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REVIEW

Association between diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth: systematic review and meta-analysis

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Abstract
Introduction The question of whether diabetes mellitus can influence the outcome of root canal treatment (RCT) remains unclear. The aim of this systematic review and meta-analysis was to analyze scientific available evidence on the association between diabetes and the presence of radiolucent periapical lesions (RPLs) in root-filled teeth (RFT).
Methods The review question was as follows: in adult patients who had endodontically treated teeth, does the absence or presence of diabetes result in an increase in the prevalence of RPL associated to RFT? A systematic MEDLINE/PubMed, Wiley Online Database, Web of Science, and Scopus search was conducted using the following MeSH and keywords: Diabetes Mellitus OR Diabetes OR Diabetic OR Hyperglycemia, AND Endodontics, Periapical Periodontitis, Periapical Diseases, Apical Periodontitis, Periradicular Lesion, Periapical Radiolucency, Radiolucent Periapical Lesion, Root Canal Treatment, Root Canal Preparation, Root Canal Therapy, Root Filled Teeth, Endodontically Treated Teeth. Seven studies reporting data on the prevalence of RPL associated to RFT both in diabetic and control subjects were included.
Results After the study selection, seven epidemiological studies fulfilled the inclusion criteria, representing data from 1593 root canal treatments, 1011 in non-diabetic control subjects, and 582 in diabetic patients. The calculated pooled odds ratio (OR = 1.42; 95 % CL = 1.11–1.80; $p = 0.0058$) indicates that diabetic patients have higher prevalence of RFT with RPLs than controls.
Conclusion Available scientific evidence indicates that diabetes is significantly associated to higher prevalence of periapical radiolucencies in endodontically treated teeth, being an important putative pre-operative prognostic factor in RCT.
Clinical relevance Taking into account that diabetes is the third most prevalent chronic medical condition among dental patients, endodontic providers should be aware of the relationship between the outcome of endodontic treatment and diabetes.

Keywords Diabetes mellitus · Meta-analysis · Periapical inflammation · Persistent apical periodontitis · Root canal treatment outcome · Root-filled teeth

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Introduction

Apical periodontitis (AP) is an inflammatory process around the apex of a tooth root, following the bacterial infection of the pulp space of the tooth [1]. The bone lesion associated with apical periodontitis is characterized radiographically by the presence of radiolucent periapical lesion (RPL), i.e., a radiolucent image surrounding the root apex of the affected tooth [2]. AP is an extraordinarily prevalent problem [3]. In the USA, radiographic signs of periapical disease are evident in

4.1–5.1 % of all teeth [4, 5]. The incidence of new cases of apical periodontitis over a 24-year period in the USA ranges from 27 to 41 % depending on age [6]. In Europe, the prevalence of AP is as high as 34–61 % of individuals and 2.8–4.2 % of the teeth [7, 8], increasing with patient's age [9]. The treatment for teeth with AP is root canal treatment (RCT) [10]. In the USA, 4.8–5.5 % of teeth have been endodontically treated [4, 5] and 10 % of young military recruits were shown to have existing RCT [11]. In Europe, the prevalence of endodontic treatment is estimated around 41–59 % of individuals and 2–6.4 % of teeth [7, 8].

When RCT fails, resolution of the periapical lesion and complete healing of periapical tissues do not occur, persisting AP [12, 13]. Persistent apical periodontitis (PAP) is characterized radiographically by a RPL associated with the root-filled tooth (RFT). The prevalence of radiographic evidence of persistent AP is 31–36 % in the USA [4, 5] and 24–65 % in European countries [7, 8, 14]. Periapical granulomas and cysts are the most common periapical lesions of endodontic origin associated with PAP. However, some of the RPL associated with RFT may not represent PAP, but incomplete healed lesions after root canal treatment, periapical connective scars [15], or non-endodontic pathosis [16].

Factors implicated in persistent AP are not only intra-operatives, such as inadequate aseptic control, missed canals, insufficient instrumentation, and leaking temporary or permanent restorations [17], but also systemic factors, such as proinflammatory status and impaired immune response associated with systemic diseases [14, 18].

One of the systemic diseases whose possible association with AP has been investigated is diabetes mellitus (DM) [14, 19], a heterogeneous group of metabolic disorders, with hyperglycemia as the main feature [20]. DM is due to pancreatic β-cell dysfunction, with deficiency in insulin secretion and/or insulin resistance in liver and muscle [21]. Diabetic patients have impaired immune cell function. Pro-inflammatory cytokines from monocytes/polymorphonuclear leukocytes are upregulated, and growth factors from macrophages are downregulated, predisposing to chronic inflammation, progressive tissue breakdown, and diminished tissue repair capacity [22]. In addition, diabetic patients have increased levels of advanced glycation end-products (AGEs), which interact with cell surface receptors for them to increase oxidative stress in tissues and upregulate the inflammatory response [23]. In poor controlled diabetics, the immune response is further diminished, with decreased leukocyte function and delay of wound healing [22–25]. Consequently, an increased number and/or size of periapical lesions would be expected in root-filled teeth of diabetic patients.

Since the pioneer study of Bender et al. [26] in 1963, several epidemiological studies have investigated the impact of diabetes on periapical health and RCT outcome. Mostly, these studies were cross-sectional and employed only radiographic examination [14, 19, 27]. However, the question of whether diabetes mellitus can influence the outcome of RCT remains unclear [14].

