A Clinical-tomographic Study. *Journal of Endodontics* **43**, 1978-83.

de Vries RB, Hooijmans CR, Langendam MW, *et al*. (2015) A protocol format for the preparation, registration and publication of systematic reviews of animal intervention studies. *Evidence-based Preclinical Medicine* **2**, 1-9.

Duan P, Tu P, Si L, *et al*. (2016) Gene Polymorphisms in the RANKL/RANK/OPG Pathway Are Associated with Type 2 Diabetes Mellitus in Southern Han Chinese Women. *Genetic Testing and Molecular Biomarkers* **20**, 285–90.

Fouad AF (2003) Diabetes mellitus as a modulating factor of endodontic infections. *Journal of Dental Education* **67**, 459-67.

Fouad AF, Burleson J (2003) The effect of diabetes mellitus on endodontic treatment outcome: data from an electronic patient record. *Journal of the American Dental Association* **134**, 43-51.

Fusar-Poli P, Radua J (2018) Ten simple rules for conducting umbrella reviews. *Evidence-Based Mental Health* **21,** 95-100.

Guariguata L, Whiting DR, Hambleton I, *et al*. (2014) Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice* **103**, 137–49.

Higgins JPT, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Holland R, Gomes JE Filho, Cintra LTA, Queiroz ÍOA, Estrela C (2017) Factors affecting the periapical healing process of endodontically treated teeth. *Journal of Applied Oral Science* **25,** 465-76.

Iacopino AM (2001) Periodontitis and diabetes interrelationships: role of inflammation. *Annals of Periodontology* **6**, 125–37.

Jansson L (2015) Relationship between apical periodontitis and marginal bone loss at individual level from a general population. *International Dental Journal* **65**, 71-6.

Khalighinejad N, Aminoshariae MR, Aminoshariae A, Kulild JC, Mickel A, Fouad AF (2016) Association between Systemic Diseases and Apical Periodontitis. *Journal of Endodontics* **42**, 1427-34.

Kharroubi AT, Darwish HM (2015) Diabetes mellitus: The epidemic of the century. *World Journal of Diabetes* **6**, 850-67.

Lai EH, Yang CN, Lin SK, *et al*. (2018) Metformin Ameliorates Periapical Lesions through Suppression of Hypoxia-induced Apoptosis of Osteoblasts. *Journal of Endodontics* **44**, 1817-25.

Lazarski MP, Walker WA, Flores CM, Schindler WG, Hargreaves KM (2001) Epidemiological evaluation of the outcomes of nonsurgical root canal treatment in a large cohort of insured dental patients. *Journal of Endodontics* **27**, 791–6.

Lima SM, Grisi DC, Kogawa EM, *et al*. (2013) Diabetes mellitus and inflammatory pulpal and periapical disease: a review. *International Endodontic Journal* **46**, 700-9.

Liu L, Zhang C, Hu Y, Peng B (2012) Protective effect of metformin on periapical lesions in rats by decreasing the ratio of receptor activator of nuclear factor kappa B ligand/osteoprotegerin. *Journal of Endodontics* **38**, 943-7.

Löe H (1993) Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* **16**, 329-34.

Madianos PN, Koromantzos PA (2018) An update of the evidence on the potential impact of periodontal therapy on diabetes outcomes. *Journal of Clinical Periodontology* **45**, 188-95.

Maki KC, Dicklin MR, Baum SJ (2016) Statins and Diabetes. *Endocrinology and Metabolism Clinics of North America* **45**, 87-100.

Malik F, Mehdi SF, Ali H, *et al*. (2018) Is metformin poised for a second career as an antimicrobial? *Diabetes/Metabolism Research and Reviews* **34**, e2975.

McAuley L, Pham B, Tugwell P, Moher D (2000) Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? *Lancet* **356**, 1228– 31.

Mealey BL, Oates TW (2006) Diabetes mellitus and periodontal diseases. *Journal of Periodontology* **77**, 1289–303.

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine* **151**, 264–9.

Nascimento GG, Leite FRM, Vestergaard P, Scheutz F, López R (2018) Does diabetes increase the risk of periodontitis? A systematic review and meta-regression analysis of longitudinal prospective studies. *Acta Diabetologica* **55**, 653-67.

Ng YL, Mann V, Gulabivala K (2011) A prospective study of the factors affecting outcomes of nonsurgical root canal treatment: part 1: periapical health. *International Endodontic Journal* **44**, 583-609.

Paez A (2017) Gray literature: An important resource in systematic reviews. *Journal of Evidence Based Medicine***10**, 233-40.

Petean IBF, Küchler EC, Soares IMV, *et al*. (2019) Genetic Polymorphisms in RANK and RANKL are Associated with Persistent Apical Periodontitis. *Journal of Endodontics* **45**, 526–31.

