A SYSTEMATIC REVIEW AND META-ANALYSIS OF EPIDEMIOLOGIC OBSERVATIONAL EVIDENCE ON GLYCAEMIC CONTROL AND RISK OF DEVELOPING DIABETES IN HEALTHY PATIENTS

Revisione sistematica e metanalisi dell'evidenza epidemiologica-osservazionale sul controllo glicemico ed il rischio di sviluppare il diabete in pazienti sani

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Running title: Effect of periodontitis on glycaemic control

Key words: Periodontal disease, diabetes, epidemiology

Abstract

Aim: to evaluate the impact of periodontal disease on glycaemic control, and new diabetes development in healthy patients.

Methods: Observational studies (cross-sectional, case-control and cohort design) on periodontitis effect on glycaemic control, published until January 2017, were identified through electronic databases and hand- searched journals. Findings were summarized by evidence tables, using PRISMA statement. Quality of the included studies was evaluated through the Newcastle Ottawa scale. Meta-analysis was performed with random approach when feasible.

Results: healthy subjects with periodontitis show a worse glycaemic control: 0.29 % of Hb1AC (0.20-0.37 %, 95% C.I. p<0.01) and a higher risk of 29% (1,11-1-46, 95% CI , p<0.0001) of developing diabetes.

Conclusions: Periodontitis has a significant impact on diabetes incidence and glycaemic control in healthy patients. Nevertheless, additional evidence is needed to further re-enforce such knowledge.

Introduction

Diabetes and periodontitis are two common chronic diseases that affect people worldwide.

The recent report published by WHO in 2016 has stated that in 2014 about 422 million adults were living with diabetes (World Health Organization 2016); this data is very alarming because the global prevalence of this condition increased from 4.7% in 1980 to 8.5% in 2014, in the adult population. Another important aspect is that diabetes increment was particularly marked in low- and middle-income countries than in high-income ones, as a consequence of such risk factors increment, like obesity and sedentary behaviours (Lear et al. 2014). In 2012 diabetes and poor

glycaemic control have caused globally about 3.7 million of deaths, affecting the risks of cardiovascular and other diseases and 43% of these occurred in people younger than 70 years old.

Periodontitis affects about the 50 % of word population, with severe forms incidence ranging between 5-10% (Petersen et al. 2005, Eke & Dye 2009, Mattila et al. 2010, Hu et al. 2011).

Currently there is an increasing interest in the literature in links between periodontitis and inflammatory systemic diseases, like hypertension, diabetes and cerebro-cardiovascular conditions

(Ylöstalo et al. 2010, Lockhart et al. 2012, Borgnakke et al. 2013). The persistence of bacterial biofilm in periodontal sites and the consequent inflammatory reaction, could lead to a cumulative inflammatory burden in the host, predisposing the patients to the development of other systemic chronic conditions. Loos et al. have shown that people affected by periodontitis are characterized by altered total numbers of leukocytes and plasma levels of C-reactive protein (CRP)(Loos et al. 2000).

The aim of this work is to perform a systematic review and meta-analysis of epidemiologic observational evidence on glycaemic control and risk of developing diabetes in healthy patients

Materials and Methods

Protocol development and eligibility criteria

The present study aimed to review observational studies published until January 2017 that analysed the effect of periodontitis on glycaemic control. In particular we have performed an update of the systematic review published by Borgnakke in 2013 and that have analysed article published until the January 2013 (Borgnakke et al. 2013).

A detailed protocol was designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Moher et al. 2009, Liberati et al. 2009). The systematic review was designed to answer the following focused questions:

1. Do people with not known diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?

2. 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?

