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REVIEW ARTICLE

Does diabetes increase the risk of periodontitis? A systematic review and meta-regression analysis of longitudinal prospective studies

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Abstract

Aim Even though the association between diabetes and periodontitis is taken for granted, results on this association are conflicting within the literature. This systematic review assessed whether poorly controlled diabetes was associated with periodontitis onset or progression.

Methods Electronic searches were performed in PubMed, Scopus and Embase databases. Hand search was carried out in the reference list of all articles included. Gray literature was investigated with a Google Scholar search. Prospective longitudinal studies on the association between diabetes and periodontitis were considered for this review. Studies should have presented at least two measurements of periodontal conditions over time. Data on study design, crude and adjusted estimates were collected. We used meta-analysis to estimate the pooled effect of hyperglycemia in people with diabetes on periodontitis onset or progression. Meta-regression and subgroup analyses were employed to investigate potential sources of heterogeneity between studies.

Results Thirteen studies matched the inclusion criteria, comprising 49,262 individuals, including 3197 diagnosed with diabetes. Meta-analyses of adjusted estimates showed that diabetes increased the risk of incidence or progression of periodontitis by 86% (RR 1.86 [95% CI 1.3–2.8]). However, there is scarce information on the association between diabetes and periodontal destruction.

Conclusions This study provides evidence that diabetes is associated with increased risk of periodontitis onset and progression in adults. Upcoming prospective longitudinal studies ought to overcome methodological caveats identified in this review.

Keywords Hyperglycemia · Periodontal diseases · Longitudinal studies · Meta-regression · Meta-analyses · Cohort studies

Introduction

Diabetes mellitus encompasses a set of metabolic disorders characterized by defects in insulin action, secretion or both causing a hyperglycemic state [1]. Diabetes mellitus is a public health problem with epidemic proportions intimately related to the rising number of overweight and obese individuals, and the current projection is over 640 million people with diabetes by 2040 [2]. Considering the current numbers and the projections [2], it is estimated that 9 million people develop diabetes each year and that up to 80% of the population with diabetes die because of its consequences [3, 4]. Secondary complications of uncontrolled glucose in individuals with diabetes comprise nephropathy, retinopathy with possible blindness [5], neuropathy, macro- and microvascular diseases [6, 7] and delayed tissue healing [8].

Periodontitis is characterized by the inflammatory destruction of the tooth-supporting tissues, including

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cement, periodontal ligament and alveolar bone, and has been listed as the sixth major complication of individuals with diabetes [9]. Even though periodontal inflammation is supposed to be triggered by bacteria, most of the damage is a consequence of a disproportionate and unbalanced host response to the biofilm presence in connection with the inability of the host to resolve the inflammatory process [10, 11]. Consequently, periodontitis can lead to tooth loss, loss of chewing ability, poor nutrition and poorer quality of life [12]. In the overall population, severe periodontitis is the sixth most prevalent chronic disease, with rising incidence ratios due to increase in life expectancy and more teeth retained across the lifespan [13].

It is biologically plausible to link diabetes with periodontitis onset and progression. There are several reasonable mechanisms explaining their connection. For example, chronic immune system activation with increased levels of circulating leukocytes and pro-inflammatory markers has been reported in people with inadequately controlled diabetes [14]. This sustained systemic low-grade inflammation could promote alterations in the physiology of the periodontium causing its breakdown [15]. Furthermore, hyperglycemia seems to alter systemic and gingival microvasculature, leading to increased inflammation of the periodontal tissues [16].

Even though several cross-sectional studies have reported an association between diabetes and periodontitis, longitudinal prospective studies with adequate design and data to infer temporal and causal relationships are scarce. Most of the methodological limitations arise from short follow-up period to allow disease occurrence, too small sample size, dropouts, and the use of convenience samples [17]. A previous systematic review, mostly based on cross-sectional studies, demonstrated a higher prevalence of periodontitis in subjects with diagnosis of diabetes [18]. Evidence from cross-sectional studies hinders the analysis of causal relationships, which is possible using prospective longitudinal studies. However, since several papers with longitudinal prospective design were published after the aforementioned systematic review, the consistency of the prospective evidence has not been appraised and summarized. Additionally, the magnitude of the effect of poorly controlled diabetes on periodontitis incidence or progression was never measured. This study aimed to systematically appraise the evidence originated from prospective longitudinal studies investigating the relationship between diabetes mellitus and periodontitis.

Materials and methods

This study was conducted following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [19]. This review was registered with the Joanna Briggs Institute database [20].

Review question

Does inadequately controlled diabetes mellitus increase the risk of periodontitis onset and progression?

Eligibility criteria

Prospective longitudinal studies investigating the association between diabetes and periodontitis were selected if they presented at least two measurements of periodontal conditions over time (e.g. attachment level—AL, periodontal probing depth—PPD or alveolar bone height—ABL). Data on periodontitis onset or progression were collected as designated by the authors. Reports on periodontal healing after periodontal treatment (initial and supportive therapy) were excluded. In addition, literature reviews, case–control studies, cross-sectional studies, retrospective longitudinal studies, case reports, comments or conference abstracts were also eliminated. In the case of multiple publications of the same population, the report with the longest follow-up was included.

Search strategy

Two independent investigators (GGN and FRML) searched in PubMed, Embase and Scopus databases for prospective studies reporting associations between diabetes and periodontitis. The initial search was elaborated on PubMed using the strategy: (((((((“Periodontal Diseases”[Mesh]) OR “Periodontal Diseases”[all]) OR “Chronic Periodontitis”[Mesh]) OR “Chronic Periodontitis”[all]) OR “Periodontitis”[Mesh]) OR “Periodontitis”[all])) AND ((((((((“Diabetes Mellitus”[Mesh]) OR “Diabetes Mellitus”[all]) OR “Insulin Resistance”[Mesh]) OR “Insulin Resistance”[all]) OR “Glucose Intolerance”[Mesh]) OR “Glucose Intolerance”[all]) OR “Metabolic Control”[all]) OR “Impaired Glycaemia”[all]) OR “Glycated Hemoglobin”[all]) OR “Glycated Haemoglobin”[all])). We added the following specific filter for restricting the search to longitudinal prospective studies: (“Cohort Studies”[all]) OR “Longitudinal Studies”[all]) OR “Longitudinal”[all]) OR “Cohort”[all]) OR “Follow-up Studies”[all]) OR “Follow-up”[all]) OR “Prospective Studies”[all]) OR “Prospective”[all]). The search included articles published up to and including May 2017 without date or language restriction.

