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Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence

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Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence.

Abstract

Background: Periodontal disease and diabetes mellitus are common, chronic diseases worldwide. Epidemiologic and biologic evidence suggest periodontal disease may affect diabetes.

Objective: To systematically review non-experimental, epidemiologic evidence for effects of periodontal disease on diabetes control, complications and incidence.

Data sources: Electronic bibliographic databases, supplemented by hand searches of recent and future issues of relevant journals.

Study eligibility criteria and participants: Longitudinal and cross-sectional epidemiologic, non-interventional studies that permit determination of directionality of observed effects were included.

Study appraisal and synthesis methods: Four reviewers evaluated pair-wise each study. Review findings regarding study results and quality were summarized in tables by topic, using the PRISMA Statement for reporting and the Newcastle-Ottawa System for quality assessment, respectively. From 2246 citations identified and available abstracts screened, 114 full-text reports were assessed and 17 included in the review.

Results: A small body of evidence supports significant, adverse effects of periodontal disease on glycaemic control, diabetes complications, and development of type 2 (and possibly gestational) diabetes.

Limitations: There were only a limited number of eligible studies, several of which included small sample sizes. Exposure and outcome parameters varied, and the generalizability of their results was limited.

Conclusions and implications of key findings: Current evidence suggests that periodontal disease adversely affects diabetes outcomes, and that further longitudinal studies are warranted.

Webcast: A brief video summarizing this review may be viewed for free at: http://www.scivee.tv/journalnode/58235.

Key words: diabetes complications; diabetes mellitus; gestational diabetes; epidemiology; haemoglobin a, glycosylated; humans; periodontal diseases; review, systematic

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Periodontal diseases, including the reversible form gingivitis, affect up to 90% of the world's population (Pihlstrom et al. 2005). While "dental caries of permanent teeth" tops the Global Burden of Disease (GBD) list with an estimated prevalence of 35.3%, chronic periodontitis (10.8%) follows with only headache/migraine and skin diseases between (Vos et al. 2013). Periodontitis is reported to affect half of adults (Hu et al. 2011,

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Eke et al. 2012a, Patel & Platform for Better Oral Health in Europe, 2012) or more (Holtfreter et al. 2010), with the severe form periodontitis affecting around 10% (range: 5–20%) of adults (Petersen et al. 2005, Dye et al. 2007, Eke & Dye 2009, Holtfreter et al. 2009, Mattila et al. 2010, Eke et al. 2012a, Patel 2012, White et al. 2012) and moderate periodontitis around one-third (Holtfreter et al. 2009, Eke et al. 2012a, White et al. 2012). In aged populations and in indigenous people, the prevalence of periodontitis is even higher: It is reported that 70–90% of individuals aged 60–74 years (Holtfreter et al. 2010, Mattila et al. 2010, Patel 2012) and indigenous people (Brothwell & Ghiabi 2009) suffer from periodontitis. It is noteworthy the actual prevalence of periodontitis may be substantially higher than hitherto reported. This is due to underestimation by prior population surveys due to their use of partial mouth recordings and reliance on only periodontal probing depth instead of clinical attachment level (Albandar & Rams 2002, Eke et al. 2010, 2012b, Beltran-Aguilar et al. 2012, White et al. 2012).

It is estimated that 346 million people have diabetes worldwide (World Health Organization 2011) with the prediction of 439 million by the year 2030, representing an increase of 54% in 20 years to encompass almost one tenth of adults 20 years and older (Chen et al. 2012). In addition, according to the Global Burden of Disease study, diabetes is a major cause of years lived with disability (YLD), estimated at 20.8 million YLDs. Diabetes is ranked as the ninth most common disorder in the world, amassing a 67.2% increase over the 20 years from 1990 to 2010 (Vos et al. 2013).

From a global perspective, although the prevalence of diabetes is high in the industrialized countries – with for example 11.3% (25.8 million) of the US population already having diabetes (Centers for Disease Control & Prevention 2011) – it is worth emphasizing that over 80% of diabetes patients live in low- and middle-income countries (World Health Organization 2011), with the Middle East encompassing six of the ten countries with the highest prevalence (International Diabetes Federation 2011).

Currently, there is increasing interest in links between periodontal disease and non-oral, systemic, inflammatory-related diseases and conditions, such as atherosclerotic cerebro-cardiovascular conditions and events (Kebschull et al. 2010, Ylöstalo et al. 2010, Borgnakke 2012, Lockhart et al. 2012). The biologic plausibility supporting such connection is based on the fact that inflammatory periodontal disease due to reaction to pathogenic biofilm stimulates a chronic systemic inflammation and thus contributes to the cumulative inflammatory burden in the host (Loos 2005, Renvert et al. 2006). Inflammation precedes diabetes onset (Duncan et al. 1999, Schmidt et al. 1999, Duncan & Schmidt 2006) and is linked to insulin resistance and development of diabetes (Wang et al. 2013) as well as its complications (King 2008). Since effective therapy and management of periodontal disease are well established, it is important to know for future prevention and control of diabetes whether periodontitis indeed plays a role in the development and control of diabetes and its potentially fatal complications (Lalla & Papapanou 2011).

If such a causal relation indeed exists, a new paradigm in dental and medical standard of care for screening, prevention and management of diabetes could be developed in the future. Close collaboration among each patient's health care professionals would be warranted, especially among medical and dental care providers (Glurich et al. 2013).

Review of Current Literature

Objective

Our aim was to conduct a systematic review to identify and evaluate the scientific evidence from epidemiologic, non-experimental, observational studies of effects of periodontal disease on diabetes mellitus. Specifically, we explored effects on glycaemic control, the development of complications and the onset of diabetes. Study populations should consist of individuals without diabetes and with known types 1 and 2 diabetes, in addition to pregnant women with and without gestational diabetes.

The specific questions addressed in this systematic review were:

1. Do people with manifest type 2 diabetes, pre-diabetes or no known diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?
2. Do people with type 1 diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?
3. Do people with diabetes, who have poorer periodontal health, have more diabetes complications than those with better periodontal health?
4. Do people without known diabetes, who have poorer periodontal health, have greater risk for developing (incident) type 2 diabetes than those with better periodontal health?
5. Do women with gestational diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?
6. Do pregnant women, who have poorer periodontal health, have greater risk for gestational diabetes than those with better periodontal health?

Only reported findings from original, epidemiologic, non-intervention, observational studies of longitudinal, case-control or cross-sectional designs were eligible for inclusion in this review. They needed to include different categories of periodontal disease (exposure) and at least one parameter related to diabetes (outcome).

Methods

Protocols

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

For describing and summarizing the results of our review, we used the 27 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement; www.prisma statement.org) (Moher et al. 2009a,b).

The Newcastle-Ottawa Scale for assessing the quality of non-randomized studies (NOS)

Assessment of the quality of non-randomized, non-interventional studies is essential for proper evaluation

of the evidence provided by each study. We followed the Newcastle-Ottawa System (NOS) protocol (Wells et al. 2011). The scale is described and the forms used displayed in the online appendix, Exhibits Appendix S6 and Appendix S7–S9 respectively.

Eligibility criteria

We limited our search to original research reports on periodontal disease and diabetes that were conducted in humans and reported in English in any year.

Information sources

We searched electronic databases and hand searched bibliographies of already identified reports, as well as online sites with reports accepted for publication ahead of print for the most relevant scientific journals. We also created automated electronic alerts for identification of additional reports. In addition, we contacted authors for clarification and additional information regarding three papers. We conducted the last comprehensive search on July 26, 2012, but ensured by the last search on January 6, 2013, that no additional eligible reports were catalogued in PubMed. While imposing the limits Humans and English language, we searched the following bibliographic databases:

- PubMed, incl. MEDLINE and Pre-MEDLINE, by OVID (from 1950)
- Web of Science by Thomson Reuters
- EMBASE by Elsevier via OVID (from 1980)
- Dentistry and Oral Sciences Source™ by EBSCO via OVID
- CINAHL® by EBSCO (from 1937)
- Evidence Based Medicine (EBM) Reviews
- SciVerse by Elsevier
- LILACS (Latin American and Caribbean Health Sciences) by Virtual Health library (from 1982)

Further details regarding these databases searched are provided in Appendix S1.

Literature search

We searched the different databases using as identical search strategies as possible within the rules of each database. As an example, the main PubMed search query follows, in which "tiab" means the terms may be found in the title, the abstract or both: ("periodontal diseases"[mh] OR periodontium[mh] OR periodontics[mh] OR periodont*[tiab]) AND ("diabetes mellitus"[mh] OR "diabetes insipidus"[mh] OR diabet*[tiab] OR "dm 1"[tiab] OR "dm i"[tiab] OR "dm 2"[tiab] OR "dm ii"[tiab] OR "hemoglobin a, glycosylated"[mh] OR a1c[tiab] OR "hb a1c"[tiab] OR hba1c[tiab] OR "blood glucose"[mh] OR "blood sugar"[tiab] OR ((glucose[ti] OR sugar[ti]) AND (level[ti] OR control[ti])) OR hyperglycemia[mh] OR hypoglycemia[mh] OR glycemi*[tiab] OR glycaemi*[tiab] OR hyperglyc*[tiab] OR hypoglyc*[tiab]). Filters used were: Humans and English language.

It was confirmed that addition of the UK spelling of the key search terms provided results identical to the search using US spelling alone. In addition to the example shown, this was ensured by extra searches using the term "haemoglobin."

The electronic bibliographic reference manager program EndNote, version X6, by Thomson Reuters (http://endnote.com/) was used to identify duplicates; screen citations and abstracts; categorize citations in ineligible and eligible groups; create lists of citations for tables; and create the in-text citations and the bibliography.