Studies to be included had to be non-intervention, observational studies such as cohort, case-control (cases represented by periodontally-affected subjects and controls by non periodontally – affected subjects) or cross-sectional in design. In the selected studies, *exposure* had to be periodontal status (measures of inflammation, sings of disease such as pocketing and attachment level excluding tooth loss/edentulousims) of the included subjects and *outcome* one parameter related to diabetes such as measures of glucidic metabolism (glycated hemoglobin (Hb1Ac), fasting and 2-h 75 g plasma glucose (FBG) level and oral glucose tolerance test (OGT)), incidence of new cases, diabetes-related complications. Only studies in English language were selected.

Information sources and Search

We conducted a search on electronic databases using the same MeSH terms and free text words,

up to January 2017. Words searched were: ("periodontal diseases"[mh] OR periodontium[mh] OR periodon- tics[mh] OR periodont*[tiab]) AND ("diabetes mellitus"[mh] OR "diabe- tes 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 glu- cose"[mh] OR "blood sugar"[tiab] OR ((glucose[ti] OR sugar[ti]) AND (level[ti] OR control[ti])) OR hyperglycemia[mh] OR hypoglyce- mia[mh] OR glycemi*[tiab] OR glycaemi*[tiab] OR hyperglyc*[tiab] OR hypoglyc*[tiab]). Filters used were: Humans and English language.

Presence of duplicates was assessed through Mendeley software.

Study selection and Data Collection

Eligibility assessment was performed through titles, abstract analysis, and full text analysis. Titles and abstracts of the search results were initially screened by the two reviewers (F.G. and M.P.), for possible inclusion in the review. Each round of calibration consisted of a duplicate, independent validity assessment of 20 titles and abstracts from the search. After two rounds of calibration, a consistent level of agreement was found.

In order to avoid excluding potentially relevant articles, abstracts providing unclear results were included in the full text analysis. The full text of all studies of possible relevance was then obtained for independent assessment against the stated inclusion criteria. Any disagreement was resolved by discussion among the reviewers.

Excluded articles were classified according to a hierarchical scale according to the main reasons for exclusion (Borgnakke et al. 2013): 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 reasons.

Manuscripts not to be excluded were categorized into the following groups: E1. Glycaemic control in not known diabetes, E2. Incident type 2 diabetes (new diabetes developed in individuals without diabetes at baseline).

Data of the included articles were extrapolated through an "ad hoc" extraction sheet.

Data Items

Risk of bias across studies

Heterogeneity among the studies was tested when feasible and evaluated through Q and I^2 test. A p value of Q statistic <0.05 was defined as an indicator of heterogeneity and data were considered heterogeneous for I^2 value higher than 40%.

Risk of bias in individual studies

The quality of each cohort and case- control study according to NOS for Assessing the Quality of Non-randomized Studies (Wells et al. 2011). Evaluation of cross-sectional studies was made according to scale suggested by Borgnakke and co-workers (Borgnakke et al. 2013). Using these forms, we rated each report at both the study and outcome levels.

Summary measures and synthesis of the results

Outcomes considered were odds ratios (OR), hazard ratios (HR) and hazard rate ratios (HRR), risk ratios, rate ratios or relative risks (RR). Results were presented as the manuscript presented by Needleman and co-workers in a recent EFP workshop highlighting results of the previous

evidence, summary of the new evidence and overall synthesis (Needleman et al. 2015). Data were collected in evidence tables and results of the meta-analysis were summarized with Forest plots.

Additional analysis

Meta-analysis was performed when outcome data were homogenous and available from at least three studies. HbA1c was expressed as whited mean differences (WMD) and 95% CI for continuous outcomes using random model. The patient was the unit of the analysis. Analyses were performed with OpenMeta[Analyst]

http://www.cebm.brown.edu/open_meta/open_meta/open_meta.

Hazard ratios (HR) was expressed as mean effect size and 95% CI for dichotomous data using random model and was calculated with Meta-Essentials: Workbooks for meta-analysis (Version 1.1) (http://www.erim.eur.nl/research-support/meta-essentials/downloads/).