Aim of the study

The purpose of this study was to conduct a systematic review and meta-analysis of the possible association between diabetes and RCT failure, assessed as the prevalence of radiolucent periapical lesions in root-filled teeth. The clinical PICO question to be answered was as follows: in adult patients who had endodontically treated teeth (problem and intervention), does the absence or presence of diabetes mellitus (comparison) result in an increase in the prevalence of RPL associated to RFT (outcome)?

Materials and methods

Literature search strategy

According to the conventional procedures to develop systematic review and meta-analysis [28, 29], firstly the PICO question was formulated, for which the search strategy was constructed. Inclusion and exclusion criteria were defined, the studies located and selected, their quality assessed, and the data extracted and interpreted [30].

The literature search strategy was as follows. A MEDLINE/PubMed, Wiley Online Database, Web of Science, and Scopus search was performed using the following combination of Mesh terms and keywords: (Diabetes Mellitus OR Diabetes OR Diabetic OR Hyperglycemia) AND (Endodontics OR Periapical Periodontitis OR Periapical Diseases OR Apical Periodontitis OR Periradicular Lesion OR Periapical Radiolucency OR Radiolucent Periapical Lesion OR Root Canal Treatment OR Root Canal Preparation OR Root Canal Therapy OR Root Filled Teeth OR Endodontically Treated Teeth) (Table 1).

Several journals (*Journal of Endodontics*; *International Endodontic Journal*; *Clinical Oral Investigations*; *Oral Diseases; Oral Surgery*, *Oral Medicine*, *Oral Pathology*, *Oral Radiology and Endodontology*; *Endodontics and Dental Traumatology*; and *Australian Endodontic Journal*) and the bibliography of all relevant papers and review papers were hand-searched.

Study selection and inclusion and exclusion criteria

Three investigators (J.M-G., D.C-B., and J.J.S-E.) screened the titles and abstracts of all articles identified in the electronic and manual searches. Articles that did not meet the inclusion

Table 1 Lists MeSH and key words combinations used for the search strategy

((“diabetes mellitus”[MeSH Terms] OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields]) OR (“diabetes mellitus”[MeSH Terms] OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields] OR “diabetes”[All Fields] OR “diabetes insipidus”[MeSH Terms] OR (“diabetes”[All Fields] AND “insipidus”[All Fields]) OR “diabetes insipidus”[All Fields]) OR Diabetic[All Fields] OR (“hyperglycaemia”[All Fields] OR “hyperglycemia”[MeSH Terms] OR “hyperglycemia”[All Fields])) AND ((“endodontics”[MeSH Terms] OR “endodontics”[All Fields]) OR (“periapical periodontitis”[MeSH Terms] OR (“periapical”[All Fields] AND “periodontitis”[All Fields]) OR “periapical periodontitis”[All Fields]) OR (“periapical diseases”[MeSH Terms] OR (“periapical”[All Fields] AND “diseases”[All Fields]) OR “periapical diseases”[All Fields]) OR (“periapical periodontitis”[MeSH Terms] OR (“periapical”[All Fields] AND “periodontitis”[All Fields]) OR “periapical periodontitis”[All Fields] OR (“apical”[All Fields] AND “periodontitis”[All Fields]) OR “apical periodontitis”[All Fields]) OR (Periradicular[All Fields] AND Lesion[All Fields]) OR (Periapical[All Fields] AND Radiolucency[All Fields]) OR (Radiolucent[All Fields] AND Periapical[All Fields] AND Lesion[All Fields]) OR ((“dental pulp cavity”[MeSH Terms] OR (“dental”[All Fields] AND “pulp”[All Fields] AND “cavity”[All Fields]) OR “dental pulp cavity”[All Fields] OR (“root”[All Fields] AND “canal”[All Fields]) OR “root canal”[All Fields]) AND (“therapy”[Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “therapeutics”[MeSH Terms] OR “therapeutics”[All Fields])) OR (“root canal preparation”[MeSH Terms] OR (“root”[All Fields] AND “canal”[All Fields] AND “preparation”[All Fields]) OR “root canal preparation”[All Fields]) OR (“root canal therapy”[MeSH Terms] OR (“root”[All Fields] AND “canal”[All Fields] AND “therapy”[All Fields]) OR “root canal therapy”[All Fields]) OR ((“plant roots”[MeSH Terms] OR (“plant”[All Fields] AND “roots”[All Fields]) OR “plant roots”[All Fields] OR “root”[All Fields]) AND Filled[All Fields] AND (“tooth”[MeSH Terms] OR “tooth”[All Fields] OR “teeth”[All Fields])) OR (“tooth, nonvital”[MeSH Terms] OR (“tooth”[All Fields] AND “nonvital”[All Fields]) OR “nonvital tooth”[All Fields] OR (“endodontically”[All Fields] AND “treated”[All Fields] AND “teeth”[All Fields]) OR “endodontically treated teeth”[All Fields]))

criteria were excluded. All remaining articles were obtained and full-text reviewed independently by four reviewers (J.M-G., D.C-B., E.V-O., and J.J.S-E) based on the following inclusion criteria: (1) the type of study: epidemiological studies published from January 1980 to March 2016, (2) studies comparing adult diabetic patients and non-diabetic controls, (3) studies involving RFT, and (4) studies establishing the periapical condition of RFT and reporting data on the prevalence of RPL associated with RFT both in diabetic and control subjects.

Exclusion criteria included the following: (1) the type of study: cell culture laboratory studies or animal studies, (2) studies that only examined diabetic patients, and (3) studies without radiographic assessment of periapical radiolucency.

Cases of disagreement between reviewers were discussed until a consensus was reached.