Study selection

We identified 4990 citations that included the search terms, amounting to 2246 unique citations after identifying and removing duplicate records. Two of the authors reviewed the 2246 citations and their abstracts and selected 114 reports for reading of the full text. The four reviewers read the papers in alternating pairs, so that each reviewer read half (57) papers each, but with different partners. Hence, each report was scored independently by two reviewers. In case of discrepancies, all four reviewers were asked to review the papers, without knowledge of the other reviewers' decisions. All four reviewers arrived at a final, mutual agreement of scoring each paper based on discussions during frequent telephone conference calls. This procedure was followed for both classification of eligibility and quality of reports deemed eligible for inclusion.

We selected reports on original epidemiologic, non-interventional, observational (descriptive and analytical) studies that concerned parameters on periodontal disease and glycaemic control or blood concentrations of glucose among people without diabetes or with any kind of diabetes (no pathological elevation in blood glucose concentration, prediabetes (impaired fasting glucose), types 1 or 2 diabetes and gestational diabetes). For cohort and case-control studies, it must be evident that the topic studied was the effect of periodontal disease on diabetes, that is, the report results must permit determination of directionality. In addition, cross-sectional studies were eligible for inclusion, but only if they reported on associations between periodontal disease (exposure) and diabetes parameters (outcomes) that were unlikely to cause periodontitis, such as the diabetes complications retinopathy and neuropathy, to ensure determination of directionality.

Data collection process

We developed forms for scoring each report as well as for the logistic administration, logging and track keeping of papers to retrieve and to review. One reviewer (WSB) assumed the administrative tasks in addition to the full reviewer tasks and created a Master file with the 114 citations that were numbered for unambiguous identification. This Master file was used to identify the assignments of reports among the four reviewers, to enter the scores from each reviewer as they became available, and to identify discrepancies between the duplicate reviewers' categorization. Subsequently, the Master file would be used for tallying the number of reports in the different categories of eligibility and ineligibility.

Prior to actual scoring, the rating forms were tested by all reviewers by trial scoring 21 relevant papers that

the administrative reviewer already had available before the actual systematic search. The scoring forms were discussed and revised in an iterative process until all four reviewers agreed on the final format.

The data extraction was performed in duplicate with two reviewers independently assessing each report, determining eligibility and indicating reasons for ineligibility.

First, each reviewer decided on a study's eligibility for inclusion in the systematic review, based on the reported parameters. At this point, the reviewer made no quality assessment of the study. Each report deemed *ineligible* for inclusion was categorized in a hierarchical manner according to one of the following main reasons for its exclusion:

Main Exclusion Reasons (in Hierarchally Prioritized Order):

N1. Not original study (review, guidelines, comment)
N3. Original, but not epidemiologic study
N4. Original, but interventional study
N2. Original study, but not on effect of periodontal disease on glycaemic control
N5. Other reason.

The ineligible study was recorded with the exclusion reasons on the form displayed in Exhibit Appendix S2.

Second, the reports deemed eligible were categorized into one of the following groups:

Eligibility Categories for Effect of Periodontal Disease on:

E1. Glycaemic control in:

E1a. Type 2 diabetes
E1b. Pre-diabetes
E1c. No known diabetes

E2. Glycaemic control in type 1 diabetes
E3. Diabetes-related complications
E6. Incident type 2 diabetes (new diabetes developed in individuals without diabetes at baseline)
E4. Gestational diabetes control
E5. Risk for [development of] gestational diabetes

Third, data were extracted from each paper by each reviewer who recorded the findings on the data collection form displayed as Exhibit Appendix S4.

Data items

Regardless of study design, we collected the following information, with the majority of data points equipped with standard response categories with the option for open-ended responses: Study Design, Population Based, Study Duration, # Subjects, Sex, Age, DM Type, DM outcomes assessed, DM Measured/Diagnosed, DM Control Definition/Groups, Other DM-Related Measures, Type of Periodontal Examination, Periodontal Measures, Periodontal Case Definition/Groups, Examiner Calibration, Analysis, Effect of Perio on DM, Effect: Parameter & Size, Dose–Response Effect, Main Findings and Comments (Medication use; Comorbidity, etc.), Exhibit Appendix S4.

Risk of bias in individual studies

As mentioned, we assessed the quality of each cohort and case-control study according to NOS for Assessing the Quality of Non-randomized Studies (Wells et al. 2011), described in Exhibit Appendix S6, but devised an additional scale for rating cross-sectional studies. The NOS evaluates three dimensions of a study, namely A) selection of the study groups; B) comparability of the study groups; and C) ascertainment of either the exposure or outcome of interest. We developed one form for each of the three study designs: cohort, case-control and cross-sectional. The three forms are displayed as Exhibits Appendix S7–S9.

Using these forms, we rated each report at both the study and outcome levels.

Summary measures

The majority of studies reported results using odds ratios (OR), hazard ratios (HR) and hazard rate ratios (HRR), but also other relative risks measures, such as risk ratios, rate ratios or relative risks.

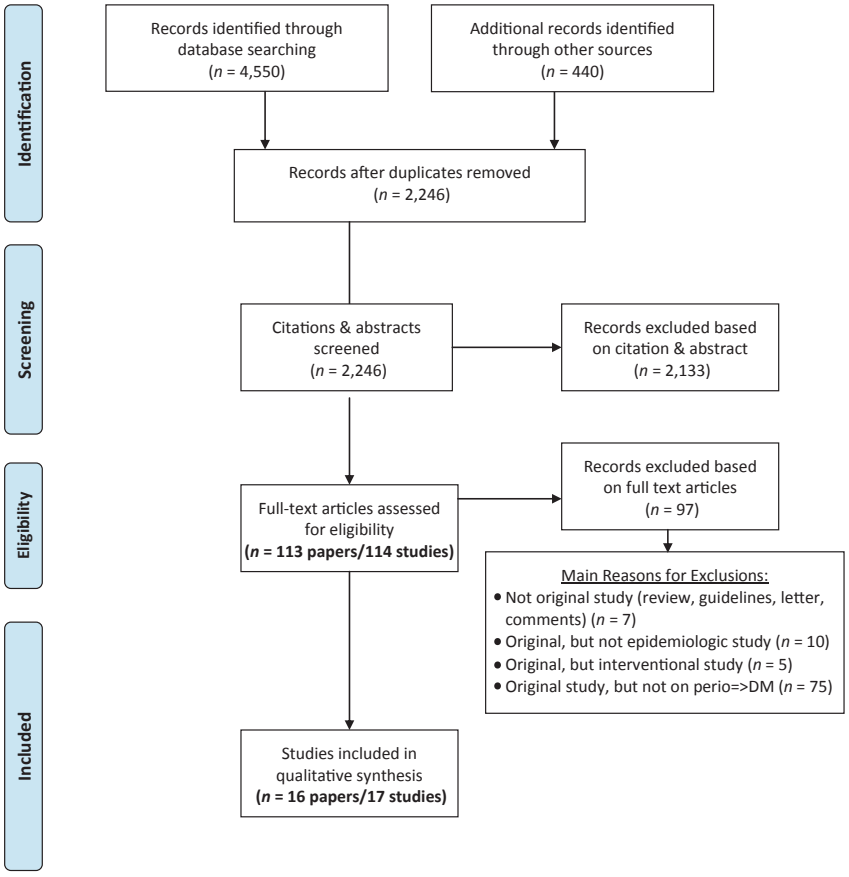

Fig. 1. Selection of studies for systematic review of epidemiologic observational evidence for the effect of periodontal disease on diabetes control, complications and incidence.