Results

Study selection

A total of 696 studies, published between 2013 and 2017, were identified for inclusion in the review (Fig. 1). Screening of titles and abstracts led to rejection of 595 papers and thus the full text of the remaining 101 papers was obtained. After full-text analysis and the exclusion of further 80 articles, the remaining 21 articles were analysed for methodological quality and availability of data for systematic review or meta-analysis (Tab.1). The final evidence was obtained including the 6 articles selected in the meta-analysis of Borgnakke et al., for what concerning the period until the January 2013.

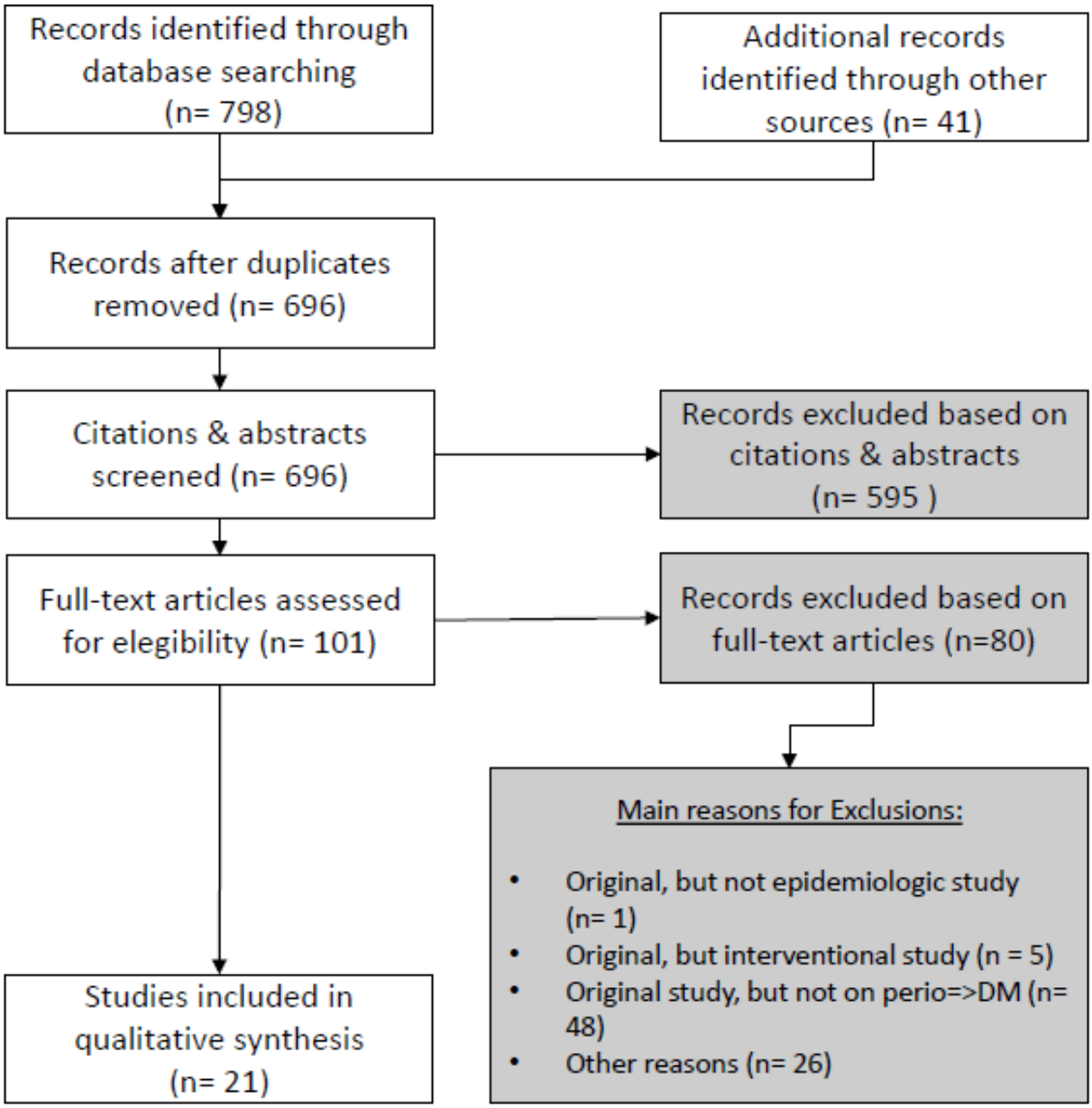
Table 1. The 27 reports included in the final review: citations; the 6 article in red have been included from Borgnakke et al. (Borgnakke et al. 2013)