Study selection

We combined the results and excluded duplicates using the EndNote X8.01 software (Thomson Reuters, New York, NY, USA). According to the eligibility criteria, titles and

abstracts were assessed independently by two authors (GGN and FRML), then the lists were compared, and disagreements were solved by consensus. The same two reviewers assessed the full-text of studies with potential to be included in the review followed by comparison of their lists, and disagreement was resolved by discussion. References of the remaining manuscripts were hand-searched for additional articles. Gray literature was examined by inspecting the first 200 items of a Google Scholar search.

Data extraction and quality assessment

Information extracted from the studies included: author and year, sample size and main characteristics, geographic location of the study, follow-up period, definition and criteria used to evaluate periodontitis and diabetes, and criteria used to evaluate changes in periodontal condition. We also collected data on the analytical approach employed, crude and adjusted results, and confounders included in the analysis. Data were independently extracted by the same two reviewers and compared, and in case of disagreement, discussions were held to reach a consensus. When more than one category of periodontitis or diabetes was reported, only the most extreme category of comparison was included in the meta-analysis. Manuscript quality was independently assessed using the nine-star Newcastle–Ottawa scale (NOS) for cohort studies [21]. Lists were compared and a consensus reached.

Data synthesis and analysis

Statistical analyses were performed in Stata 14.2 (StataCorp, College Station, TX, USA). Fixed- and random-effects models were fitted to the data to obtain a combined relative risk estimate. In the presence of significant or considerable heterogeneity ($I^2 > 50\%$ or Chi-square P value < 0.05) [22], the random-effect model was preferred since it considers both between-study and within-study variability. Estimates reported in odds ratio (OR) were converted into relative risk (RR) when possible [23]. In the absence of RR or OR measures, when the study presented the necessary data or the authors provided the data after contact, RR estimates were calculated. Separate models were used for analyzing crude and adjusted results, but only the pooled model of adjusted results was further analyzed. Studies with both estimates were included in both models.

Meta-regression including subgroup analyses were performed to investigate potential sources of between-study variability. For analysis, the characteristics of the studies were combined accordingly: socioeconomic status of the country where the study was conducted (high-income/low-middle-income) [24]; geographic location (Americas/Europe/Asia-Oceania); sample size (< 500/≥ 500 people); follow-up period (< 5 years/≥ 5 years); criteria for diabetes diagnosis (fasting plasma glucose—FPG/HbA_{1c} or HOMA/self-reported); periodontal examination protocol (full mouth/partial mouth or index teeth/radiographic assessment/self-reported); criteria for periodontal diagnosis (AL/PPD/ABL); number of sites/teeth used to evaluate incidence or progression of periodontitis—extent (1/≥ 2); amount of periodontal destruction used to evaluate incidence or progression of periodontitis—severity (1–2 mm/≥ 3 mm). One at a time, each study characteristic was entered as covariate in the meta-regression model. Thus, the adjusted R^2 of each bivariate model was taken as the percentage of heterogeneity explained by the covariate. Subgroups analysis was performed according to the study characteristics that explained some heterogeneity. Small-study effect was tested using the Egger test and contour-enhanced funnel-plot. This plot details statistical significance on a funnel-plot, indicating the level of significance of each estimate pooled in the meta-analysis. Sensitivity analysis was performed by omitting one estimate at a time from the meta-estimate model.

Results

Altogether, 1787 studies were identified, and after removal of duplicates and title/abstract screening, the full-text document of 23 studies was obtained and assessed. Thirteen studies matched the inclusion criteria, comprising 49,262 participants, including 3197 diagnosed with diabetes and/or metabolic syndrome with a diabetes component (Fig. 1). Main reasons for study exclusion after full-text assessment are shown in Appendix 1. Data for inclusion in meta-analysis were available only for six studies.

Follow-up mean was approximately 4.8 years, ranging from 8 months to 20 years, and five studies presented follow-up shorter than 4 years [25–29]. Two studies [30, 31] were

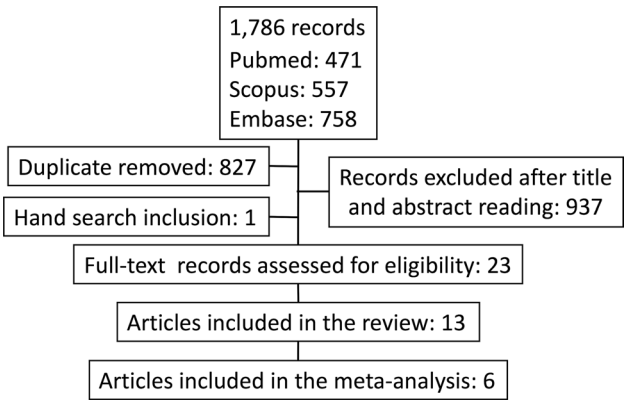

Fig. 1 Flowchart diagram of studies selection for the systematic review

conducted in middle-income countries, while the remaining in high-income countries. The majority of the studies used the absence of diabetes mellitus diagnostic group as reference, while in two studies the reference category was presenting controlled diabetes [28, 30], because the sample comprised diabetic adults only. Diabetes mellitus presence was clinically determined except in one study [32], in which self-reported information was used. Among the clinical measures, HbA_{1c} was used in seven studies [25, 27, 28, 30, 33–35] and FPG in two studies [36, 37], and three investigations just reported that the participants were referred from a diabetes service with previous diagnostic of diabetes mellitus [26, 29, 31]. Self-reported questionnaire [32] and detection of proximal bone loss in radiographs [35] were used in one study each to determine the periodontitis presence. Among the eleven studies with clinical examination, the whole mouth was preferred except for two studies where index teeth were chosen [34, 37]. A combination of AL and PPD was used in four studies [25, 29, 31, 33], AL in two studies [26, 27], PPD only in one study [30] and development of a Community Periodontal Index (CPI) score ≥ 3 in four [28, 34, 36, 37]. A large variation in the number of variables chosen for analysis adjustment was observed, with four studies not presenting adjusted estimates [26, 29–31]. The key characteristics of the studies included in the systematic review are shown in Table 1.