Table 1. The 16 reports (on 17 studies) included in the final review: citations

1. Abrao, L., Chagas, J. K. & Schmid, H. (2010) Periodontal disease and risk for neuropathic foot ulceration in type 2 diabetes. *Diabetes Res Clin Pract* **90**, 34–39. doi:10.1016/j.diabres.2010.06.014.
2. Dasanayake, A. P., Chhun, N., Tanner, A. C., Craig, R. G., Lee, M. J., Moore, A. F. & Norman, R. G. (2008) Periodontal pathogens and gestational diabetes mellitus. *J Dent Res* **87**, 328–333. doi:10.1177/154405910808700421.
3. Demmer, R. T., Desvarieux, M., Holtfreter, B., Jacobs, D. R., Jr., Wallaschofski, H., Nauck, M., Volzke, H. & Kocher, T. (2010) Periodontal status and A1C change: longitudinal results from the study of health in Pomerania (SHIP). *Diabetes Care* **33**, 1037–1043. doi:10.2337/dc09-1778.
4. Demmer, R. T., Jacobs, D. R., Jr. & Desvarieux, M. (2008) Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. *Diabetes Care* **31**, 1373–1379. doi:10.2337/dc08-0026.
5. Ide, R., Hoshuyama, T., Wilson, D., Takahashi, K. & Higashi, T. (2011) Periodontal disease and incident diabetes: a seven-year study. *J Dent Res* **90**, 41–46. doi:10.1177/0022034510381902.
6. Li, Q., Chalmers, J., Czernichow, S., Neal, B., Taylor, B. A., Zoungas, S., Poulter, N., Woodward, M., Patel, A., de Galan, B., Batty, G. D. & ADVANCE Collaborative Group. (2010) Oral disease and subsequent cardiovascular disease in people with type 2 diabetes: a prospective cohort study based on the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial. *Diabetologia* **53**, 2320–2327. doi:10.1007/s00125-010-1862-1.
7. Morita, I., Inagaki, K., Nakamura, F., Noguchi, T., Matsubara, T., Yoshii, S., Nakagaki, H., Mizuno, K., Sheiham, A. & Sabbah, W. (2012) Relationship between periodontal status and levels of glycated hemoglobin. *J Dent Res* **91**, 161–166. doi:10.1177/0022034511431583.
8. Morita, T., Yamazaki, Y., Mita, A., Takada, K., Seto, M., Nishinoue, N., Sasaki, Y., Motohashi, M. & Maeno, M. (2010) A cohort study on the association between periodontal disease and the development of metabolic syndrome. *J Periodontol* **81**, 512–519. doi:10.1902/jop.2010.090594.
9. Noma, H., Sakamoto, I., Mochizuki, H., Tsukamoto, H., Minamoto, A., Funatsu, H., Yamashita, H., Nakamura, S., Kiriyama, K., Kurihara, H. & Mishima, H. K. (2004) Relationship between periodontal disease and diabetic retinopathy. *Diabetes Care* **27**, 615. doi:10.2337/diacare.27.2.615.
10. Saito, T., Shimazaki, Y., Kiyohara, Y., Kato, I., Kubo, M., Iida, M. & Koga, T. (2004) The severity of periodontal disease is associated with the development of glucose intolerance in non-diabetics: the Hisayama study. *J Dent Res* **83**, 485–490. doi:10.1177/154405910408300610.
11. Saremi, A., Nelson, R. G., Tulloch-Reid, M., Hanson, R. L., Sievers, M. L., Taylor, G. W., Shlossman, M., Bennett, P. H., Genco, R. & Knowler, W. C. (2005) Periodontal disease and mortality in type 2 diabetes. *Diabetes Care* **28**, 27–32. doi:10.2337/diacare.28.1.27.
12. Shultis, W. A., Weil, E. J., Looker, H. C., Curtis, J. M., Shlossman, M., Genco, R. J., Knowler, W. C. & Nelson, R. G. (2007) Effect of perio-dontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. *Diabetes Care* **30**, 306–311. doi:10.2337/dc06-1184.
13. Southerland, J. H., Moss, K., Taylor, G. W., Beck, J. D., Pankow, J., Gangula, P. R. & Offenbacher, S. (2012) Periodontitis and diabetes associations with measures of atherosclerosis and CHD. *Atherosclerosis* **222**, 196–201. doi:10.1016/j.atherosclerosis.2012.01.026.
14. Taylor, G. W., Burt, B. A., Becker, M. P., Genco, R. J., Shlossman, M., Knowler, W. C. & Pettitt, D. J. (1996) Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol* **67**, 1085–1093. doi:10.1902/jop.1996.67.10s.1085.
15. Thorstensson, H., Kuylenstierna, J. & Hugoson, A. (1996) Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. *J Clin Periodontol* **23**, 194–202. doi:10.1111/j.1600-051X.1996.tb02076.x.
16. Xiong, X., Elkind-Hirsch, K. E., Vastardis, S., Delarosa, R. L., Pridjian, G. & Buekens, P. (2009) Periodontal disease is associated with gestational diabetes mellitus: a case-control study. *J Periodontol* **80**, 1742–1749. doi:10.1902/jop.2009.090250.

Synthesis of results

Due to the small number of studies for each topic and their pronounced heterogeneity with regard to their design and outcome measures, their data could not be pooled and meta-analyses conducted. Instead, findings from each study were described together with the remaining studies on the same topic, with one Table for each original question posed.

Risk of bias across studies

As with other bodies of scientific evidence, the potential effect of publication bias, favouring reporting of positive outcomes, cannot be excluded. Likewise, it is not known whether the authors reported only their most favourable results.

Additional analyses

Pre-review knowledge of the limited scope of the existing evidence prevented pre-specification of any additional analyses to conduct, based on the reported results.

Results

Study selection

A total of 2246 unique citations were identified. The numbers of studies screened, assessed for eligibility, undergoing reading of full text, and included in the final review are shown in Fig. 1. Table 1 displays the final 16 papers selected for the review that yielded results from 17 studies, as one report included findings for two different outcomes (Saito et al. 2004). The citations for the 97 reports excluded upon full text perusing are displayed in Exhibit Appendix S3, along with the main reason for exclusion of each paper. Exhibit Appendix S5 lists the 17 reports included in the final review.

Description of characteristics, results and quality of each study

The findings from this review are described in the following for each of the originally posed questions. For each topic, a table displays the characteristics and findings from each study, and a brief summary is provided of only the longitudinal results, that is, any cross-sectional findings at baseline are not shown. Importantly, all confounders for which the analyses are controlled are displayed for each outcome or model, respectively, in Tables 2–5 under the heading "Confounders Controlled." In consideration of space and readability, these confounders will not be re-cited in the text. Risk of bias within and across studies is addressed briefly and the consensus NOS quality scores for each study are displayed in the online Appendix, with such tables

corresponding by topic to the results tables included in this main report. All studies were conducted among adults.

1. Do people with manifest type 2 diabetes; pre-diabetes; or no known diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health? (E1)

Brief summary of characteristics and results

Table 2 displays a summary of the four studies identified. No eligible study was conducted among subjects with baseline pre-diabetes (*Eligibility Category E1b*), so only reports on studies among participants with either manifest type 2 diabetes (*E1a*) or no known diabetes (*E1c*) at baseline were included.

Of the four studies, three were of prospective and one retrospective cohort design. They included 4512 participants ages 18–81 years in three countries (Germany, Japan and USA). Clinical periodontal examination results were reported based on periodontal probing depth (PPD), clinical attachment loss (CAL), gingival bleeding and number of teeth present. Radiographic examination in one study assessed per cent bone loss. Glucose measures included glycosylated haemoglobin (HbA1c) as well as fasting and 2-h 75 g plasma glucose level, and oral glucose tolerance test (OGTT).

One study was conducted among individuals with type 2 diabetes (Taylor et al. 1996) and three in people without diabetes at baseline (Saito et al. 2004, Demmer et al. 2010, Morita et al. 2010). The former included American Indians of the Gila River Indian Community (Pima Indians) and demonstrated that severe periodontitis was associated with poor glycaemic control after a 5-year period. Those with CAL of at least 6 mm had over six times the risk of poor glycaemic control compared to those without; and individuals 35 years and younger at baseline with radiographic bone loss of at least 50% of the root length had 4.2–13.6 times the risk of poor control (Taylor et al. 1996).

Over a 4-year period, initially systemically healthy Japanese employees with periodontal disease were in a dose–response manner more likely to develop metabolic syndrome (that includes hyperglycaemia) than those periodontally healthy (Morita et al. 2010).

In large population studies in Germany and Japan, the former found that after five years, an increase in mean CAL, but not in PPD, was associated with an increase in HbA1c (Demmer et al. 2010). In addition, individuals with a healthy periodontium at both baseline and follow-up had less HbA1c increase than those with poor baseline and 5-year deterioration in periodontal health (0.005 *versus* 0.143%; $p = 0.003$).

However, the latter demonstrated after 10 years a significant increase in impaired glucose tolerance (IGT) with mean PPD, but not CAL, with each additional millimetre mean PPD corresponding to 0.13% increase in HbA1c (Saito et al. 2004).

Quality assessment

All studies used multivariate analyses, and all controlled for age and smoking, except for one study (Taylor et al. 1996). All four studies earned eight or nine of the nine possible stars in the NOS quality rating as shown in Appendix S10.

Major weaknesses

There were very few studies. They were conducted only in Germany, Japan and USA and were not generalizable. All clinical studies used partial mouth periodontal examinations. Periodontal and metabolic outcome parameters varied.

2. Do people with type 1 diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?

No studies were found eligible (E2).

3. Do people with diabetes, who have poorer periodontal health, have more diabetes-related complications than those with better periodontal health?

Brief summary of characteristics and results

The seven studies are summarized in Table 3 (E3). They were conducted in Brazil, Japan, Sweden, USA (3) and in 20 different countries respectively. Four were of cohort and three of cross-sectional design. Only one study focused on type 1 diabetes, five studied type 2 diabetes, and one did not specify diabetes type. A total of 18,397 subjects participated, ranging from 39 to 10,958, with five of the studies combined including 1391 persons. Participants were at least 25 years old.

Clinical periodontal examination results were reported based on PPD and CAL, bleeding on probing; and number of teeth present. Radiographic examinations assessed per cent bone loss. In the multi-country study, self-reported number of teeth present and number of days with gingival bleeding the past year were described. Diabetes-related complications encompassed retinopathy; nephropathy (macroalbuminuria, proteinuria and end-stage renal disease); neuropathic foot ulceration; cardiovascular disease (coronary heart disease, ischaemic heart disease, carotid intima media thickening and calcification of atherosclerotic plaque); cerebrovascular events (stroke); and death due to cardiorenal disease.

In the study among people with type 1 diabetes, all cardiorenal complications, but not retinopathy, were significantly associated with periodontal disease (PD). All studies in subjects with types 1 and 2 diabetes found that those with periodontal disease, especially severe disease, and edentulism, had higher risk for diabetes-related complications than participants without or with mild periodontal disease. A dose–response effect was seen between severity of periodontal disease and complications. For instance, moderate and severe PD, as well as edentulousness significantly predicted both macroalbuminuria and end-stage renal disease in a dose-dependent manner among Pima Indians (Shultis et al. 2007). In this population, those with severe PD had 3.5 times higher risk for cardiorenal death; moreover, nephropathy and death from ischaemic heart disease were significantly predicted by PD (Saremi et al. 2005).