Quality assessment and data extraction

The texts of the potentially relevant studies were systematically evaluated. Data were extracted, synthesized, and analyzed, and the quality of the methodology was assessed. For each study, the following parameters recorded: authors' names, date of publication, study design, sample size and included subjects and RCTs, diagnosis of RPLs, main results on association between diabetes and RFT with RPLs, and evidence level, determined according to guidelines provided by The Centre for Evidence-Based Medicine at Oxford [31].

Outcome variables and statistical analysis

The odds ratio (OR) for the prevalence of RPL in RFT of control and diabetic subjects was established as primary outcome variable and measure of the effect. The pooled OR was calculated using the method of Mantel-Haenszel with fixed effects, and 95 % confidence intervals for the OR were calculated using the Robins, Breslow, and Greenland variance formula. To test for heterogeneity among the ORs calculated, the Breslow-Day test (BDT) and the I^2 test [32] were used. L'Abbé plots [33] were used to illustrate the homogeneity. A forest plot [34] was used to display the OR results, along with the Mantel-Haenszel (MH) pooled estimate. Significance level of $p < 0.05$ was considered, and the meta-analysis was carried out with the StatsDirect software [35].

Results

The search strategy is presented in Fig. 1. The combinations of the initial electronic search terms and manual searches identified 545 titles. Duplicated references (349 items) and articles published before 1980 (16 items) were discarded. A subsequent search at the title and abstract level among the 180 remaining titles, taking into account the inclusion and exclusion criteria, revealed 16 articles for full-text reading. At this level, nine studies were excluded for the following reasons: one of them was referred to periodontal disease [36], six did not provide data about the prevalence of RFT with RPLs in diabetics and controls [37–41], and two others only provide data regarding retention of RFT in diabetic and controls [42, 43].

Study characteristics

In the final analysis, the following seven studies were included: (1) Falk et al. [44]) [44]; (2) Fouad and Burleson [45]) [45]; (3) Britto et al. [46]) [46]; (4) Segura-Egea et al. [47]) [47]; (5) López-López et al. [48]) [48]; (6) Marotta et al. [49]) [49]; and (7) Marques-Ferreira et al. [50]) [50]. Table 2 summarizes the study design, subjects and sample size, diagnosis

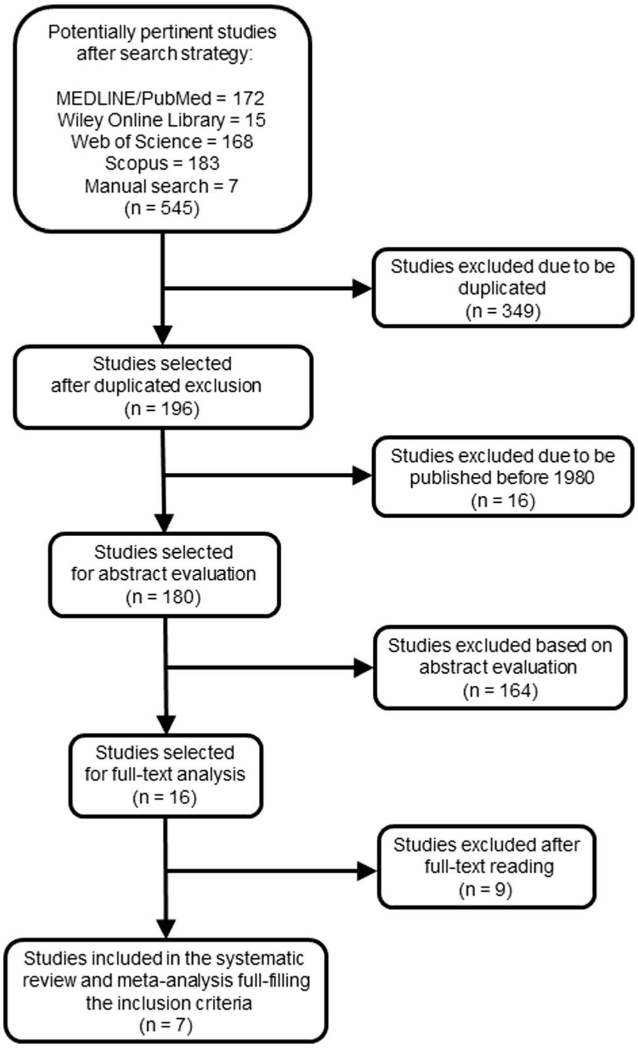

Fig. 1 Selection process of the studies included in the systematic review and meta-analysis

of RPLs, main results, and evidence level [31]. Radiographic criteria for the diagnosis of apical periodontitis, when are provided, are shown; two studies [46, 49] used the Strindberg's criteria [51], one study had longitudinal data and used clinical and radiographic analysis by supervising endodontists [45] and three others [47, 48, 50] the PAI system score [52].

Meta-analysis

For each selected article, the results were extracted and compiled into a table of evidence, and descriptive statistics and odds ratios calculated (Table 3). When the OR is greater than 1, it indicates that diabetic patients show higher prevalence of RFT with RPLs than control subjects. The BDT was non-significant (Breslow-Day = 4.63; df = 6; $p = 0.59$), indicating homogeneity among the ORs of the included studies (Fig. 2, L'Abbé plot). Moreover, the proportion of variation through studies due to heterogeneity was very low ($I^2 = 0$ %; 95 % CI = 0 to 59 %). Mantel-Haenszel method and the Robins, Breslow, and Greenland variance formula, with fixed effects, provide a pooled OR = 1.42 (95 % CI = 1.11–1.80; $chi^2 = 7.60$; $p = 0.0058$), indicating that the calculated pooled OR differs significantly from 1. Forest plot shows the ORs for each study and the overall OR calculated from the meta-analysis (Fig. 3). These results indicate that diabetic patients have significantly higher prevalence of RFT with RPLs than control subject.