Using crude data from meta-analysis, diabetic subjects present a 70% higher incidence or progression risk of periodontitis than non-diabetics (RR 1.70; 95% CI 1.3–2.3). Even though heterogeneity between studies was high (I^2 89.7%; Chi square < 0.001), after adjustment estimates showed that diabetes increased the risk of incidence or progression of periodontitis by 86% (RR 1.86 [95% CI 1.3–2.8]) (Fig. 2).

The relatively small number of studies with sufficient data to be included in meta-regression analysis precluded the exploration of multiple variables as possible sources of heterogeneity. The criteria used for periodontitis and diabetes assessment and the sample size explained 22.7, 12.8 and 25.2% of the variability between studies, respectively (Table 2). Appendix 2 displays the subgroup analysis considering the criteria used for periodontitis assessment. Appendix 3 displays the quality assessment of each study according to the NOS scale for cohort studies. Scores were shown according to each of the three domains of the instrument (selection, comparability and outcome).

The small number of studies included in the meta-analysis precluded also the statistical and the visual assessments for small-study effect (Appendix 4). The Egger's test has low statistical power when sample size is lower than 20 studies [38]; additionally, the interpretation of a funnel-plot with a small number of studies could misrepresent the actual findings. The removal of any study from meta-regression did not affect the pooled RR according to the sensitivity analysis (Fig. 3).

Discussion

All prospective studies included in this systematic review reported positive associations between high levels of glucose and periodontitis onset and progression. Our data showed an 86% increase in the incidence or progression risk of having periodontitis among inadequately controlled diabetes compared with non-diabetics or well-controlled diabetics. The assumption that diabetes mellitus is a risk factor for periodontitis has largely been based on results from cross-sectional and animal studies, with scarce longitudinal prospective data. The uniqueness of this review was the idea to pool together diabetes effect on periodontitis using only prospective longitudinal studies to assert the temporality of the effects. Despite the significant association obtained in the meta-analysis, this estimate should be cautiously interpreted, due to methodological aspects of the studies included in the review.

Our results demonstrated that some methodological aspects have a direct influence on this association. Results of the meta-regression and subgroup analyses revealed that the sample size explained approximately 25% of the variability between studies (Table 2). As corroborated by previous studies, small sample size may overestimate the association between presumed exposure and outcome [39, 40]. In addition, one may also speculate whether the sample size may be a proxy of the convenience of the sample. Indeed, among the studies included in our review, we could observe that most of the small studies did not present a representative sample (e.g., sample chosen according to the researcher interest). Therefore, the evidence on the association between diabetes and periodontitis originated from large population-based studies with representative samples is scant.

Furthermore, the use of self-reported information about having been told previously to have had diabetes or to use or have used medication to control diabetes resulted in lower RR compared to results from blood tests (HbA_{1c} or FPG), explaining approximately 13% of the heterogeneity between studies (Table 2). Despite the applicability of self-reported information on the assessment of general health conditions, this is a common source of variability in meta-analysis [41]. However, the omission of such an estimate from the pooled analysis would not nullify our results (Fig. 3).

One point that should be critically examined is the criteria defined by the authors to determine the presence of periodontitis. In the meta-regression analysis, it explained 22.7% of the heterogeneity between studies (Table 2). Even though clinical attachment level is the gold-standard measurement to detect periodontitis progression, half of the studies included

Table 1 Main characteristics of the studies included in the systematic review

Author	Country	Sample	Follow-up	Criteria for diabetes diagnosis	Assessment of periodontitis	Criteria periodontitis diagnosis	Incidence of periodontitis	Analytical approach	Crude results	Adjusted results	Confounders/mediators	Observations
Bandyopadhyay et al. [25]	USA	*N* = 88 (all DM) Age = 55.6 ± 9 yrs (34–77) Male = 19 (21.6%)	1.9–4.1 yrs (mean 3.0 ± 0.4)	HbA_{1c} ≥ 7%	Clinical examination (6 sites/tooth) whole mouth	AL, PPD, BOP	≥ 2 mm worsening CAL, ≥ 2 mm increase in PPD	Multivariable logistic regression using generalized estimating equations	≥ 2 mm increase in PPD if baseline: PPD = 3 mm: OR 2.0 (1.2–3.3) PPD = 5 mm: OR 2.8 (1.5–5.1) PPD = 7 mm: OR 3.9 (1.7–8.7) ≥ 2 mm increase in CAL if baseline: PPD = 3 mm: OR 1.9 (1.2–3.1) PPD = 5 mm: OR 2.6 (1.3–5.1) PPD = 7 mm: OR 3.6 (1.4–8.9)	≥ 2 mm increase PPD if baseline: PPD = 3 mm: OR 2.0 (1.2–3.2) PPD = 5 mm: OR 2.8 (1.5–5.0) PPD = 7 mm: OR 3.8 (1.7–8.5) ≥ 2 mm increase CAL if baseline: PPD = 3 mm: OR 1.9 (1.2–3.1) PPD = 5 mm: OR 2.6 (1.4–5.1) PPD = 7 mm: OR 3.6 (1.5–9.1)	Smoking, PPD at baseline, age, BMI, molar tooth site, upper-jaw tooth site	The Gullah have a higher genetic risk for diabetes, with a 3.3 relative risk of diabetes to siblings, which exceeds that in many other communities
Chiu et al. [36]	Taiwan	*N* = 4387 (35 DM) Age = 35–44 yrs Male = 55 (44.0%) Low SES = 18 (14.4%) Smokers = 49 (39.2%)	5 yrs (mean 1.7 ± 1.0)	FPG ≥ 126 mg/dL	Clinical examination (6 sites/tooth) whole mouth	CPI	Development of CPI ≥ 3 after baseline	Cox proportional hazards regression model	HR 1.9 (1.3–2.9)	HR 2.0 (1.2–3.1)	Age, sex, betel quids chewing, cigarette smoking, alcohol drinking, waist size and triglyceride	
Cohen et al. [26]	USA	*N* = 39 (21 DM) Age = 27.6 ± 4.4 yrs (18–35) All female	2 yrs	Not clear (clinical examination)	Clinical examination whole mouth	AL	Change in mean AL values from baseline	Analysis of variance	AL (baseline and follow-up) Healthy: 0.7 ± 0.2 and 0.8 ± 0.2 mm Diabetes: 0.9 ± 0.2 and 1.2 ± 0.3 mm			