Preshaw PM, Alba AL, Herrera D, *et al*. (2012) Periodontitis and diabetes: a two-way relationship. *Diabetologia* **55**, 21-31.

Rangel-Rincón LJ, Vivares-Builes AM, Botero JE, Agudelo-Suárez AA (2018) An Umbrella Review Exploring the Effect of Periodontal Treatment in Pregnant Women on the Frequency of Adverse Obstetric Outcomes. *Journal of Evidence Based Dental Practice* **18**, 218-39.

Robertson GL (2016) Diabetes insipidus: Differential diagnosis and management. *Best Practice & Research Clinical Endocrinology & Metabolism* **30**, 205-18.

Rotstein I (2017) Interaction between endodontics and periodontics. *Periodontology 2000* **74**, 11-39.

Sánchez-Domínguez B, López-López J, Jané-Salas E, Castellanos-Cosano L, Velasco-Ortega E, Segura-Egea JJ (2015) Glycated hemoglobin levels and prevalence of apical periodontitis in type 2 diabetic patients. *Journal of Endodontics* **41**, 601-6.

Sanz M, Ceriello A, Buysschaert M, *et al*. (2018) Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. *Journal of Clinical Periodontology* **45**, 138-49**.**

Sasaki H, Hirai K, Martins CM, Furusho H, Battaglino R, Hashimoto K (2016) Interrelationship Between Periapical Lesion and Systemic Metabolic Disorders. *Current Pharmaceutical Design* **22**, 2204-15.

Segura-Egea JJ, Cabanillas-Balsera D, Jiménez-Sánchez MC, Martín-González J (2019) Endodontics and diabetes: association versus causation. *International Endodontic Journal* **52**, 790-802.

Segura-Egea JJ, Castellanos-Cosano L, Machuca G, *et al*. (2012) Diabetes mellitus, periapical inflammation and endodontic treatment outcome. *Medicina Oral Patologia Oral y Cirugia Bucal* **17**, e356-61.

Segura-Egea JJ, Martín-González J, Cabanillas-Balsera D, Fouad AF, Velasco-Ortega E, López-López J (2016) Association between diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth: systematic review and meta-analysis. *Clinical Oral Investigations* **20**, 1133-4.

Segura-Egea JJ, Martín-González J, Castellanos-Cosano L (2015) Endodontic medicine: connections between apical periodontitis and systemic diseases. *International Endodontic Journal* **48**, 933-51.

Sharif MO, Janjua-Sharif FN, Ali H, Ahmed F (2013) Systematic reviews explained: AMSTAR-how to tell the good from the bad and the ugly. *Oral Health and Dental Management*. **12**, 9-16.

Shea BJ, Grimshaw JM, Wells GA, *et al*. (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* ***7***, 10.

Shea BJ, Hamel C, Wells GA, *et al*. (2009) AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *Journal of Clinical Epidemiology* **62**, 1013-20.

Straus S, Moher D (2010) Registering systematic reviews. *Canadian Medical Association Journal* **182**, 13-4.

Tibúrcio-Machado CD, Bello MC, Maier J, Wolle CF, Bier CA (2017) Influence of Diabetes in the Development of Apical Periodontitis: A Critical Literature Review of Human Studies. *Journal of Endodontics* **43**, 370-6.