Interpretation and assessment of the included studies

The time frame of publication of the seven studies was 1989 and 2014; however, six of them were published between 2003 and 2014 (Table 2). One was a longitudinal study with two or more years of follow-up, in which successful versus uncertain/failed treatments were compared [45], and the other six were cross-sectional studies [44, 46–50]. The included studies represent data from 1368 subjects, 730 controls, and 319 diabetic patients.

In the study of Falk et al. [44], long-duration diabetics showed higher frequency of RFT with RPLs (26 %) compared to non-diabetic patients (21 %) (OR = 1.31; 95 % CL = 0.85–2.01; $p = 0.20$). However, diabetic women had significantly more RFT with RPLs than control women ($p < 0.01$). Fouad and Burleson [45] investigated 531 RCT, 72 in diabetic patients, finding increased likelihood of RPLs diabetics, but without statistical significance (OR = 1.24; 95 % CL = 0.70–2.13; $p = 0.20$). Nevertheless, the frequency of RPLs in RFT of diabetic patients with preoperative periradicular lesions was significant compared to controls ($p = 0.007$) and when controlling for a number of confounding variables [45]. The study of Britto et al. [46] assessed the periapical status of 99 subjects (56 diabetics) using periapical and panoramic radiographs. Strindberg's criteria [51] were used to diagnose RPLs. The results did not find significant difference in the percentage of RFT with RPLs between controls [44 %] and diabetics [46] (OR = 1.09; 95 % CL = 0.46–2.63; $p = 0.82$). However, type 2 diabetic men were more likely to have residual RPLs in their RFT ($p < 0.05$). The study sample in this investigation showed a striking prevalence of RPLs, finding one or more teeth with RPLs in 97 and 87 % of diabetic patients and control subjects, respectively. Segura-Egea et al. [47] included in their study 38 control subjects and 32 diabetic patients, using periapical radiographs and PAI score system [52] to assess the periapical status. RPLs were found in 83 % of RFT in the diabetic group, whereas only 60 % of RFT in the control group had periapical lesions (OR = 3.33; 95 % CL = 0.48–37.93; $p = 0.17$). The study of López-López et al. [48] compared the prevalence of RFT with RPLs in well-controlled diabetic patients and control subjects. In this study, patients and controls were age- and sex-matched, and diabetic patients had glycated hemoglobin levels (HbA1c)

Table 2 Studies included in the systematic review. Study design, subjects and sample size, diagnosis of radiolucent periapical lesions, and main results on association between diabetes and RFT with RPL and evidence level

Authors	Year	Study design	Subjects	Diagnosis of radiolucent periapical lesions	Association diabetes—RFT*RPL	Evidence level (31)
1. Falk et al.	[44]	Cross-sectional	Controls: 77 Diabetics: 82	Periapical radiographs	No; $p = 0.20$ Diabetic women Yes; $p < 0.01$	C
2. Fouad and Burleson	[45]	Longitudinal (≥ 2 years)	Controls: 459 Diabetics: 72	Periapical radiographs	No; $p = 0.42$ Preoperative RPL Yes; $p = 0.0073$	C
3. Britto et al.	[46]	Cross-sectional	Controls: 23 Diabetics: 30 Type 1: 11 Type 2: 19	Periapical radiographs Strindberg criteria (52)	No; $p = 0.82$ Men with type 2 Yes; $p < 0.05$	D
4. Segura-Egea et al.	[47]	Cross-sectional	Controls: 38 Type 2 diabetics: 32	Periapical radiographs PAI index (53)	No; $p = 0.17$	D
5. López-López et al.	[48]	Cross-sectional	Controls: 50 Type 2 diabetics: 50 Well controlled Age/sex-matched	Digital panoramic radiographs PAI index (53)	No; $p = 0.09$	D
6. Marotta et al.	[49]	Cross-sectional	Controls: 60 Type 2 diabetics: 30 Age/sex-matched	Full-mouth periapical and panoramic radiographs Strindberg criteria (52)	No; $p = 0.21$	D
7. Marques-Ferreira et at.	[50]	Cross-sectional	Controls: 23 Diabetics: 23 Type 1: 4 Type 2: 17	Periapical and panoramic radiographs PAI index (53)	No; $p = 0.06$	D

RCT: root canal treatment, *RFT* root-filled teeth, *RFT*RPL* root-filled teeth with radiolucent periapical lesion, *RPL* radiolucent periapical lesion

≤ 6.5 %. Periapical status of RFT was assessed using panoramic digital radiographs and the PAI index [52]. The results showed that the percentage of RFT with RPLs was almost twice higher in diabetic patients (46 %) than in control subjects (24 %), but the difference was not statically significant (OR = 2.67; 95 % CL = 0.76–10.06; $p = 0.09$).