Table 1 (continued)

Author	Country	Sample	Follow-up	Criteria for diabetes diagnosis	Assessment of periodontitis	Criteria periodontitis diagnosis	Incidence of periodontitis	Analytical approach	Crude results	Adjusted results	Confounders/mediators	Observations
Demmer et al. [33]	Germany	$N = 2626$ (346 DM) Age = 46 ± 14 yrs Male = 1260 (48.0%)	5 yrs	$HbA_{1c} \geq 7\%$	Clinical examination (4 sites/tooth) half-mouth	AL, PPD	Increase in AL, in PPD or in the percentage of sites PPD ≥ 5 mm	Multivariable linear regression	–	Mean PPD change estimate 0.2 Mean AL change estimate 0.4	WHR, CRP, WBC, age, sex, education, smoking, dentist and physician visit	
Firatli [31]	Turkey	$N = 64$ (44 DM) Age = 12.2 ± 4.1 yrs	5 yrs	Not clear (clinical examination)	Clinical examination whole mouth	AL, PPD	Change in mean PPD and AL values from baseline	*t* test	PPD (baseline and follow-up) Healthy: 1.2 ± 0.2 and 1.2 ± 0.2 mm Diabetes: 1.7 ± 0.6 and 1.8 ± 0.6 mm AL (baseline and follow-up Healthy: 1.5 ± 0.6 and 1.66 ± 0.5 mm Diabetes: 2.4 ± 0.9 and 3.5 ± 1.0 mm			
Iwasaki et al. [27]	Japan	$N = 125$ (27 MetS) Age = 75 yrs Male = 55 (44.0%) Low SES = 18 (14.4%) Smokers = 49 (39.2%)	3 yrs	$HbA_{1c} \geq 6\%$ and/or the current use of medication	Clinical examination (6 sites/tooth) whole mouth	AL	Development ≥ 2 teeth with proximal AL ≥ 3 mm after baseline	Multivariable Poisson regression	RR 1.1 (0.5–2.4)	RR 0.9 (0.4–2.1)	Sex, income, education, smoking status, number of the teeth at baseline, mean AL at baseline, pattern of visits to a dentist, and brushing frequency	Main outcome was MetS individuals enrolled in the Niigata Study

Table 1 (continued)

Author	Country	Sample	Follow-up	Criteria for diabetes diagnosis	Assessment of periodontitis	Criteria periodontitis diagnosis	Incidence of periodontitis	Analytical approach	Crude results	Adjusted results	Confounders/mediators	Observations
Jimenez et al. [32]	USA	$N = 35,247$ (2285 DM) Age = 54.1 ± 0.7 yrs All male	20 yrs	Positive answer to presence of diabetes or classical symptoms of diabetes	Self-reported, validated in a subsample using bitewing radiographs	Positive answer to presence of periodontal disease	Develop periodontitis after baseline	Multivariable adjusted time-varying Cox models	Age-adjusted HR 1.4 (1.2–1.6)	HR 1.3 (1.1–1.5)	Age, race, BMI, fruit/vegetable intake, physical activity, alcohol consumption, dental profession, history of CVD and number of teeth at baseline	Male health professionals aged 40–75 years at baseline (1986)
Karikoski and Murtomaa [28]	Finland	$N = 115$ (all DM) Age = 44.6 ± 13.5 yrs (18–70) Male = 67 (58.3%)	2 yrs	$HbA_{1c} \geq 8.6\%$ uncontrolled diabetes	Clinical examination (whole mouth)	CPI	Development of CPI ≥ 3 after baseline or increase in the CPI score	Multivariable logistic regression	OR 0.8 (0.4–1.9)	OR 0.78 (0.3–2.1)	Age, sex, education, smoking, dental visit, brushing, interdental cleaning, calculus, CPI code 3 or 4, duration of diabetes, complications	Regular visitors of a Diabetes Clinic in Southwest Finland
Lee et al. [37]	South Korea	$N = 313$ (38 DM) Age = mean 72.3 yrs Male = 171 (42.9%)	Approx. 6 yrs	FPG ≥ 126 mg/dL	Clinical examination (index teeth)	CPI	Development of CPI ≥ 3 after baseline	Multivariable logistic regression	< 6 yrs of diabetes: OR 3.7 (1.0–13.1) ≥ 6 yrs of diabetes: OR 6.6 (2.9–15.0)	< 6 yrs of diabetes: OR 3.3 (0.9–11.9) ≥ 6 yrs of diabetes: OR 8.0 (3.3–19.3)	Age, sex	Main outcome was MetS
Morita et al. [34]	Japan	$N = 5856$ (150 DM) Age = 30–69 yrs Male = 4511 (77.0%)	5.0 yrs	$HbA_{1c} \geq 6.5\%$	Clinical examination (index teeth)	CPI	Development of PPD ≥ 4 mm and CPI ≥ 3 after baseline	Generalized linear model	RR 1.5 (1.3–1.7)	RR 1.17 (1.0–1.4)	BMI, smoking status, sex and age	

Table 1 (continued)