1. Arora, N., Papapanou, P.N., Rosenbaum, M., Jacobs, D.R., Desvarieux, M. & Demmer, R.T. (2014) Periodontal infection, impaired fasting glucose and impaired glucose tolerance: results from the Continuous National Health and Nutrition Examination Survey 2009-2010. Journal Of Clinical Periodontology 41, 643–52.
2. Banu, S., Jabir, N.R., Mohan, R., Manjunath, N.C., Kamal, M.A., Kumar, K.R.V., Zaidi, S.K., Khan, M.S. & Tabrez, S. (2015) Correlation of Toll-like receptor 4, interleukin-18, transaminases, and uric acid in patients with chronic periodontitis and healthy adults. Journal Of Periodontology 86, 431–9.
3. Chang, J.-F., Yeh, J.-C., Chiu, Y.-L., Liou, J.-C., Hsiung, J.-R. & Tung, T.-H. (2017) Periodontal Pocket Depth, Hyperglycemia, and Progression of Chronic Kidney Disease: A Population-Based Longitudinal Study. The American Journal Of Medicine 130, 61–69.e1.
4. Chiu, S.Y.-H., Lai, H., Yen, A.M.-F., Fann, J.C.-Y., Chen, L.-S. & Chen, H.-H. (2015) Temporal sequence of the bidirectional relationship between hyperglycemia and periodontal disease: a community-based study of 5,885 Taiwanese aged 35-44 years (KCIS No. 32). Acta Diabetologica 52, 123–31.
5. Choi, Y.-H., McKeown, R.E., Mayer-Davis, E.J., Liese, A.D., Song, K.-B. & Merchant, A.T. (2014) Serum C-reactive protein and immunoglobulin G antibodies to periodontal pathogens may be effect modifiers of periodontitis and hyperglycemia. Journal Of Periodontology 85, 1172–81.
6. 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.
7. 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.
8. El-Beshbishy, H.A., Maria, R.A. & Bardi, F.A. (2014) Biochemical and C-reactive protein alterations in myocardial infarction periodontitis patients. The American Journal Of The Medical Sciences 348, 181–5.
9. Flores, M.F., Montenegro, M.M., Furtado, M. V, Polanczyk, C.A., Rösing, C.K. & Haas, A.N. (2014) Periodontal status affects C-reactive protein and lipids in patients with stable heart disease from a tertiary care cardiovascular clinic. Journal Of Periodontology 85, 545–53.
10. Garcia, D., Tarima, S. & Okunseri, C. (2015) Periodontitis and glycemic control in diabetes: NHANES 2009 to 2012. Journal Of Periodontology 86, 499–506.
11. Gokhale, N.H., Acharya, A.B., Patil, V.S., Trivedi, D.J., Setty, S. & Thakur, S.L. (2014) Resistin Levels in Gingival Crevicular Fluid of Patients With Chronic Periodontitis and Type 2 Diabetes Mellitus. Journal Of Periodontology 85, 610–617.
12. Hong, J.W., Noh, J.H. & Kim, D.-J. (2016) The Prevalence and Associated Factors of Periodontitis According to Fasting Plasma Glucose in the Korean Adults: The 2012-2013 Korea National Health and Nutrition Examination Survey. Medicine 95, e3226.
13. 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.
14. Islam, S.K.M.A., Seo, M., Lee, Y.-S. & Moon, S.-S. (2015) Association of periodontitis with insulin resistance, β-cell function, and impaired fasting glucose before onset of diabetes. Endocrine Journal 62, 981–9.
15. Javed, F., Ahmed, H.B., Saeed, A., Mehmood, A. & Bain, C. (2014) Whole salivary interleukin-6 and matrix metalloproteinase-8 levels in patients with chronic periodontitis with and without prediabetes. Journal Of Periodontology 85, e130-5.
16. Kapellas, K., Skilton, M., Maple-Brown, L., Do, L., Bartold, P., O'Dea, K., Brown, A., Celermajer, D. & Jamieson, L. (2014) Periodontal disease and dental caries among Indigenous Australians living in the Northern Territory, Australia. Australian Dental Journal 59, 93–99.
17. Lee, K.-S., Lee, S.G., Kim, E.-K., Jin, H.-J., Im, S.-U., Lee, H.-K., Merchant, A.T., Song, K.-B. & Choi, Y.-H. (2015) Metabolic syndrome parameters in adolescents may be determinants for the future periodontal diseases. Journal Of Clinical Periodontology 42, 105–12.
18. Lin, S.-Y., Lin, C.-L., Liu, J.-H., Wang, I.-K., Hsu, W.-H., Chen, C.-J., Ting, I.-W., Wu, I.-T., Sung, F.-C., Huang, C.-C. & Chang, Y.-J. (2014) Association between periodontitis needing surgical treatment and subsequent diabetes risk: a population-based cohort study. Journal Of Periodontology 85, 779–86.
19. Longo, P.L., Artese, H.P.C., Rabelo, M.S., Kawamoto, D., Foz, A.M., Romito, G.A., Dib, S.A. & Mayer, M.P.A. (2014) Serum levels of inflammatory markers in type 2 diabetes patients with chronic periodontitis. Journal Of Applied Oral Science : Revista FOB 22, 103–8.
20. 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.
21. 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.
22. Perayil, J., Suresh, N., Fenol, A., Vyloppillil, R., Bhaskar, A. & Menon, S. (2014) Comparison of glycated hemoglobin levels in individuals without diabetes and with and without periodontitis before and after non-surgical periodontal therapy. Journal Of Periodontology 85, 1658–66.
23. Rao Deepika, P.C. & Saxena, R.M. (2013) Comparison of glycosylated hemoglobin levels in severe periodontitis patients and healthy controls: a study in an Indian population. Quintessence International (Berlin, Germany : 1985) 44, 319–25.