Legends

Figure

Figure 1: Literature search process

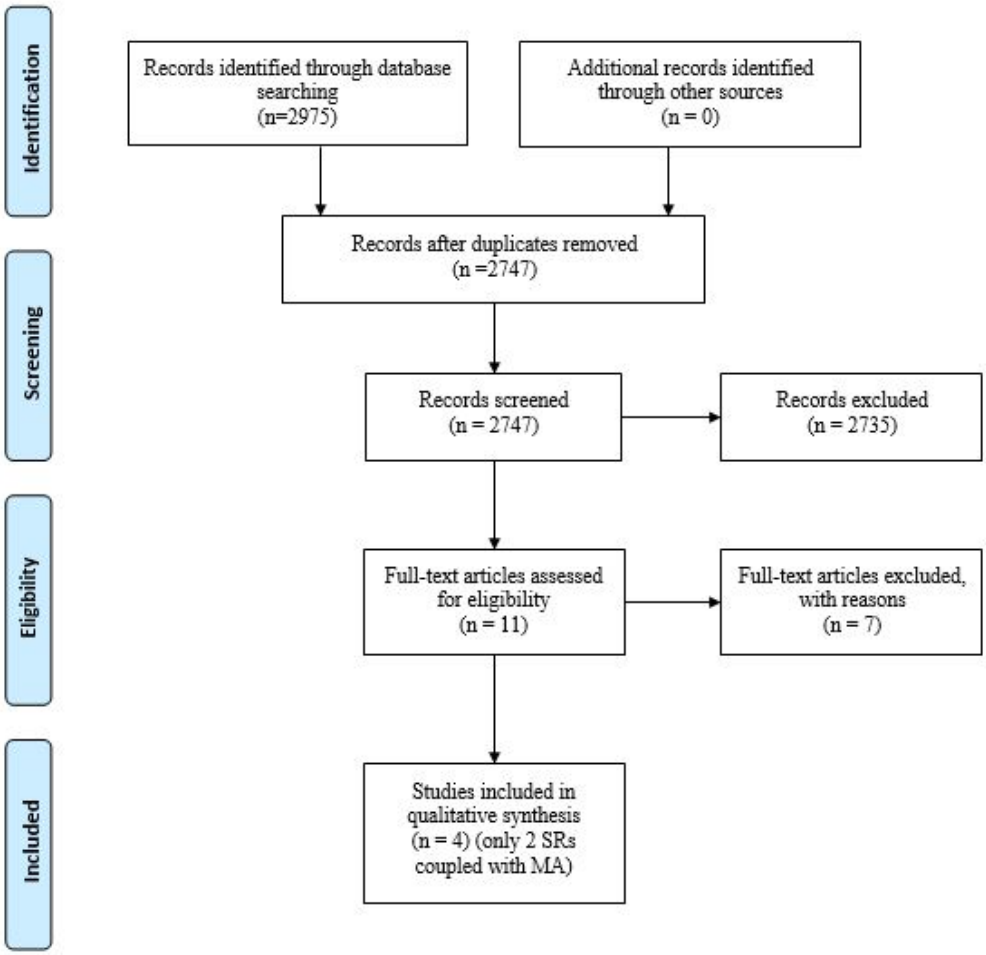
Identification
Screening
Eligibility
Included
Records identified through database searching (n=2975)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n =2747)
Records screened (n = 2747)
Records excluded (n = 2735)
Full-text articles assessed for eligibility (n = 11)
Full-text articles excluded, with reasons (n = 7)
Studies included in qualitative synthesis (n = 4) (only 2 SRs coupled with MA)

Figure 1

Table 1: Main characteristics of the included systematic reviews

S No	Author, year	Name of the journal published	Database searched	Country of the first author	Search Period	Language	Meta-analysis performed	Number of included studies	Study design – included studies	Instrument of quality Assessment
1	Segura-Egea *et al*. 2016	*Clinical Oral Investigations*	MEDLINE/PubMed, Wiley Online Database, Web of Science, and Scopus	Spain	1980 to 2016	NR	Yes	7	Cross-sectional, longitudinal	Centre for Evidence-Based Medicine
2	Aminoshariae *et al*. 2017	*Journal of Endodontics*	MEDLINE, Embase, Cochrane, and PubMed	USA	1997 to 2016.	English	No	11	Case control, longitudinal	Specific quality assessment scale (based on three domains)
3	Tiburcio-Machado *et al.* 2017	*Journal of Endodontics*	PubMed/MEDLINE, LILACS, Scientific Electronic Library Online (Scielo), and Cochrane Collaboration	Brazil	Upto 2016	English	No	9	Nonrandomized clinical trial, Cross-sectional,	observational studies - STROBE statement, Clinical studies - basic principles of research.

4	Cabanillas-Balsera et al. 2019	*International Endodontic Journal*	MEDLINE/PubMed, Web of Science, Scopus and the Wiley Online	Spain	1988 to 2018	NR	Yes	3	Longitudinal	Oxford CEBM guidelines

Note: NR- Not reported, STROBE - STrengthening the Reporting of OBservational studies in Epidemiology, USA – United states of America

Table 2: Summary of the meta-analysis

S No	Author, year	Number of samples				Meta-analysis metric	Estimate (95 % CI)	Total studies included	I2 (%)	Outcome assessed
		Diabetic		Non Diabetic (Control)						
1	Segura-Egea *et al.* 2016	*Total RTF*	*RFT*RPL*	*Total RTF*	*RFT*RPL*	OR	1.44 (1.11–1.80)	7	0	Diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth
		582	208	1011	314					
2	Cabanillas-Balsera *et al.* 2019	*Total RFT*	*E*RFT*	*Total RFT*	*E*RFT*	OR	2.44 (1.54–3.88)	3	70.8	Diabetes and non-retention of root filled teeth
		4635	262	1575	50 301					

Note: RFT - root-filled teeth, RFT*RPL root-filled teeth with radiolucent periapical lesions, E*RFT, extracted root filled teeth, OR – Odds ratio,