Author	Country	Sample	Follow-up	Criteria for diabetes diagnosis	Assessment of periodontitis	Criteria periodontitis diagnosis	Incidence of periodontitis	Analytical approach	Crude results	Adjusted results	Confounders/mediators	Observations
Novaes Jr. et al. [30]	Brazil	*N* = 11 (all DM) Age = 15–28 yrs Male = 3 (27.3%)	10 yrs	HbA_{1c} 8.4–9.6% controlled diabetes $HbA_{1c} \geq 10.7$ uncontrolled diabetes	Clinical examination (06 sites/tooth)	PPD, ABL in periapical	Change in mean PPD and ABL values from baseline	*t* test	Mean PPD between baseline and follow-up for upper buccal and palatal, lower buccal and lingual regions were 2.0 and 2.8, 2.0 and 2.6, 1.9 and 2.8, and 2.0 and 2.6 mm. Mean ABL between baseline and follow-up for upper buccal and palatal, lower buccal and lingual regions were 1.9 and 2.7, 1.7 and 2.4, 1.9 and 3.0, and 1.7 and 2.3 mm			
Sbordone et al. [29]	Italy	*N* = 32 (16 DM) Age = 9–17 yrs	3 yrs	Not clear (clinical examination)	Clinical examination (whole mouth)	PPD, AL	Change in mean PPD and AL values from baseline	Wilcoxon with the Bonferroni correction	PPD (mean difference) Healthy: 3.3 mm Diabetes: 2.8 mm AL (mean difference) Healthy: 3.3 mm Diabetes: 2.8 mm			
Taylor et al. [35]	USA	*N* = 359 (21 DM) Age = 23.45 yrs (15–57) Male = 146 (40.3%)	1.2–6.9 yrs (mean 2.3 yrs)	controlled DM: $HbA_{1c} \leq 8.9\%$ Uncontrolled DM: $HbA_{1c} \geq 9.0\%$	Panoramic radiographs	ABL	Change in ABL from baseline	Multivariable logistic regression analysis		OR 11.4 (2.5–53.3)	Age, time to follow-up, calculus	Gila River Indian Community

ABL alveolar bone loss, *AL* attachment level, *BMI* body mass index, *BOP* bleeding on probing, *CAL* clinical attachment loss, *CPI* Community Periodontal Index, *CRP* C-reactive protein, *CVD* cardiovascular disease, *DM* diabetes mellitus, *FPG* fasting plasma glucose, HbA_{1C} hemoglobin A_{1C}, *HR* hazard ratio, *MetS* metabolic syndrome, *OR* odds ratio, *PPD* pocket probing depth, *RR* risk ratio, *SES* socioeconomic status, *WBC* white blood cells, *WHR* waist/hip ratio, *yrs* years

in the meta-analysis used the Community Periodontal Index, which is based on the pocket probing depth, a poor proxy of changes in attachment level [42]. Despite the widespread use of CPI, it presents serious limitations on the diagnosis and monitoring of periodontitis [43]. Additionally, pocket probing depth can either under- or overestimate attachment loss depending on the background features of the study group under investigation [44]. Information on clinical attachment level is preferred, because it reflects cumulative periodontal destruction [45]. However, the only study using clinical attachment level to assess periodontitis was not able to find an association between diabetes and periodontal destruction. Therefore, it remains unclear whether diabetes is associated with long-term periodontal destruction.

Other concerns of this study should be also examined. Firstly, even though the role of diabetes in the risk of periodontitis is frequently taken for granted in the literature, we could find modest evidence on the topic. Furthermore, there is scarce evidence on the association between diabetes and incident cases of periodontitis, and most of the few studies investigating the incidence of periodontitis have used pocket probing depth (i.e., CPI) to define this disease. It is not possible to guarantee that all data in the literature regarding the association between diabetes and periodontitis were included in this review, since glucose levels might have been used as a covariate for analysis adjustment in studies not captured with our search strategy. Nevertheless, it is expected that the comprehensive search in three broad databases plus Google Scholar identified most of the prospective longitudinal studies available, if not all. Another concern is the pooling of results from studies with different methodological characteristics. Risk factor studies, most of the time, intend to address questions that cannot be answered with randomized studies, simply because they focus on exposures that cannot be controlled, and due to ethical consideration, participants cannot be exposed to harmful risk factors or just followed in the expectancy to disease to occur [46]. Well-conducted meta-analysis of observational studies is a valid method for assessing data, since it helps to identify reasons for variability in results among the studies and to identify areas in need of further exploration [46]. Moreover, a previous publication demonstrated that meta-analyses of observational studies usually present effect estimates comparable to those arising from randomized controlled trials meta-analysis [47]. Considering this information, we decided to supplement our appraisal with a meta-analysis.

Bearing in mind the high heterogeneity observed in meta-analysis of observational studies, we conducted meta-regression and subgroup analyses to identify the potential sources of variability between studies. This approach allowed us to identify differences in the estimates originating from studies using different criteria for periodontitis risk and progression, for instance, so as the need for more studies on the topic using clinical attachment level to diagnose and monitor periodontitis. Finally, since diabetes and periodontitis share common risk factors, and detrimental conditions usually coexist, it is not possible to rule out the residual effect of those conditions associated with both diabetes and periodontitis [48]. Even though eight studies in this review have adjusted their analysis for potential confounders, only three of them included at least age, sex, socioeconomic status, smoking and a weight-related variable in the analysis [49]. Additionally, one should bear in mind that despite the useful applicability of analytical adjustment, it might not be enough. Let us examine the case of smoking, for example. Even though some studies have presented results adjusted for smoking, one should remember the limitations of measuring the dimension of exposure to tobacco smoking. First, its assessment relies mainly on self-reported information of the current smoking status and not on smoking over time. Second, there is a social undesirability in reporting unhealthy conditions, and regardless of the truthfulness in reporting, the inclusion of a dichotomous variable in the analytical models does not rule out the effect of such a condition.