24. Saito, T., Shimazaki, Y., Kiyohara, Y., Kato, I., Kubo, M., Iida, M. & Koga, T. (2004) The severity of periodontal disease isassociated with the development of glucose intolerance in non-diabetics: the Hisayama study. J Dent Res 83, 485–490. doi:10.1177/154405910408300610.
25. Srinivasa, T.S., Agrawal, P., Goyal, P., Farista, S., Sowmya, N.K. & Deonani, S. (2015) Comparative clinical evaluation of glycosylated haemoglobin level in healthy and chronic periodontitis patients: A chairside diagnostic method. Indian Journal Of Dental Research : Official Publication Of Indian Society For Dental Research 26, 504–7.
26. Tu, Y.-K., D'Aiuto, F., Lin, H.-J., Chen, Y.-W. & Chien, K.-L. (2013) Relationship between metabolic syndrome and diagnoses of periodontal diseases among participants in a large Taiwanese cohort. Journal Of Clinical Periodontology 40, 994–1000.
27. Xiong, X., Elkind-Hirsch, K.E., Xie, Y., Delarosa, R., Maney, P., Pridjian, G. & Buekens, P. (2013) Periodontal disease as a potential risk factor for the development of diabetes in women with a prior history of gestational diabetes mellitus. Journal Of Public Health Dentistry 73, 41–9.