Quality assessment

Two studies used full-mouth and four partial mouth clinical periodontal examinations, and radiographic bone loss assessment was performed in four studies, of which three used all teeth. The seventh

Table 2. Effect of periodontal disease on metabolic control in subjects with type 2 diabetes or without diabetes (E1a & E1c)

Author Year Country Study Design BL DM Type	A) # Subjects: a. Perio Cases b. Comparison group(s) B) Age C) Study Duration	EXPOSURE Perio Measure & Case Definition	OUTCOME Metabolic Control Measure & Definition	Effect on Metabolic Control? & Generalisable?	Effect Size: Odds Ratio (OR), Trend & Significance (95%CI)	Effect on Metabolic Control/ Conclusion	Confounders Controlled
E1a. Type 2 Diabetes (DM2):							
Taylor et al. 1996 USA Cohort DM2	A1)X-ray Exams: N=105(31M+74F), incl. 88 w/≥2 exams A2) Clin. Exams: N=89(27M+62F) B) All ≥18yrs [18-67yrs] C1) X-ray Exams: 2.4yrs [2-4yrs] C2) Clin. Exams: 5yrs	Partial mouth (6 index teeth) • PPD • CAL • X-ray bone loss PD@BL: >1 tooth with: 1) X-ray bone loss ≥50% or 2) CAL≥ 6 mm	• OGTT • HbA1c FU Metabolic Control: HbA1c ≥9%: Poor	Yes, stat. sign. in Pima American Indians in the Gila River Indian Community, Arizona, USA Not generalisable	OR for Poor Glycaemic Control by Baseline Age: 1) Bone Loss: • 25yrs: OR=13.6 (1.7- 106.0) • 30yrs: OR=7.3 (1.5-38.2) • 35yrs: OR 4.2 (1.2- 14.9) • 40yrs: OR=2.3 (0.8-6.8) • 45yrs: OR=1.3 (0.4–4.0) • 50yrs: OR=0.7 (0.2–2.9) 2) CAL: Severe *vs.* no periodontitis: OR=6.2 (1.5–25.3)	Severe periodontitis was associated with poor metabolic control in type 2 diabetes after 2 to 5 years	1)Bone loss: • Age • Hba1c @ BL 2) CAL: • smoking • diabetes severity • diabetes duration Multivariate
COMMENTS: Good examiner calibration agreement for clinical & radiographic examinations							
E1c. No Diabetes:							
Morita et al. 2010 Japan Cohort No DM No MetS	A) N=1,023 (727M+296F) B) 37.3yrs [20-56yrs] C) 4yrs	Partial mouth (sextants) CPI Codes: 0: healthy 1: bleeding 2: calculus 3: ≥1 PPD 4-5mm 4:≥1 PPD> 6mm PD Groups: CPI ≤ 2 *vs.* CPI ≥ 3	• Incidence of metabolic syndrome (association w/PD) • HbA1c • fasting glucose • OGTT	Yes, stat. sign. in (71% male) Japanese employees under 60 years Not generalisable	OR=1.6 (1.1-2.2; p<0.05) for ≥1 positive MetS component *vs.* no positive MetS component in PD; OR=1.4 (1.0-2.1) for ≥1; OR=2.2 (1.1-4.1) for ≥2 MetS components	In initially healthy individuals, periodontal disease is associated in a dose-response manner with development of ≥1 components of metabolic syndrome over 4 years	• age • gender • cigarette smoking • exercise • eatingbtw. meals • weight at BL Multivariate
COMMENTS: No examiner calibration; Dose-response effect stat. sign for trend; CPI is a poor measure of PD							
Demmer et al. 2010 Germany (Pomerania) Cohort No DM	A) N=2,793 (47%M+53%F) a1) 488 a2) 463 a3) 479 a4) 241 b) 1,122 B) 48(±15)yrs [20-81yrs] C) 5yrs	Perio Exam: Partial mouth* Tooth count: Full mouth ≤28 teeth • PPD • CAL • # teeth PD groups based on% BL sites w/CAL>5mm: a1) 1-8% a2) 9-33% a3) 34-100% a4) Edentulous b) 0%	• HbA1c	Yes, stat. sign. in Caucasians in Pomerania in former East Germany Not generalisable	1) BL # teeth was not consistently associated with 5yr change in HbA1c (p_{trend}=0.84) 2) Those perio healthy at BL & FU had less 5yr HbA1c change than those w/poor BL perio health and 5yrs perio deterioration: 0.005 *vs.* 0.143% (p=0.003)	5-year change in mean CAL (but not in mean PPD) was associated with HbA1c change	• age • waist/hip ratio • systolic BP • triglycerides • physical activity • white blood cellcount • fibrinogen • hsCRP • sex • region • smoking • education

Table 2. (continued)

Author Year Country Study Design BL DM Type	A) # Subjects: a. Perio Cases b. Comparison group(s) B) Age C) Study Duration	EXPOSURE Perio Measure & Case Definition	OUTCOME Metabolic Control Measure & Definition	Effect on Metabolic Control? & Generalisable?	Effect Size: Odds Ratio (OR), Trend & Significance (95%CI)	Effect on Metabolic Control/ Conclusion	Confounders Controlled
		Used 3 additional PD groupings based on: 1) BL PPD 2) BL # teeth 3) 5yr change in % sites w/CAL≥5mm					• education • family DM history Multivariat linear regression
COMMENTS: Study of Health In Pomerania (SHIP); *right or left side of mouth; Good to excellent agreement in intra- and inter-examiner periodontal exam calibration							
Saito et al. 2004 Japan Retrospective Cohort* No DM	All without DM @BL in 1988 A) @ FU in 1998: N1=961 (377M+584F) N2=591=those among N1 aged ≥40yrs in 1988 N3=545 w/HbA1c values both at BL and FU A) 40-79 yrs B) 10 yrs	Partial mouth** • PPD • CAL PD-1: Mean DDP: a1) Intermediate: 1.3-2.0mm a2) Deep/High: >2.0mm b) Shallow/Low: <1.3mm PD-2: Mean CAL: a1) Intermediate: 1.5-2.5mm a2) High: >2.5mm b) Low: <1.5mm	• 2hr 75g OGTT (BL) • IGT • HbA1c • Incident Glucose Intolerance: NGT in 1988& IGT in 1998 • Glucose Intolerance progression= HbA1c (1998) – HbA1c (1988) ≥0.2% (=difference after 10 years)	Yes, stat.sign. in Japanese (Hisayama) 40-79yrs community dwellers Not generalisable	1) High *vs.* Low PPD categories: OR=2.4 (1.4-2.6; p= 0.009) for risk of IGT 2) No sign. increase in IGT with mean CAL	1) Proportion w/IGT increased significantly w/mean PPD 2) Those w/normal BL GT who developed IGT over 10 years were sign. more likely to have deep PPD, but not CAL, at FU 3) Each additional mm mean PPD corresponded to 0.13% HbA1c increase (p=0.007) 4) Severity of perio-dontal disease expressed as PPD, but not CAL, was sign. associated with development of glucose intolerance	• age • sex • smoking • BMI • exercise • alcohol
COMMENTS: *May be regarded as 1998 cross-sectional exam plus 1988 OGGT data, i.e., oral health data only from 1998 (not from BL 1988); **NHANES III protocol (1 max. + 1 mand. quadrant); 4 "trained" examiners; No calibration reported							

BP, Blood Pressure; CPI,Community Periodontal Index; Excl.,Excluding/Excluded; MetS, Metabolic Syndrome; Perio, Periodontal/Periodontally; #, Number (of); &, and; BL, Baseline/Beginning of Study Period; CAL, Clinical Attachment Loss; CI, Confidence Interval; CPI, Community Periodontal Index; DM, Diabetes Mellitus; DM2, Type 2 Diabetes Mellitus; F, Female; FU, Follow-Up/End of Study Period; GT, Glucose Tolerance; HbA1c, Glycosylated(Glycated) Haemoglobin; hr, hour; HR, Hazard Ratio; hsCRP, high-sensitivity C-reactive protein; IGT, Impaired Glucose Tolerance; M, Male; NGT, Normal Glucose Tolerance; NHANES, National Health and Nutrition Examination Survey; OGTT, Oral Glucose Tolerance Test; OR, Odds Ratio; Perio/PD, Periodontal Disease; PPD, Periodontal Probing (Pocket) Depth; RR, Risk Ratio; Stat. sign., statistically significant; *vs., versus*; yr(s), Year(s).

study relied on self-report only. The large international study states the participants were representative of people with type 2 diabetes. It used a non-traditional definition of oral health status, stating that "Lower numbers of natural teeth and higher numbers of days of gum bleeding indicated poorer oral health," deducted exclusively from self-report by asking about the participants' number of teeth present and

Table 3. Effect of periodontal disease on diabetes complications (E3)