We should also examine the strengths of this study. The included prospective longitudinal studies represent the best sources of evidence available for determining the strength and the temporality of effects of the relationship between poorly controlled diabetes and periodontitis as well as the best attempt to identify sources of bias. A strong point of this review is the combined sample size of approximately 49,262 people including 3197 diagnosed with diabetes mellitus. Furthermore, in the meta-analysis, five out of the six included manuscripts received between six and eight points in the Newcastle–Ottawa quality assessment scale [21], and none could be classified as of high risk of bias. This way, data combination from these studies into a meta-analysis results in a more trustful estimate of the association between diabetes and periodontitis than the estimate of any of these studies alone [50].

It is biologically plausible to link diabetes with periodontitis onset and progression. Polymorphonuclear leukocytes (PMNs) permanence in tissues after an insult results in extensive tissue damage, frequently related to faster progression of chronic inflammatory diseases in general [51]. The formation of advanced glycation end products (AGEs) is a well-documented consequence of chronic hyperglycemia [8]. PMNs, monocytes and macrophages express the AGE receptor and produce excessive superoxide, interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α, resulting in tissue destruction [52, 53]. The elevated prolonged inflammation process induces high proportions of apoptotic cells, resulting in periodontitis [54]. Moreover, since fibroblasts go into apoptosis by the action of AGEs and pro-inflammatory

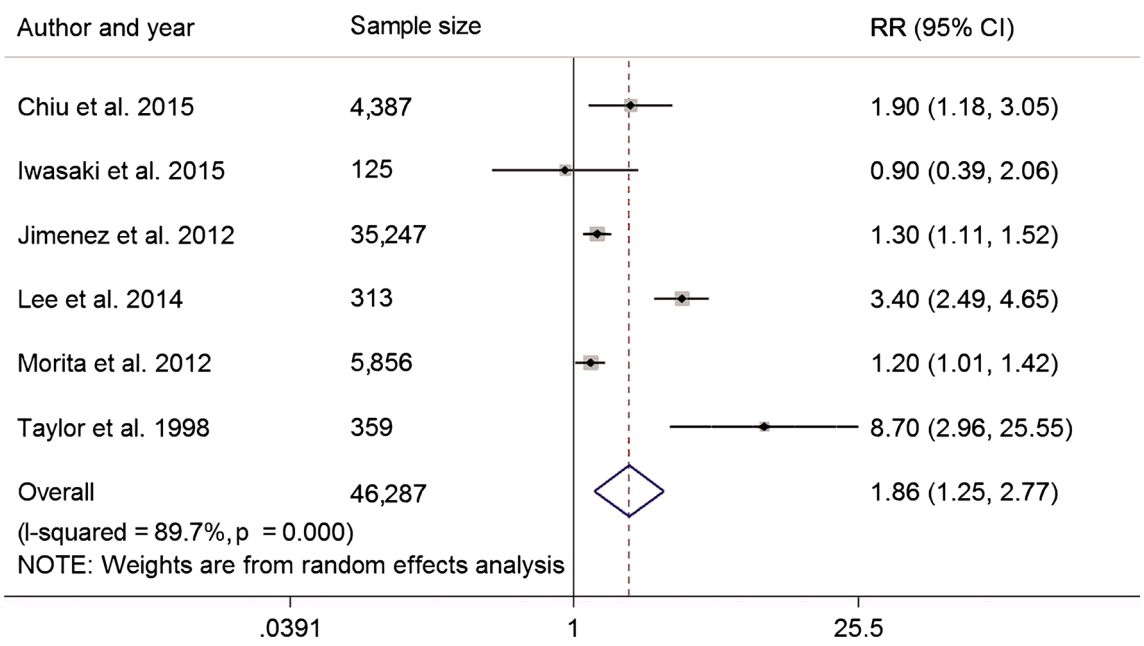

Fig. 2 Pooled effect of inadequately controlled diabetes mellitus on periodontitis. Data are presented as relative risk (RR) for each study (boxes), 95% CIs (horizontal lines) and summary as RR with 95% CI (diamond)

cytokines, periodontal tissues healing is compromised [52]. At the same time, inadequately controlled diabetes mellitus is known by the high formation of reactive oxygen species (ROS), even in unstimulated cells, which may directly injure vital structures, the cell membrane, and cause cell necrosis or apoptosis in both connective and bone tissues [52, 53]. This hyper-responsive phenotype of diabetic inflammatory cells can be reversed with pharmacological AGE receptor blockage or by the reduction of the number of AGE receptor ligands through hyperglycemia control [55]. Additionally, diabetes may cause microvascular pathological alterations in the gingiva, which in turn lead to increased periodontal inflammation. Thus, it is suggested that uncontrolled hyperglycemia may explain exacerbated gingival hemorrhaging [16].

Table 2 Meta-regression results and highest sources of heterogeneity

	Number of estimates	Risk ratio	95% CI	Adjusted R^2 (%)
Periodontitis criteria				22.7
Community Periodontal Index (CPI)	3	2.0	1.0–4.0	
Attachment level	1	0.9	0.4–2.1	
Radiographic bone loss	1	3.1	0.5–19.9	
Self-reported	1	1.3	1.1–1.5	
Diabetes diagnosis				12.8
HbA_{1c}/FPG	5	2.2	1.6–3.9	
Self-reported	1	1.3	1.1–1.5	
Sample size				25.2
Less than 500	3	2.9	1.1–8.1	
500 and beyond	3	1.3	1.1–1.5	

Persistent inflammatory conditions associated with diabetes mellitus significantly boost the pro-inflammatory activity and infiltration of PMNs into infected sites [51], and it is hypothesized whether the same happens in periodontitis sites [56]. The exchange of PMNs from animals with systemic inflammation to healthy ones, and vice versa, demonstrated that PMNs and tissue environment are altered during chronic inflammation [51]. It is suggested that when individuals with systemic inflammation are exposed de novo to a bacterial infection, the immune response seems even more exaggerated [51]. Thus, it is possible to extrapolate that recurrent exposure of uncontrolled diabetes mellitus individuals to periodontopathogenic bacteria will lead to or accelerate the destruction of periodontal tissues.