Marotta et al. [49], in another cross-sectional study, used periapical and panoramic radiographs and Strindberg's criteria [51] for the diagnostic of RPLs in RFT of diabetic and control subjects. They found that RPLs were significantly more common in untreated teeth from diabetics (10 %) than in non-diabetic controls (7 %) ($p = 0.03$). However, there was not significant difference in the prevalence of RPLs associated with RFT in diabetics (46 %) and control subjects (38 %) (OR = 1.39; 95 % CL = 0.81–2.39; $p = 0.21$). Finally, the study conducted by Marques-Ferreira et al. [50] compared the success rate of RFT in two groups of 23 patients, healthy control group and diabetic group. Periapical status was assessed radiographically using the PAI score system [52]. The results demonstrated no significant differences between

Table 3 Results extracted and compiled, descriptive statistics, and odds ratios calculated

Authors	Year	No. RFT	Non-diabetic controls		Diabetic patients		Odds Ratio (95 % CL	*p* value
			RFT*RPL/total RFT	RFT*RPL (%)	RFT*RPL/total RFT	RFT*RPL (%)		
1. Falk et al.	[44]	518	50/233	21	75/285	26	1.31 (0.85–2.01)	0.20
2. Fouad and Burleson	[45]	531	144/459	31	26/72	36	1.24 (0.70–2.13)	0.42
3. Britto et al.	[46]	99	19/43	44	26/56	46	1.09 (0.46–2.63)	0.82
4. Segura-Egea et al.	[47]	32	12/20	60	10/12	83	3.33 (0.48–37.93)	0.17
5. López-López et al.	[48]	60	6/25	24	16/35	46	2.67 (0.76–10.06)	0.09
6. Marotta et al.	[49]	291	78/206	38	39/85	46	1.39 (0.81–2.39)	0.21
7. Marques-Ferreira et at.	[50]	62	5/25	20	16/37	43	3.05 (0.84–12.48)	0.06
Overall		1593	314/1011	31	208/582	36	1.42 (1.11–1.80)*	0.006

RFT root-filled teeth, *RFT*RPL* root-filled teeth with radiolucent periapical lesions

*Mantel-Haenszel and Robins-Breslow-Greenland variance formula: $chi^2 = 7.60$, $p = 0.0058$

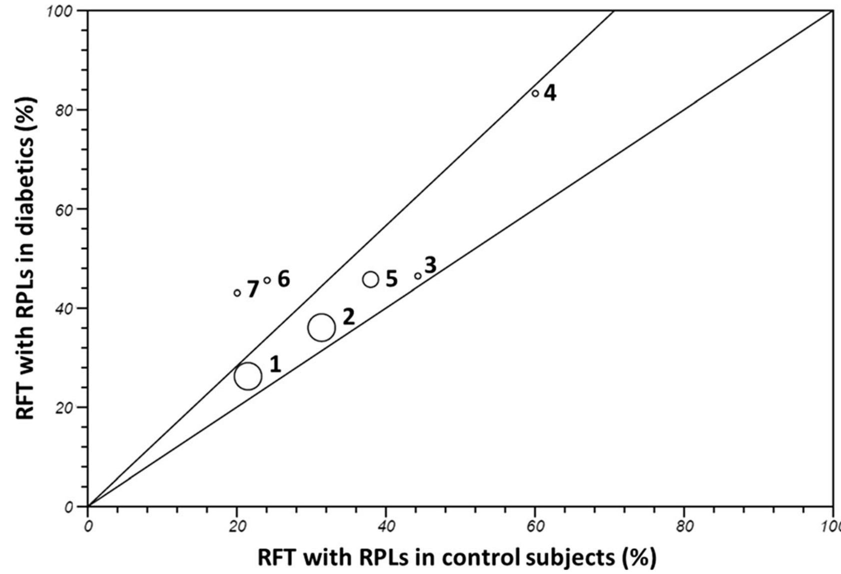

Fig. 2 L'Abbé plot showing the percentage of root-filled teeth (RFT) with radiolucent periapical lesions (RPLs) in the seven studies for the comparison of diabetic and controls. Size of circle is proportional to size of study. Study designations: (1) Falk et al. [44]); (2) Fouad and Burleson [45]); (3) Britto et al. [46]); (4) Segura-Egea et al. [47]); (5) López-López et al. [48]); (6) Marotta et al. [49]); and (7) Marques-Ferreira et al. [50])

both groups in the prevalence of RFT with RPLs (OR = 3.05; 95 % CL = 0.84–12.48; $p = 0.06$).

Discussion

Since the mid-twentieth century to today, numerous animal [53–60] and human studies [2, 26, 27, 40, 45–50, 61] have investigated the possible relationship between endodontic infections and DM. The endodontic variables analyzed in human studies have been the prevalence of RPLs, the prevalence of RCT, and the outcome of RCT, assessed as the percentage of RFT with or without RPLs, or as the prevalence of tooth extraction after nonsurgical RCT (NSRCT) [14]. Even though the results of these studies are not conclusive, available scientific evidence suggest an association between DM and a higher prevalence of RPLs, greater size of RPLs, and frequency of odontogenic infections [14, 19]. On the contrary, the existing data about the association of diabetes with the prevalence of RCT are sparse and inconclusive [14]. Finally, several studies have investigated the potential relationship between diabetes mellitus and the survival of root canal-treated teeth analyzing the prevalence of tooth extraction after NSRCT [41–43]. Three of these studies [17, 42, 43] provide a very significant OR ($p < 0.01$) for the contribution of diabetes to decreased retention of RFT. Four studies have provided