Author Year Country Study Design BL DMType	A) # Subjects: a. Perio Cases b. Comparison group(s) B) Age C) Study Duration	EXPOSURE Perio Measure & Case Definition	OUTCOME Diabetes Complications: Measure & Assessment	Effect on Metabolic Control? & Generalisable?	Effect Size: HR, HRR, OR & Significance (95%CI)	Effect on Metabolic Control/ Conclusion	Confounders Controlled
			Type 1 Diabetes:				
Thorstensson et al. 1996 Sweden Cohort DM1*	A) N@FU=39(21M +18F) w/DM1 B) 55 yrs [36–70] C) 6 yrs [1–11 yrs]	Full-Mouth Exam • ging./BOP • PPD • X-ray bone loss PD: • pathologically deepened pockets (PDP) • bone loss >1/3 root length No PD may have: • gingivitis • PDP • no bone loss>1/3 root length	• Retinopathy • Proteinuria • Cardiovascular disease • Cerebrovascular events Assessed by: Medical examination	Yes, stat. sign. for proteinuria& cerebro-cardiovascular complications, but not for retinopathy & EKG abnor-malities Not generalisable	Proteinuria: p< 0.05 • Stroke: p< 0.01 • Angina: p<0.001 • TIA: p< 0.05 • MI: p< 0.01 • Heart failure: p< 0.01 • Intermittent claudication: p< 0.01 • Retinopathy: ns • EKG abnormalities: ns	People with type 1 diabetes and periodontal disease have more renal and cerebro-cardiovascular diabetes complications than periodontally healthy DM1 patients	None Bivariate analyses**
COMMENTS: *Most likely DM1, deducted from report; No examiner calibration reported; Dose-response effect not tested; **Partially controlled by study design							
			Type 2 Diabetes:				
Saremi et al. 2005 USA Cohort DM2	A) N=628(406M+222F) w/DM2 B) All >35 yrs: a1) Moderate: 47 (±10) yrs a2) Severe Perio: 55 (±11) yrs b) No/Mild: 43 (±7) yrs C) 11 yrs[0.3-16yrs]	1) CAL: 4 sites/ 6 index teeth 2) Bone Loss: Panoramic X-ray/All teeth 3) # teeth PD: a1) Moderate: ≥15 teeth; median bone loss 50-75% or median CAL 2-5mm a2) Severe: <15 teeth; median BL > 75% or median CAL ≥6mm b) No/mild: ≥15 teeth; median BL<50%and median CAL< 1mm	Death due to cardio-renal disease* Assessed by: • medical records • death certificates	Yes, stat. sign. in Pima American Indians in the Gila River Indian Community, Arizona, USA Not generalisable	Death due to cardio-renal disease rate ratio for severe *vs*. no /mild and moderate PD: HRR: Model 1: 4.5 (2.0-10.2; p<0.01) Model 2: 3.5 (1.2-10.0; p=0.02)	• Subjects with DM2 and periodontal disease have a higher death rate from cardio-renal disease* than those without periodontal disease • Among subjects with DM2, PD significantly predicted death from IHD (P-trend=0.04) and diabetic nephropathy (P-trend<0.01)	Model 1: • age • sex • DM duration Model 2: • age • sex • DM duration • fasting glucose • macroalbuminuria • BMI • cholesterol • hypertension • EKG abnormalities • Smoking (current) Multivariate
COMMENTS: *cardio-renal disease = ischemic heart disease (IHD) & diabetic nephropathy combined; Good intra- & inter-examiner calibration agreement for clinical & radiographic examinations (*as per personal communication with authors*); 72% of extractions due to PD, therefore edentulism regarded as most severe form of PD							
Shultis et al. 2007 USA Cohort DM2	A) N=529(168M+361F) w/DM2 a1) Moderate Perio: 200(80M+120F) a2) Severe Perio: 117(39M+78F) a3) Edentulous: 105(25M+80F) b) No/Mild Perio: 107(24M+83F) B) All >25yrs [25-79yrs]: a1) 44yrs [25-72yrs] a2) 49yrs[26-77yrs] a3) 55yrs [25-79yrs] b) 33yrs [25-72yrs]	1) CAL: 4 sites/ 6 index teeth 2) Bone Loss: Panoramic X- ray/All teeth 3) # teeth PD: a1) Moderate: ≥15 teeth; <7 teeth w/ 50-74% bone loss &<4 teeth w/≥75% bone loss a2) Severe: <15 teeth or greater bone loss than no/mild and moderate a3) Edentulous b) No/mild: ≥24 teeth; <6 teeth w/25-49% bone	• macroalbumin-uria (MA): n=193 • end stage renal disease (ESRD): n=68	Yes, stat. sign. in Pima American Indians in the Gila River Indian Community, Arizona, USA Not generalisable	MA: • Severe *vs*. no/mild PD: HRR=2.1(1.2–3.8) • Moderate *vs*. no/mild PD: HRR 2.0 (1.2 – 3.5) • Edentulous *vs*. no/mild PD: HRR 2.6 (1.4 – 4.6) Overall p=0.01 ESRD: • Severe *vs*. no/mild PD: HR=3.5(0.96-12.4) • Moderate *vs*. no/mild PD: HR 2.3 (0.6–8.1) • Edentulous vs. no/mild PD: HRR 4.9 (1.4–17.4);	Moderate & severe PD as well as edentulism each significantly predicted both macroalbuminuria (MA) and end stage renal disease (ESRD) in a dose-dependent manner	MA & ESRD: • age • sex • DM duration • BMI at BL • Smoking* • PD status* Multivariate

Table 3. (continued)

Author Year Country Study Design BL DMType	A) # Subjects: a. Perio Cases b. Comparison group(s) B) Age C) Study Duration	EXPOSURE Perio Measure & Case Definition	OUTCOME Diabetes Complications: Measure & Assessment	Effect on Metabolic Control? & Generalisable?	Effect Size: HR, HRR, OR & Significance (95%CI)	Effect on Metabolic Control/ Conclusion	Confounders Controlled
	C) Duration: C1) Macro-albuminuria: 9.4yrs [0.03-21.6yrs] C2) End Stage Renal Disease:14.9yrs [0.03–21.8yrs]	loss and <4 teeth w/≥75% bone loss			Overall p=0.02		
COMMENTS: Good intra- & inter-examiner calibration agreement for clinical & radiographic examinations (*as per personal communication with authors*); *Smoking & PD status updated at each examination; **Insignificant in models also adjusted for HbA1c; 72% of extractions due to PD, thus edentulism regarded as most severe form of PD							
Li et al. 2010 20 countries (215 centres) Cohort DM2	A1) N@BL=11,140 (57.5% M+42.5 %F) A2) N@FU=10,958 1) nbyNatural Teeth*: a1) 1–21 teeth: 4,174 a2) 0 teeth: 2,308 b) ≥22 teeth: 4,476 2) # in Groups by #Days w/BleedingGums/1yr: a1) <12 days/1yr: 686 a2) ≥12 days/1yr:719 b) 0 days/1yr: 9,553 B) 65.8(+6.4)yrs[55-88yrs] 1) Age by Natural Teeth*: a1)1–21 teeth:6.3(±6.2) a2) 0 teeth:68.6(±6.4)yrs b) ≥22 teeth: 63.9(±5.9) 2) # Days of Bleeding Gums/1yr: a1) 64.2(±6.0) a2) 63.6(±5.9) b) 66.1(±6.4) C) 5yrs	Self-report: • number of natural teeth • number of days gums bled during previous year	• Cardiovascular disease • Cerebrovascular events • Mortality	Yes, number of natural teeth in most cases associated stat. sign with out-comes, but not number of days w/bleeding gums Not generalisable, even though population stated to be represent-tative of people with type 2 diabetes	# Natural Teeth: I) CHD events: 1) HR=1.24 (0.98–1.56) for 1-21 *vs.*≥22 teeth 2) HR=1.04 (0.81-1.23) for 0 *vs.*≥22 teeth. P=0.34 for trend II) Cerebro-vascular events: 1) HR=1.24 (1.03-1.49) for 1-21 *vs.*≥22 teeth 2) HR=1.10 (0.87-1.38) for 0 *vs.*≥22 teeth; P=0.29 for trend III) CVD mortality: 1) HR= 1.32 (1.06-1.65) for 1-21 *vs.*≥22 teeth 2) HR=1.35 (1.05-1.74) for 0 *vs.*≥22 teeth; P=0.02 for trend IV) # Days of Bleeding Gums/1Year: Association with cerebrovascular outcomes somewhat weaker & statistically non-significant	Number of teeth associated weakly with cardiovascular mortality and cardio- and cerebrovascular events in men and women with DM2 Number of days with bleeding gums/year weakly and non-significantly associated with cardio- & cerebrovascular events & mortality	• age • sex • randomized treatment allocation • ethnicity • quality of life • existing illness • smoking • alcohol intake • physical activity • HbA1c • creatinine • BMI • total cholesterol • HDL-cholesterol • resting heart rate • systolic blood pressure (BP) • diastolic BP • Mini Mental State Examination score • height • education Multivariate
COMMENTS: Action in Diabetes and Vascular Disease: Preterax and Diami-cron Modified-Release Controlled Evaluation (ADVANCE) study; *Dichotomized values >0 at median to create cate-gories (0, 1–21, ≥22 teeth &0, <12, ≥12 days); Dose response effect for number of teeth, but not bleeding gums; Inadequate assessment of periodontal condition: Non-validated, non-standard self-report items used; no clinical or radiologic periodontal examination; No knowledge of reason for tooth loss; may not be due to PD; may not be alike in the 20 countries/215 centres							
Abrao et al. 2010 Brazil Cross-sectional DM2	A)N=122 (53M+69F) w/DM2 a1) Moderate/Severe: n=39 (32.0%) a2) Edentulous: n=34 (27.8%) b) No/Mild:=49 (40.2%) B) 60.5(±10.5)yrs [27.9-80.6yrs] C) n/a (cross-sectional)	Partial mouth Exam CPI (ging./BOP/PPD) PD: a1) Moderate/ Severe: CPI codes 3 or 4 a2) Edentulous due to PD b) No/Mild: CPI= 0, 1, 2	Risk for neuro-pathic foot ulceration	Yes, stat. sign. Not generalisable	Edentulous *vs.* No/Mild: OR=4.9 (1.6- 15.3; p≤0.01) Moderate/ Severe *vs.* No/Mild: OR=6.6 (2.3-18.8; p≤0.001)	Periodontal status was associated with risk for neuropathic foot ulceration	• DM duration • education • age • dental care Multivariate logistic regression
COMMENTS: Not controlled for metabolic control; Mean DM duration= 14.5(+9.6)yrs [1–40yrs]; Mean HbA1c=9.3(± 2.2)% [4.9–14.7%]							