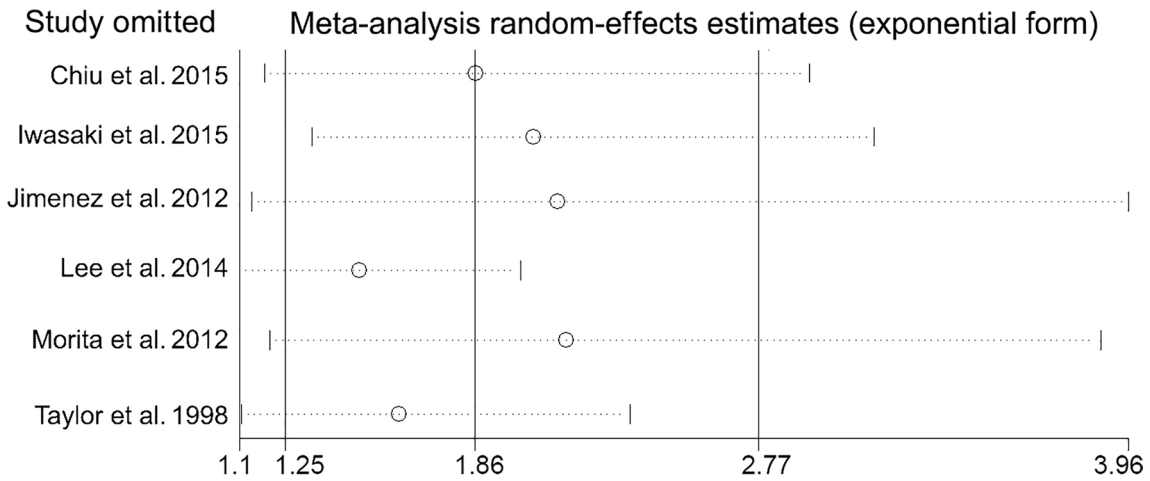

Fig. 3 Sensitivity analysis demonstrating the influence of each study in the pooled effect of uncontrolled diabetes mellitus on the risk and progression of periodontitis. Data are presented as new overall relative risk for each study omission (circles) and 95% CI (horizontal lines)

Taken together, our findings show that diabetes is associated with increased risk of periodontitis onset and progression. Even though the role of diabetes in the risk of periodontitis is taken for granted in the literature, there are several ways in which the fundament of this knowledge can improve. Upcoming prospective longitudinal studies ought to overcome methodological caveats identified in our review, like scarce information on periodontal destruction and small sample sizes. Furthermore, future studies should estimate the cluster effect of common risk factors to determine their combined effect with blood glucose level on periodontitis onset and progression.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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

Informed consent Not applicable.

Appendix 1

See Table 3.

Table 3 Excluded articles and main reason for exclusion

Study	Reason for exclusion
Seppälä et al. 1993 [57]	Follow-up to analyze the effect of periodontal treatment
Seppälä & Ainamo 1994 [58]	Follow-up to analyze the effect of periodontal treatment
Novaes Jr et al. 1996 [59]	Detection of bacteria species according to pocket depth
Taylor et al. 1998 [60]	Sample included in another manuscript selected for this review
Thomson et al. 2004 [61]	Lack of data for the six participants with diabetes
Morita et al. 2011 [62]	Sample included in another manuscript selected for this review
Timonen et al. 2013 [63]	Participants with diabetes were excluded in the analysis
Knight et al. 2015 [64]	Collected data on periodontal disease and diabetes only once
Chang et al. 2016 [65]	Effect of periodontal disease and diabetes on pancreatic cancer
Shearer et al. 2017 [66]	Effect of periodontal disease on HbA_{1c} results

Appendix 2

See Fig. 4.