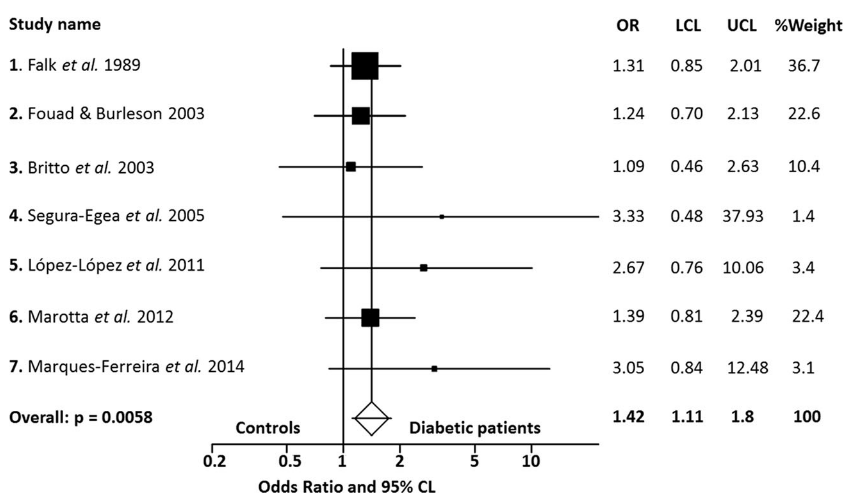

Fig. 3 Forest plot of odds ratios and 95 % confidence limits (CL) based on data from seven studies for the comparison of diabetic patients and control subjects with regard to the prevalence of RFT (root-filled teeth) with RPLs (radiolucent periapical lesions). The size of each rectangle is proportional to the total sample size for the diabetic/control comparison in that study. Overall estimate based on combined data from the seven studies. The size of the *diamond* is proportional to the percent weight of each study, i.e., the combined sample size for the diabetic/control comparison. The *solid line* indicates an odds ratio of 1.0. The *dashed line* indicates the overall odds ratio. *OR* odds ratio, *LCL* lower confidence level, *UCL* upper confidence level

longitudinal evaluation of the success of root canal treatment longitudinally [17, 18, 41, 45]. The Marending et al. [18] paper showed that diabetes was one of a number of medical problems that significantly influenced the outcomes. The three other studies [17, 41, 45] agreed that when the treatment of all teeth is considered, diabetes did not affect the outcome. The Fouad and Burleson study [45] showed that when only teeth with preoperative lesions are considered, and when controlling for a number of important confounding variables, teeth from diabetics were more significantly classified as uncertain or failing, at two or longer years after treatment.

The objective of this systematic review and meta-analysis has been to analyze the potential association between diabetes mellitus and the percentage of RFT with or without RPLs. The observational epidemiological studies involved were "outcomes" research, including one longitudinal study with two or more years of follow-up [45], level of evidence 2, and six cross-sectional studies [44, 46–50], level of evidence 3 [31]. The homogeneity of the seven studies (Breslow-Day = 4.63; df = 6; $p = 0.59$; and $I^2 = 0$ %; 95 % CI = 0 to 59 %) was high. Thus, the variations across studies were casual rather than due to heterogeneity.

The reasonable time frame of publication of the studies included in this review (1989 to 2014) reinforces the possibility of comparison, discarding important changes in dental concepts, materials, and/or treatments over time [62, 63]. The analysis of the study designs is also very important in a systematic review like this. However, in the present review, most of the included studies were cross-sectional studies. Cross-sectional studies demonstrate differences in the prevalence of PAP, but longitudinal studies could show differences between diabetic and control subjects regarding the healing process of the periapical pathosis.

Individually, none of the studies provides significant OR regarding the association of diabetes with the prevalence of RFT with periapical lesions. However, pooled OR provided by MH method, with fixed effects, was significant (OR = 1.42; 95 % CI = 1.11–1.80; $p = 0.006$) indicating that diabetes is associated to the prevalence of RFT with RPLs. It can be concluded that available scientific evidence supports the association between diabetes and persistent apical periodontitis. This result is in agreement with the studies showing that diabetic patients have delayed periapical repair and greater likelihood of RFT loss [17, 42, 43, 45].

The biological mechanisms linking periapical status of RFT and diabetes mellitus could be the following: (1) diabetes predisposes to chronic inflammation, (2) diabetes reduces tissue repair capacity, (3) diabetes impaired the immune response enhancing the susceptibility to infections, and (4) diabetes impaired bone turnover and delayed wound healing [14, 23, 64, 65]. In inflamed periapical tissues of endodontically treated teeth, diabetes could compromise immune response, upregulating periapical inflammation and altering bone turnover and wound healing, increasing the prevalence of apical periodontitis in RFT [14].

Considering that diabetes is the third most prevalent chronic medical condition among dental patients [66], endodontic providers should be aware of the relationship between the outcome of endodontic treatment and diabetes, should keep current data on the diabetic status of their patients, and should inform diabetic patients of the risks involved in endodontic therapy for them.

Conclusion

Available scientific evidence indicates that diabetes is significantly associated with higher prevalence of periapical radiolucencies in endodontically treated teeth. Well-designed prospective studies are required to further investigate the association between diabetes and RCT outcome and to definitively determine the precise increased risk of treatment failure in diabetic patients. However, at this time, diabetes should be recognized as an important putative pre-operative prognostic factor in endodontic treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Siqueira JRJF, Rôças IN (2014) Present status and future directions in endodontic microbiology. Endod Topics 30:3–22
2. Bender IB, Seltzer S (2003) Roentgenographic and direct observation of experimental lesions in bone: I. 1961. J Endod 29:702–706
3. Figdor D (2002) Apical periodontitis: a very prevalent problem. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 94:651–652
4. Buckley M, Spångberg LS (1995) The prevalence and technical quality of endodontic treatment in an American subpopulation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 79:92–100
5. Chen CY, Hasselgren G, Serman N, Elkind MS, Desvarieux M, Engebretson SP (2007) Prevalence and quality of endodontic treatment in the Northern Manhattan elderly. J Endod 33:230–234
6. Caplan DJ, Chasen JB, Krall EA, et al. (2006) Lesions of endodontic origin and risk of coronary heart disease. J Dent Res 85:996–1000