Table 3. (continued)

Author / Year / Country / Study Design / BL DMType	A) # Subjects: a. Perio Cases b. Comparison group(s) B) Age C) Study Duration	EXPOSURE Perio Measure & Case Definition	OUTCOME Diabetes Complications: Measure & Assessment	Effect on Metabolic Control? & Generalisable?	Effect Size: HR, HRR, OR & Significance (95%CI)	Effect on Metabolic Control/ Conclusion	Confounders Controlled
Southerland et al. 2012 USA Cross-sectional DM2*	A) N=6,048: n1=791 w/DM2 n2=5,257 w/o DM B) [52-74yrs] C) n/a (cross-sectional)	Full mouth (6 sites/tooth) • PPD • CAL Extent of PD (>4mm &CAL>3 mm) : a1) mild/ moderate: 1to<15% a2) severe:≥15% b) none: 0% PD & DM status also combined in 6-category variable	• Carotid IMT • Calcification of athero-sclerotic plaque • CHD	Yes, stat. sign. Not generalisable	I) Severe PD assoc. with: 1) IMT>1mm: OR=1.3(1.0-1.7) 2) Acoustic shadowing: OR=1.3 (1.0-1.9) 3) CHD: OR=1.3 (0.9-1.7) II) Severe PD & DM *vs.* No PD & No DM asso c. with: 1) IMT>1mm: OR=2.2 (1.4-3.5; p<0.001) 2) Acoustic shadowing: OR=2.5 (1.3-4.6; p<0.001) 3) CHD:OR=2.6 (1.6-4.2;p<0.001)	1) Severe periodontal disease was associated with subclinical heart disease** in all subjects (± DM) 2) Among subjects with type 2 diabetes, periodontal disease was significantly associated with subclinical heart disease** and CHD	• age • sex • race/field centre • BMI • smoking • income • education • hypertension • LDL cholesterol • HDL cholesterol • triglycerides
COMMENTS: Dental data from Athero-sclerosis Risk in Communities (ARIC) Study; **DM2 as per personal communication w/authors;* Excellent to outstanding inter-examiner calibration agreement for PD; **1) thickened carotid IMT & 2) more advanced atheroma lesions (atherosclerotic plaque calcification measured by acoustic shadowing); Results not controlled for level of glycaemic control							
Noma et al. 2004 Japan Cross-sectional Unspecified DM type	A) N =73 B) Age not stated C) n/a (cross-sectional)	X-ray bone loss PD: a) bone loss >median b) bone loss <median	Retinopathy	Yes, stat. sign. Not generalisable	PD sign. associated w/diabetic retinopathy: OR=2.80; p=0.036	1) PD sign. assoc. w/ diabetic retinopathy: OR=2.80; P=0.036 2) Severity of PD sign. correlated w/severity of diabetic retinopathy (P=0.0012)	None
COMMENTS: No examiner calibration reported							

#, Number (of); &, and; Acoustic Shadowing, Advanced atherosclerotic lesions or plaque formation; Assoc., Association/Associated; BL, Baseline/Beginning of Study Period; CAL, Clinical Attachment Loss; CHD, Coronary Heart Disease; CI, Confidence Interval; CPI, Community Periodontal Index; DM, Diabetes Mellitus; DM2, Type 2 Diabetes Mellitus; EKG, Electro Cardiogram; ESRD, End-Stage Renal Disease; F, Female; FU, Follow-Up/End of Study Period; HRR, Hazard Rate Ratio; HbA1c, Glycosylated (Glycated) Haemoglobin; HDL, High-Density Lipoprotein; HR, Hazard Ratio; IMT, Intimal-Medial Thickness; M, Male; MA, Macroalbuminuria; ns, non-significant; OR, Odds Ratio; Perio/PD, periodontal disease; PDP, Pathologically Deepened Pockets; PPD, Periodontal Probing (Pocket) Depth; RR, Risk Ratio; Stat. sign., statistically significant; *vs., versus*; w/, with; w/o, without; yr(s), Year(s).

"number of days their teeth had bled in the preceding year" (Li et al. 2010). Using the number of teeth as an expression of past periodontal disease may not be appropriate in all these 20 countries, without information on the reason for tooth loss.

All studies regarding type 2 diabetes used multivariate analyses to control for the important confounders displayed in Table 3. Results were statistically significant after adjustment.

As seen in Exhibit Appendix S11, only one study earned the maximum of nine stars for cohort studies (Saremi et al. 2005). The four longitudinal studies earned between seven and nine stars, averaging eight. None of the three cross-sectional studies were awarded the maximum six stars for studies with such design, but two attained five, and the mean was four stars. The study of the lowest quality was included in this review only for completeness (Li et al. 2010).

Major weaknesses

Only one, small study was conducted in type 1 diabetes (Thorstensson et al. 1996). No high quality cohort studies were conducted in samples representative of individuals with type 2 diabetes. Two of the three cohort studies on type 2 diabetes were conducted in a special population of Pima Indians, and the international study did not use any commonly accepted assessment of periodontal disease. Due to their design, cross-sectional studies can provide information regarding only associations, not causation, and are thus not able to provide strong evidence.

4. Do people without known diabetes, who have poorer periodontal health,

Table 4. Effect of periodontal disease on diabetes incidence (in individuals without diabetes at baseline) (E6)

Author Year Country Study Design (No DM@BL)	A) # Subjects: a. Perio Cases b. Comparison group B) Age C) Study Duration	EXPOSURE Perio Measure & Case Definition	OUTCOME Diabetes Measure & Definition at BL/FU	Effect on Metabolic Control? & Generalisable?	Effect Size: HR, OR, RR & Significance (95%CI)	Effect on Metabolic Control/ Conclusion	Confounders Controlled
Ide et al. 2011 Japan Retrospective Cohort	A) # w/oral exams:N=8,752@BL /5,848@FU (3,883M+1,965F) Perio: a1) Moderate: 2,167 (37.1%) (1,511M+656F) a2) Severe:490 (8.4%) (384M+106F) b) No:3,191 (54.6%) (1,988M+1,203F) B) 30-59yrs; At FU: M:43.4(±7.5)yrs; F:43.9(±7.5)yrs C) 6.5yrs [2-7yrs]	Partial mouth (sextants) CPI Codes: 0: healthy 1: bleeding 2: calculus 3: ≥1 PPD 4-5mm 4:≥1 PPD> 6mm BL CPI Scores: a1) Mod.: 3 a2) Sev.: 4 b) No: 0, 1, or 2	FPG>125mg/dL @ FU	1) Unadjusted: Yes, in employed 30-59yrs old Japanese 2) Adjusted: No Not generalisable	1) Unadjusted: HR for trend <0.0001 DM Incidence: a) No Perio (4.0% DM): HR=1(Referent) b) Mod.Perio(5.4% DM): HR=1.38(1.08-1.78) c) Sev.Perio(8.4% DM): HR=2.23(1.57-3.17) 2) Fully Adjusted: Females only: Mod.Perio: HR=2.3(1.30-4.08)	1) Moderate&severe perio sign. associated w/DM risk (Unadjusted only) 2) Tendency for increased risk, but not sign. after adjustment 3) Females w/mod. perio. have sign. higher risk for DM	• age • sex • smoking • BMI • triglycerides • hypertension • HDL cholesterol • gamma-glutamyl-trans-peptidase
COMMENTS: 7 "trained" examiners; Intra- & inter-examiner calibration done, but not recorded; Oral exam at BL only; FPG measured 1-6 times 2000-2007; No FU data on n = 2,904 w/oral exam@BL = 33.2% of original study population; No adjustment for education, income, exercise, medication, co-morbidities							
Saito et al. 2004 Japan Retrospective Cohort* No DM	All without DM @BL in 1988 A)@ FU in 1998: N1=961 (377M+584F); N2=591=those among N1 aged ≥40yrs in 1988; N3=545 w/HbA1c values both at BL and FU B) 40-79yrs C)10yrs	Partial mouth** • PPD • CAL PD-1: Mean DDP: a1) Intermediate: 1.3-2.0mm a2) Deep/High: >2.0mm b) Shallow/Low: <1.3mm PD-2: Mean CAL: a1) Intermediate: 1.5-2.5mm a2) High: >2.5mm b) Low: <1.5mm	• 2hr 75g OGTT @BL • HbA1c	Yes, stat.sign. in Japanese (Hisayama) 40-79yrs community dwellers Not generalisable	1) High *vs.* Low PPD categories: Risk of DM:OR=2.6 (1.3-5.0;p=0.004) 2) Sign. increase in DM with mean CAL	1) Proportion w/DM increased significantly w/mean PPD 2) Each additional mm mean PPD corre-sponded to 0.13% HbA1c increase (p=0.007) 3) Severity of periodontal disease (expressed as either PPD or CAL) was sign. associated with development of manifest diabetes	• age • sex • smoking • BMI • exercise • alcohol
COMMENTS: *May be regarded as 1998 cross-sectional exam plus 1988 OGGT data, i.e., oral health data only from 1998 (not from BL 1988); **NHANES III protocol (1 max.+ 1 mand. quadrant) 4 "trained" examiners; No calibration reported							
Demmer et al. 2008 USA Prospective Cohort	A) N @ BL =11,375 (40%M+60%F) n @ FU =9,296 PD Groups@BL: PD-1#(PI)=Periodontal Index: a1) 762 (>0-0.87) a2) 761 (0.88-1.60) a3) 759 (1.61-2.44)	NHANES I protocol • gingival inflammation extent • presence or absence of periodontal pockets • tooth mobility PDGroups@BL: PD-1#(PI): "Periodontal Index"	• death certificates • DM discharge diagnosis from health care facility • self-reported DM requiring medication	Yes, stat. sign. in US adults Generalisable to US adults	1) Compared to those periodontally healthy (PI=0), the risk of incident DM were: 1a) PD-1#: OR for PI quintiles w/increasing PD: a1) 1.10(0.73-1.64) a2) 1.03(0.65–1.63)	1) The extent of periodontal disease (using PD-1) and periodontitis (using PD-2) were associated with incident diabetes 2) The association of periodontal disease (PD-1) and periodontitis (PD-2) with incident diabetes was	• age • sex • race • education • smoking status • BMI • subscapular skinfold • physical activity • hypertension