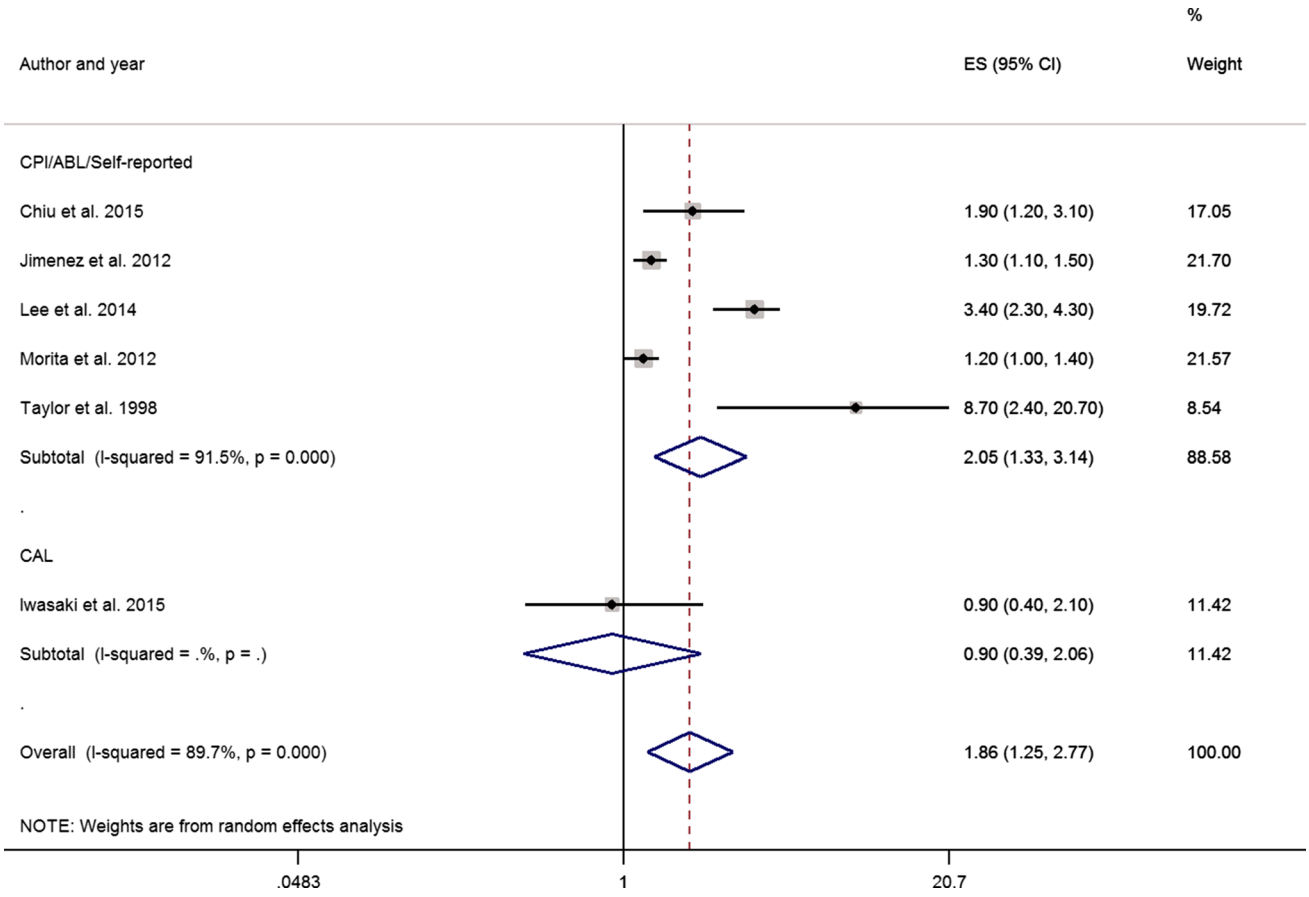

Fig. 4 Subgroup analysis of the pooled estimate by the criteria used for periodontitis assessment. Data are presented as relative risk (RR) for each study (boxes), 95% CIs (horizontal lines) and summary as RR with 95% CI (diamond)

Appendix 3

See Fig. 5.

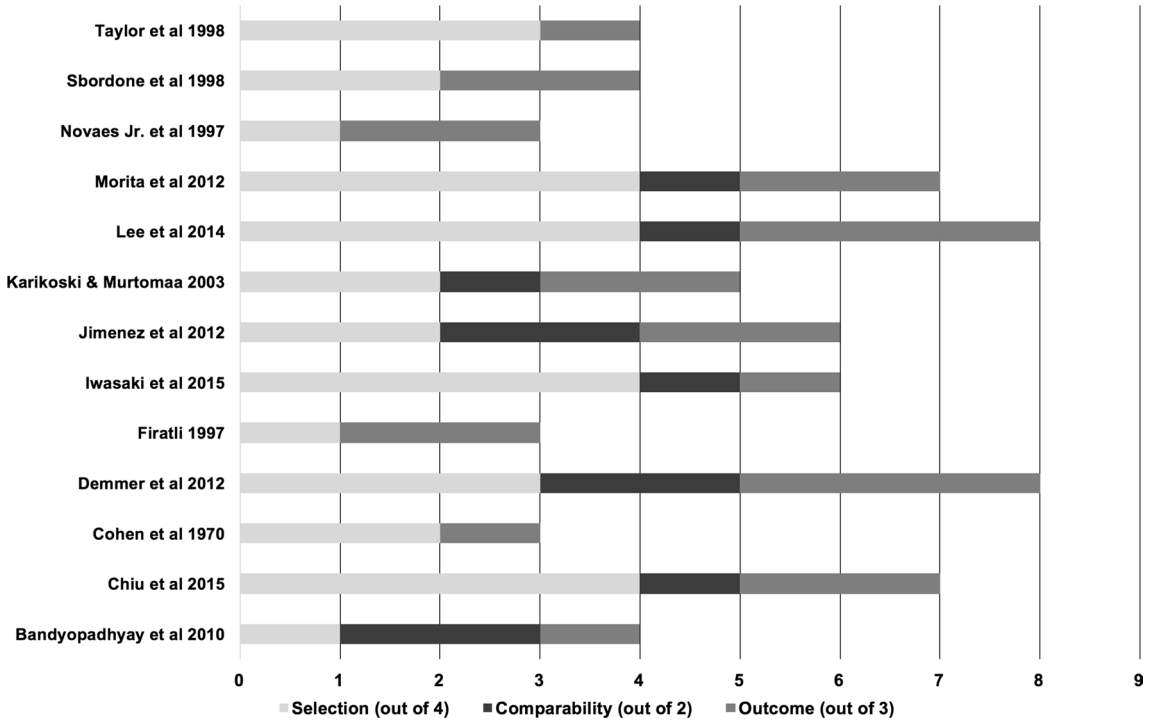

Fig. 5 Quality assessment of the studies according to the Newcastle–Ottawa scale for cohort studies. Scores are displayed according to each of the three domains of the instrument: selection, comparability and outcome

Appendix 4

See Fig. 6.

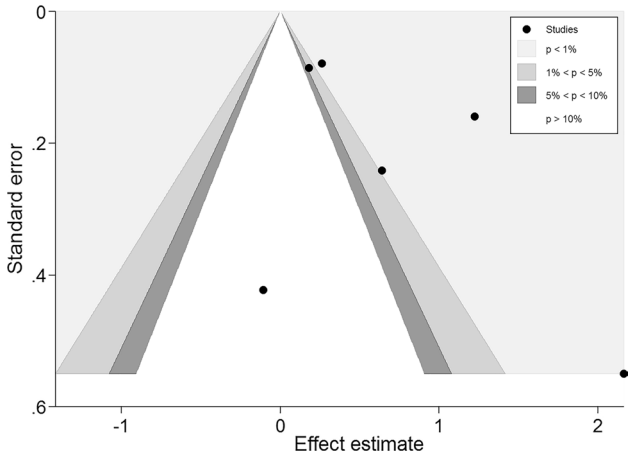

Fig. 6 Funnel plot of studies exploring the association between diabetes mellitus and periodontitis. Information on the statistical significance of each estimate pooled in the meta-analysis can be observed according to the different colors of the plot

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