7. Jiménez-Pinzón A, Segura-Egea JJ, Poyato M, Velasco E, Ríos JV (2004) Prevalence of apical periodontitis and frequency of root-filled teeth in an adult Spanish population. Int Endod J 37:167–173
8. López-López J, Jané-Salas E, Estrugo-Devesa A, et al. (2012) Frequency and distribution of root filled teeth and apical periodontitis in an adult population of Barcelona, Spain. Int Dental J 62:40–46
9. Eriksen HM (1998) Epidemiology of apical periodontitis. In: Ørstavik D, Pitt Ford TR (eds) Essential Endodontology. Prevention and treatment of apical periodontitis. Blackwell Science, London, pp. pp.179–pp.191
10. Ørstavik D, Pitt Ford T (2007) Apical periodontitis: microbial infection and host responses. In: Ørstavik D, Pitt Ford TR (eds) Essential Endodontology. Prevention and treatment of apical periodontitis, 2nd edn. Wiley-Blackwell, London, UK, pp. pp:179–pp:191
11. Winward BJ, Yaccino JM, Kirkpatrick TC (2014) A panoramic survey of air force basic trainees: how research translates into clinical practice. J Endod 40:1332–1337
12. Sundqvist G, Figdor D (1998) Endodontic treatment of apical periodontitis. In: Ørstavik D, Pitt Ford TR (eds) Essential Endodontology. Blackwell, Oxford, pp. pp:242–pp:277
13. Nair PNR (2006) On the causes of persistent apical periodontitis: a review. Int Endod J 39:249–281
14. Segura-Egea JJ, Martín-González J, Castellanos-Cosano L (2015) Endodontic medicine: connections between apical periodontitis and systemic diseases. Int Endod J 48:933–951
15. Love RM, Firth N (2009) Histopathological profile of surgically removed persistent periapical radiolucent lesions of endodontic origin. Int Endod J 42:198–202
16. Koivisto T, Bowles WR, Rohrer M (2012) Frequency and distribution of radiolucent jaw lesions: a retrospective analysis of 9723 cases. J Endod 38:729–732
17. Ng YL, Mann V, Gulabivala K (2011) A prospective study of the factors affecting outcomes of non-surgical root canal treatment: part 2: tooth survival. Int Endod J 44:610–625
18. Marending M, Peters OA, Zehnder M (2005) Factors affecting the outcome of orthograde root canal therapy in a general dentistry hospital practice. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99:119–124
19. Segura-Egea JJ, Castellanos-Cosano L, Machuca G, et al. (2012) Diabetes mellitus, periapical inflammation and endodontic treatment outcome. Med Oral Patol Oral Cir Bucal 17:e356–e361
20. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2000) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 23(Suppl.1):S4–S19
21. Mealey BL, Oates TW (2006) American Academy of Periodontology. Diabetes mellitus and periodontal diseases. J Periodon 77:1289–1303
22. Iacopino AM (2001) Periodontitis and diabetes interrelationships: role of inflammation. Ann Periodontol 6:125–137
23. Fouad AF, Huang GT-J (2015) Chapter 9: inflammation and Immunological response, in Ingle's Endodontics 7th Ed. Rotstein I. Editor (in press)
24. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B (1997) Impaired leucocyte functions in diabetic patients. Diabetes Med 14:29–34
25. Salvi GE, Carollo-Bittel B, Lang NP (2008) Effects of diabetes mellitus on periodontal and peri-implant conditions: update on associations and risks. J Clin Periodontol 35(8 Suppl):398–409
26. Bender IB, Seltzer S, Freedland J (1963) The relationship of systemic diseases to endodontic failures and treatment procedures. Oral Surg Oral Med Oral Pathol 16:1102–1115
27. Bender IB, Bender AB (2003) Diabetes mellitus and the dental pulp. J Endod 29:383–389
28. Stroup DF, Berlin JA, Morton SC, et al. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. J Am Med Assoc 283:2008–2012
29. Bader JD (2004) Systematic reviews and their implications for dental practice. Tex Dent J 121:380–387
30. Pak JG, Fayazi S, White SN (2012) Prevalence of periapical radiolucency and root canal treatment: a systematic review of cross-sectional studies. J Endod 38:1170–1176
31. Centre for Evidence Based Medicine (2005) Critical Appraisal for therapy articles. University of Oxford. Medical Sciences Division. Available at: http://www.cebm.net/wp-content/uploads/2014/04/RCT_Appraisal_sheets_2005_English.doc
32. Higgins JPT, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558
33. L'Abbé KA, Detsky AS, O'Rourke K (1987) Meta-analysis in clinical research. Ann Intern Med 107:224–233
34. Lewis S, Clarke M (2001) Forest plots: trying to see the woods and the trees. BMJ 322:479–480
35. Freemantle N (2000) CD: StatsDirect—statistical software for medical research in the 21st century. Bmj 321(7275):1536. http://www.statsdirect.com/
36. Mohamed HG, Idris SB, Ahmed MF, et al. (2013) Association between oral health status and type 2 diabetes mellitus among Sudanese adults: a matched case-control study. PLoS One 12: e82158
37. Lin PY, Huang SH, Chang HJ, Chi LY (2014) The effect of rubber dam usage on the survival rate of teeth receiving initial root canal treatment: a nationwide population-based study. J Endod 40:1733–1737
38. Iqbal MK, Kim S (2008) A review of factors influencing treatment planning decisions of single-tooth implants versus preserving natural teeth with nonsurgical endodontic therapy. J Endod 34:519–529
39. Ilgüy M, Ilgüy D, Bayirli G (2007) Dental lesions in adult diabetic patients. N Y State Dent J 73:58–60
40. Ueta E, Osaki T, Yoneda K, Yamamoto T (1993) Prevalence of diabetes mellitus in odontogenic infections and oral candidiasis: an analysis of neutrophil suppression. J Oral Pathol Med 22:168–174
41. Doyle SL, Hodges JS, Pesun IJ, Baisden MK, Bowles WR (2007) Factors affecting outcomes for single-tooth implants and endodontic restorations. J Endod 33:399–402
42. Wang CH, Chueh LH, Chen SC, Feng YC, Hsiao CK, Chiang CP (2011) Impact of diabetes mellitus, hypertension, and coronary artery disease on tooth extraction after nonsurgical endodontic treatment. J Endod 37:1–5
43. Mindiola MJ, Mickel AK, Sami C, Jones JJ, Lalumandier JA, Nelson SS (2006) Endodontic treatment in an American Indian population: a 10-year retrospective study. J Endod 32:828–832
44. Falk H, Hugoson A, Thorstensson H (1989) Number of teeth, prevalence of caries and periapical lesions in insulin-dependent diabetics. Scand J Dental Res 97:198–206
45. Fouad AF, Burleson J (2003) The effect of diabetes mellitus on endodontic treatment outcome: data from an electronic patient record. JADA 134:43–51
46. Britto LR, Katz J, Guelmann M, Heft M (2003) Periradicular radiographic assessment in diabetic and control individuals. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96:449–452
47. Segura-Egea JJ, Jiménez-Pinzón A, Ríos-Santos JV, Velasco-Ortega E, Cisneros-Cabello R, Poyato-Ferrera M (2005) High prevalence of apical periodontitis amongst type 2 diabetic patients. Int Endod J 38:564–569
48. López-López J, Jané-Salas E, Estrugo-Devesa A, et al. (2011) Periapical and endodontic status of type 2 diabetic patients in Catalonia, Spain: a cross-sectional study. J Endod 37:598–601