Table 4. (continued)

Author Year Country Study Design (No DM@BL)	A) # Subjects: a. Perio Cases b. Comparison group B) Age C) Study Duration	EXPOSURE Perio Measure & Case Definition	OUTCOME Diabetes Measure & Definition at BL/FU	Effect on Metabolic Control? & Generalisable?	Effect Size: HR, OR, RR & Significance (95%CI)	Effect on Metabolic Control/ Conclusion	Confounders Controlled
	a4) 759 (2.45-5.07) a5) 760 (5.08-8.0) a6) 2,127edentulous b) 3,368 (PI=0) (healthy) PD-2&#: a1) 2,135 gingivitis a2) 1,662 perio b) 3,372 healthy B) 50+19yrs [25-74yrs] C) 17(+4)yrs [1-22yrs]	(Mean Score(0-8) for Dentition): a1) lowest PI to a5) highest PI quintile a6) edentulous b) healthy: PI=0 PD-2&#: a1) 2,135 gingivitis a2) 1,662 perio b) 3,372 healthy PD-3: # Natural Teeth: a1) 18-23 a2) 8-17 a3) 1-7 b) 24-32			a3) 2.08(1.51-2.87) a4) 1.71(1.19-2.45) a5) 1.50(0.98–2.27) 1b) PD-2#&: Those with gingivitis had 40% and those with periodontitis 50% increased odds of developing DM (p< 0.05 for both) 1c) Edentulous: OR=1.3(1.00-1.70) 2) PD-3: Dentate with advanced tooth loss (25-31 teeth missing) had OR=1.70 (P<0.05) relative to those with minimal tooth loss (0-8 teeth)	found also in normo-weight andin never-smoking participants	• total cholesterol • total caloric intake • total protein • total carbohydrate • total fat • poverty index • white blood cell count
COMMENTS: Data from NHANES 1 [1971-1976 (BL)] & NHEFS 1982-1992 (FU); n = 817 incident DM cases were reported (cumulative incidence = 9%); &) *Wu et al. 2000*; #) *Hujoel et al. 2000*							
Morita et al. 2012 Japan Cohort	A) # @ BL unknown* N @ FU=6,125 (76.6%M+23.4%F) w/BL HbA1c<6.5% Nby CPI Code: a1) 4,114 (3,383M+731F) a2) 1,634 (1,424M+210F) b) 377 (240M+137F) B) [30-69yrs] C) 4-5.5yrs	Partial mouth CPI CPI Code 0: Healthy gingiva CPI Code 3: ≥1 PPD= 4-5mm CPI Code 4: ≥1 PPD> 6mm PD by CPI Code: a1) 3 a2) 4 b) 0	• HbA1c≥6.5% @ FU	Yes, stat. sign. in employed 30-69 years old (76.6% male) Japanese (Nagoya) Not generalisable	Relative risk (RR) for HbA1c≥6.5% at 5yr FU in groups w/PPD of 4-5mm was 2.47 (0.78-7.79; p=0.122) and for those w/PPD of ≥6mm: 3.45 (1.08-11.02; p=0.037)	Periodontal disease (pockets ≥6mm) leads to increased inci-dence of type 2 diabetes (HbA1c>6.5%) in 5 years	• BMI • alcohol • smoking status • sex • age
COMMENTS: *No FU of those who left the workplace during study period; Kappa statistics 0.7-0.9 for calibration of 7 dentist periodontal examiners; Dose-response effect % of BL CPI codes 0, 3, & 4 w/5yr HbA1c>6.5%: 0.8%, 2.5%, and 3.9% (p = 0.001)							

#, Number (of); &, and; BL, Baseline/Beginning of Study Period; CAL, Clinical Attachment Loss; CI, Confidence Interval; CPI, Community Periodontal Index; DM, Diabetes Mellitus; F, Female; FPG, Fasting Plasma Glucose; FU, Follow-Up/End of Study Period; HbA1c, Glycosylated(Glycated) Haemoglobin; HDL, High-Density Lipoprotein; hr, hour; HR, Hazard Ratio; M, Male; Mod. , Moderate; NHANES 1, First National Health and Nutrition Examination Survey; NHEFS, NHANES 1 epidemiologic Follow-up Survey; OGTT, Oral Glucose Tolerance Test; OR, Odds Ratio; Perio/PD, Periodontal Disease/Periodontal/Periodontally; PPD, Periodontal Probing (Pocket) Depth; RR, Risk Ratio; Sev., Severe; Stat. sign., Statistically Significant; *vs., Versus*; w/o, Without; yr(s), Year(s).

have greater risk for developing (incident) type 2 diabetes than those with better periodontal health? (E6)

Brief summary of characteristics and results

Three of the four eligible studies displayed in Table 4 were conducted in Japan and one in the USA. Numbers of participants at the end of the studies were 12,934 in the former three and 9296 in the latter, totalling 22,230 individuals. The two largest Japanese studies included employed adults aged 30–59 and 30–69, respectively, and the third was community based among 40–79 year olds. Demmer et al. analysed data representative of the US population between 25 and 74 years of age (Demmer et al. 2008).

During study periods of 1–22 years, three of the four studies demonstrated a statistically signifi-

cant increase in development of manifest diabetes in people with severe periodontal disease, determined by periodontal probing depth, after adjustment for potential confounders (Saito et al. 2004, Demmer et al. 2008, Morita et al. 2012). In the fourth, the tendency for increased risk was not significant upon adjustment, except in Japanese employed females with moderate periodontal disease (Ide et al. 2011).

For instance, those with PPD of 6 mm or greater at baseline had 3.45 times higher risk of developing diabetes than those without periodontal disease (Morita et al. 2012). In the US population, people with gingivitis had 40% increased odds of developing diabetes and those with periodontitis had 50% elevated risk. In edentulous individuals, the risk was increased by 30 per cent and those with advanced, but not complete, tooth loss had a 70 per cent increased risk of incident type 2 diabetes. Measured by two different indices, the association of periodontal disease with incident diabetes was found also in individuals who were of normal weight as well as among people who had never smoked cigarettes (Demmer et al. 2008).

In addition, severity of periodontal disease expressed by clinical attachment loss at follow-up was significantly associated with development of diabetes over ten years in the smallest study (Saito et al. 2004), in which each additional millimetre mean PPD corresponded to 0.13% HbA1c increase ($p = 0.007$).

Quality assessment

The generally high quality of this group of large, longitudinal studies is reflected in the high NOS star ratings as displayed in Exhibit Appendix S12, with two earning the maximum of nine stars, one-eight and one-seven, averaging 8.3.

Major weaknesses

Eligible studies were performed exclusively in Japan and the United States with only one smaller Japanese (Saito et al. 2004) and the large US (Demmer et al. 2008) studies being representative of the general population. Two were conducted in Japan among employees (Ide et al. 2011, Morita et al. 2012). Major concerns regarding the Japanese work place studies were, *firstly*: The oral health examinations were not conducted for research and used the Community Periodontal index (CPI) (Ainamo et al. 1982), a quick periodontal assessment of ten index teeth that does not adequately represent the periodontal health status. *Secondly*, employees who left the company during the study period were not re-examined at the end. In one study, it remains unknown how many were lost to follow-up (Morita et al. 2012); and in the other, a total of 2904 or one-third (33.2%) of the employees who received oral exams at baseline were not re-examined at the end of the study (Ide et al. 2011). Such unknown and large attrition, respectively, does not lead to confidence that those remaining in the study were representative of those originally examined. *Thirdly*, the employees included two to three times more males than females, and the analyses were not adjusted for education level that could be different in the two sexes. The Japanese community-based study included an oral examination only at follow-up and therefore did not provide any knowledge of the periodontal status at baseline (Saito et al. 2004). This study could be regarded as a cross-sectional examination, supplemented with additional oral glucose tolerance test (OGTT) data from ten years earlier. Even though the results from the three Japanese studies were significant, this evidence may not be transferable to other race/ethnic groups since differences in fat storage and other factors may be operative. The national US study used periodontal inflammation, PPD and number of teeth present to evaluate the periodontal health status, whereas CAL was not assessed.

5. Do women with gestational diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health? (E4)

AND

6. Do pregnant women, who have poorer periodontal health, have greater risk for gestational diabetes than those with better periodontal health? (E5)

Brief summary of characteristics and results

Shown in Table 5 are the only two eligible small American case-control studies that examined the effect of periodontal disease on prevalence of gestational diabetes (GDM). One demonstrated that GDM in a dose–response manner consistently was associated with clinical PD using three different PD definitions (Xiong et al. 2009). The other concluded that having sites with periodontal probing depths of 3 mm or greater was not associated with GDM, although high vaginal levels of the periodontal pathogen, *Tannerella forsythia*, was associated with gestational diabetes (Dasanayake et al. 2008).

Quality assessment

One study used full-mouth periodontal probing, applied three PD definitions, and controlled for several potential confounders (Xiong et al. 2009), whereas the other defined PD as having at least one site with PPD of 3 mm or greater and controlled for only history of GDM. In pregnant women, PPD of 3 mm could represent non-pathological conditions, namely increased probing depths due to hormonal changes and oedema. Exhibit Appendix S13 displays the consensus ratings regarding the quality of these two studies.

Major weaknesses

There were only two studies, and they were small, of case-control design, and conducted among non-representative samples, making their findings non-generalizable.

Discussion

Summary of the evidence

Current evidence for effects of periodontal disease on glycaemic control is scarce. However, it suggests that *compared to periodontally healthy individuals*, people with poor periodontal health and:

- *type 2 diabetes* or *no diabetes:* have greater risk of developing poorer glycaemic control

Table 5. Effect of periodontal disease on gestational diabetes (E4/E5)

Author Year Country Study Design (All GDM)	A) # Subjects: a. Gestational Diabetes Cases (GDM) b. Comparison group B) Age	EXPOSURE Perio Measure & Case Definition	OUTCOME Gestational Diabetes Measure & Definition	Effect on Metabolic Control? & Generalisable?	Effect Size: OR & Significance (95%CI)	Effect on Gestational Diabetes Conclusion	Confounders Controlled
Xiong et al. 2009 USA Case-Control GDM	A) N=159 pregnant: a. 53 GDM b. 106 non-GDM B) Age (Mean+SD): a. 29.9(±5.6)yrs b. 27.1(±5.9)yrs	Full mouth exam (6 sites/tooth) • ging/BOP • PPD • CAL • gingival recession PD1: ≥1 PPD ≥4mm or ≥1 CAL ≥4mm PD2&3: 2 additional PD definitions used Extent measured by PPD & CAL	• 50g oral glucose challenge test (GCT) • 100g OGTT b. Comparison group: • Passed 50g GCT • No DM of any type	Yes, stat.sign. for most exposure parameters Not generalisable	OR for GDM: • PD (PPD ≥4mm or CAL≥4mm) *vs.* perio-dontally healthy: OR=2.6 (1.1-6.1;p=0.014) • PPD highest quartile *vs.* lowest: adj.OR=3.8 (1.0-14.0; p_{trend}=0.011) • CAL highest quartile *vs.* lowest: adj. OR=4.5 (1.2-16.9; p_{trend}= 0.007)	1) Periodontitis was consistently associated with increased risk of GDM, regardless of PD definition 2) There was a dose-response relationship of increased GDM risk with increasing severity of periodontal di-sease, assessed by PPD or CAL	• maternal age • parity • race • marital status • education • income • family income • smoking • alcohol • systemic antibiotics in pregnancy • family DM history • dental insurance • BMI Multivariate
COMMENTS: Intra- & inter-examiner calibration reported; but only1 dental examiner; PD extent (PPD, CAL) used as continuous & categorical variables; Dose-response effect stat. sign. for trend; PD (≥1 PPD ≥4 mm or ≥1 CAL ≥4 mm) in 77.4% of GDM *vs.* 57.5% without GDM: OR = 2.5 (1.2-5.3; p < 0.05)							
Dasanayake et al. 2008 USA Case-Control GDM	A1) N @ BL=268* A2) N @ FU=265 pregnant: a. 22 GDM b. 243 non-GDM B) a. 28.7(±5.3)yrs b. 26.6 (±5.8)yrs	1) 5 Periodontal Patho-gens** from: • dental plaque • cervix • vagina 2) Clinical PD: Partial mouth • PPD • BOP PD: ≥1 PPD≥3mm	GDM OGTT: 1hr, 2hrs, or 3hrs	Yes:Vaginal *Tannerella forsythia* had a stat. sign. effect on GDM Not generalisable	1) Elevated risk for GDM in women with high vaginal levels of *Tannerella forsythia:* OR=1.27 (1.05-1.55; p=0.01). 2) *T. forsythia* in cervix (OR=1.04; 0.85-1.28) &dental plaque (OR=0.97;0.83-1.12); not stat. sign. 3) Having PD (OR=1.68; 0.52-5.43): not stat. sign.	1) Levels of *Tannerella forsythia* in the vagina, but not in the cervix or in dental plaque, emerged as a risk factor for GDM 2) Having one or more sites with periodontal probing depth of 3mm or more was not a risk factor for GDM	• Prior GDM
COMMENTS: *83% Hispanic Examiner calibration not reported; **Clinical, bacteriological, immunological, and inflammatory mediator parameters assessed 7 weeks prior to diagnosis of GDM; Prevalence of ≥1 PPD ≥3 mm: 50% in GDM *vs.* 37% in non-GDM; difference not stat. sign. (p = 0.38)							

#, Number (of); &, and; BL, Baseline/Beginning of Study Period; BOP, Bleeding On Probing; CAL, Clinical Attachment Loss; CI, Confidence Interval; DM, Diabetes Mellitus; FU, Follow-Up/End of Study Period; GCT, Glucose Challenge Test; GDM, Gestational Diabetes Mellitus; Ging., Gingival; hr(s), Hour(s); HR, Hazard Ratio; OGTT, Oral Glucose Tolerance Test; OR, Odds Ratio; Perio/PD, Periodontal Disease, Periodontal/Periodontally; PPD, Periodontal Probing (Pocket) Depth; RR, Risk Ratio; Stat. sign., Statistically Significant; *T. forsythia, Tannerella forsythia; vs., Versus*; yr(s), Year(s).

- *type 1 or type 2 diabetes:* have greater risk for diabetes-related complications
- *no diabetes:* have greater risk of developing manifest diabetes.

Results of only two studies exploring the effect of periodontal disease on gestational diabetes are inconclusive.

Limitations

Study and outcome level

Only 17 reports were eligible for inclusion in the final review and included only one study on type 1 and two on gestational diabetes. Most studies were small, except those exploring diabetes incidence. The studies were conducted in a limited number of countries. A major limitation in all studies regarding periodontal disease is the lack of generally accepted case definitions for periodontal disease, which severely impedes or prevents comparison of studies (Tonetti & Claffey 2005, Page & Eke 2007, Manau et al. 2008, Costa et al. 2009, Leroy et al. 2010). Because both diabetes and periodontal disease are multifactorial, chronic diseases, most studies were not sufficiently extensive in size, duration and number or kinds of parameters to control for all potentially important confounders.

Review level

To maximize comprehension and interpretation of the findings, only reports published in the English language were included, which may have excluded potentially valuable evidence. Moreover, we may have overlooked evidence in English that we failed to identify, but we succeeded in retrieving all but one full text article that, based on the abstract, probably was a cross-sectional study, and thus ineligible for inclusion. As with any scientific evidence, publication bias resulting from a tendency to preferentially publish positive study findings may have played a role in creating the pool of published reports.

Conclusion

Scant current evidence suggests that periodontal disease adversely affects glycaemic control and diabetes complications or promotes development of type 2 diabetes. Consequently, large-scale, definitive studies of long duration and in multiple different population groups in many different countries are needed in all the areas this review explored.

Consequences

Should it be possible to demonstrate an adverse effect of periodontal disease on glycaemic control, with periodontal disease being a risk factor for diabetes complications and incident diabetes, such evidence could have far-reaching consequences. Impacted would be patients and families, health care providers, insurance companies, policy-makers and societies in general, due to the high prevalence of both periodontal disease and diabetes that incurs immense societal, economic consequences and human suffering. Controlling and managing periodontal disease may be a new alternative to eventually include in standards for diabetes care. Such shift in paradigm for management and prevention of diabetes and its complications may occur in the future.

While waiting for definitive evidence, it may be wise to make efforts to prevent – and treat to resolution any existing – periodontal disease, in order to ensure good health.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix S1. Overview: Databases Searched for Evidence.
Appendix S2. Scoring Form: Recording Ineligible Studies and Reasons.
Appendix S3. Overview: The 97 Reports Excluded Based on Full Text: Citations and Main Exclusion Reason.
Appendix S4. Scoring Form: Description and Findings (All Study Designs).
Appendix S5. Overview: The 16 Reports (17 Studies) Included in the Final Review: Eligibility Category & Citation.
Appendix S6. Description of the Newcastle-Ottawa Scale (NOS) for Quality Rating.
Appendix S7. Scoring Form: Quality of a Cohort Study.
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Appendix S9. Scoring Form: Quality of a Cross-sectional Study.
Appendix S10. Consensus Quality Rating: 4 Studies on Effect of Periodontal Disease in Type 2 Diabetes (E1a) and No Diabetes (E1c).
Appendix S11. Consensus Quality Rating: Studies on Effect of Periodontal Disease on Diabetes Complications(E3).
Appendix S12. Consensus Quality Rating: Studies on Effect of Periodontal Disease on Incidence of Diabetes Mellitus (E6).
Appendix S13. Consensus Quality Rating: Studies on Effect of Periodontal Disease on Gestational Diabetes (E4/E5).

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Clinical Relevance

Scientific rationale for the study: Periodontal disease and diabetes mellitus are common chronic diseases occurring worldwide. This systematic review explored the epidemiologic, non-experimental, observational evidence for effects of periodontal disease on diabetes.

Principal findings: Poor periodontal health is associated with worsening of glycaemic control and complications in diabetes, as well as development of type 2 diabetes.

Practical implications: The current, limited evidence suggests that periodontal disease negatively influences diabetes outcomes, and that further longitudinal studies are warranted. In the meantime, dental care professionals should prevent or definitively treat periodontal disease, especially among patients with diabetes.