49. Marotta PS, Fontes TV, Armada L, Lima KC, Rôças IN, Siqueira JF Jr (2012) Type 2 diabetes mellitus and the prevalence of apical periodontitis and endodontic treatment in an adult Brazilian population. J Endod 38:297–300
50. Marques-Ferreira M, Carrilho E, Carrilho F (2014) Diabetes mellitus and its influence on the success of endodontic treatment: a retrospective clinical study. Act Med Portuguesa 27:15–22
51. Strindberg LZ (1956) The dependence of the results of pulp therapy on certain factors. Acta Odontol Scand 14(suppl 21):1–75
52. Ørstavik D, Kerekes K, Eriksen HM (1986) The periapical index: a scoring system for radiographic assessment of apical periodontitis. Endod Dent Traumatol 2:20–34
53. Kohsaka T, Kumazawa M, Yamasaki M, Nakamura H (1996) Periapical lesions in rats with streptozotocin-induced diabetes. J Endod 22:418–421
54. Fouad A, Barry J, Russo J, Radolf J, Zhu Q (2002) Periapical lesion progression with controlled microbial inoculation in a type I diabetic mouse model. J Endod 28:8–16
55. Bain JL, Lester SR, Henry WD, Naftel JP, Johnson RB (2009) Effects of induced periapical abscesses on rat pregnancy outcomes. Arch Oral Biol 54:162–171
56. Kodama Y, Matsuura M, Sano T, et al. (2011) Diabetes enhances dental caries and apical periodontitis in caries-susceptible WBN/KobSlc rats. Comp Med 61:53–59
57. Astolphi RD, Curbete MM, Colombo NH, et al. (2013) Periapical lesions decrease insulin signal and cause insulin resistance. J Endod 39:648–652
58. Cintra LT, da Silva Facundo AC, Azuma MM, et al. (2013) Pulpal and periodontal diseases increase triglyceride levels in diabetic rats. Clin Oral Invest 17:1595–1599
59. Cintra LT, da Silva Facundo AC, Prieto AK, et al. (2014) Blood profile and histology in oral infections associated with diabetes. J Endod 40:1139–1144
60. Pereira RF, de Oliveira da Mota MS, de Lima Coutinho Mattera MS, et al. (2015) Periapical lesions decrease Akt serine phosphorylation and plasma membrane GLUT4 content in rat skeletal muscle. Clin Oral Investig Nov 23. (Epub ahead of print)
61. Sánchez-Domínguez B, López-López J, Jané-Salas E, Castellanos-Cosano L, Velasco-Ortega E, Segura-Egea JJ (2015) Glycated haemoglobin levels and prevalence of apical periodontitis in type 2 diabetic patients. J Endod 41:601–606
62. Patel S (2009) New dimensions in endodontic imaging: part 2. Cone beam computed tomography. Int Endod J 42:463–475
63. Walter C, Rodriguez FR, Taner B, Hecker H, Weiger R (2012) Association of tobacco use and periapical pathosis – a systematic review. Int Endod J 45:1065–1073
64. Garber SE, Shabahang S, Escher AP, Torabinejad M (2009) The effect of hyperglycemia on pulpal healing in rats. J Endod 35:60–62
65. Gurav AN (2013) Advanced glycation end products: a link between periodontitis and diabetes mellitus? Curr Diabetes Rev 9:355–361
66. Dhanuthai K, Sappayatosok K, Bijaphala P, Kulvitit S, Sereerat T (2009) Prevalence of medically compromised conditions in dental patients. Med Oral Patol Oral Cir Bucal 14:e287–e291