Fig.1. Flow of studies during 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 2–3 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.

Do people without manifest type 2 diabetes, who have poorer periodontal health, have poorer glycaemic control than those with better periodontal health?

Findings of New Evidence

Non-diabetic subjects, in a follow-up ranging from 4 to 10 years, showed a greater deterioration of glycaemic control as showed by an increase of Hb1Ac, impaired glucose tolerance or metabolic syndrome incidence associated with higher values of periodontal parameters such as PPD or CAL (Saito et al. 2004, Demmer et al. 2010b, Morita et al. 2010). Each additional millimeter of PPD determined a 0,13% increase of Hb1Ac (Saito et al. 2004). Overall, it appeared that subjects with periodontits have a higher risk of worse glycaemic control.

An important increase of studies was noted in the last four years. The actual evidence can be drawn on twenty manuscripts, involving a total of 117077 non-diabetic subjects, ranging from 30 to 67284, conducted over 4 continents except Europe (Javed et al. 2013, Tu et al. 2013, Xiong et al. 2013, Rao Deepika & Saxena 2013, Boland et al. 2013, Longo et al. 2014, Garcia et al. 2014, Kapellas et al. 2014, Flores et al. 2014, Gokhale et al. 2014, Arora et al. 2014, Choi et al. 2014, El-Beshbishy et al. 2014, Perayil et al. 2014, Banu et al. 2015, Islam et al. 2015, Lee et al. 2015, Srinivasa et al. 2015, Hong et al. 2016, Chang et al. 2017) (Tab.2). The total evidence almost unanimously reported a worse glycemic control in subjects with periodontitis. Subjects with periodontal disease showed greater level of fasting blood glucose (Xiong et al. 2013, Islam et al. 2015), Hb1aC (Javed et al. 2013, Arora et al. 2014, Perayil et al. 2014, Srinivasa et al. 2015, Hong et al. 2016, Chang et al. 2017) and prevalence of pre-diabetes/diabetes (Kapellas et al. 2014, Choi et al. 2014, El-Beshbishy et al. 2014).

The data allowed meta-analysis of the Hb1Ac values based on 47,781 subjects. Subjects with periodontitis showed a weighted mean (WM) of 5.64 % (5.54-5.74 %, 95% C.I.). Whilst non-affected subjects showed a WM 5.31 % (5.18-5.44 %, 95% C.I.), showing a statistically significant ($p<0.01$) WM difference of 0.29 % Hb1AC (0.20-0.37 %, 95% C.I.).

Quality Assessment

The quality of the included study is depicted in the Table S1-3. A significant heterogeneity was noted among the included studies. Periodontal outcomes were taken in full-mouth examination (Javed et al. 2013, Xiong et al. 2013, Arora et al. 2014, Perayil et al. 2014, Banu et al. 2015, Hong et al. 2016, Chang et al. 2017), partial-mouth (Taylor et al. 1996, Saito et al. 2004, Morita et al. 2010, Demmer et al. 2010a, Longo et al. 2014, Kapellas et al. 2014, Choi et al. 2014, Lee et al. 2015) or gathered from electronic clinical notes/database (Boland et al. 2013). The majority of the studies were of cross-sectional design.

Some of the included articles were performed in selected populations such as adolescents (Lee et al. 2015) or young adults (Chiu et al. 2015a) and thus not generalizable. Some of the data are gathered form cross-sectional studies which primary intention was not to compare periodontitis versus non-periodontitis affected subjects. Moreover, these studies may highlight association rather than causality.

Fig.2. Forrest Plot from random effect of meta-analysis evaluating the difference in Hb1Ac among periodontitis affected subjects (cases) and non-affected ones (control) as gathered from observational studies (weighted mean difference (WMD), 95% Confidence Interval (C.I.).

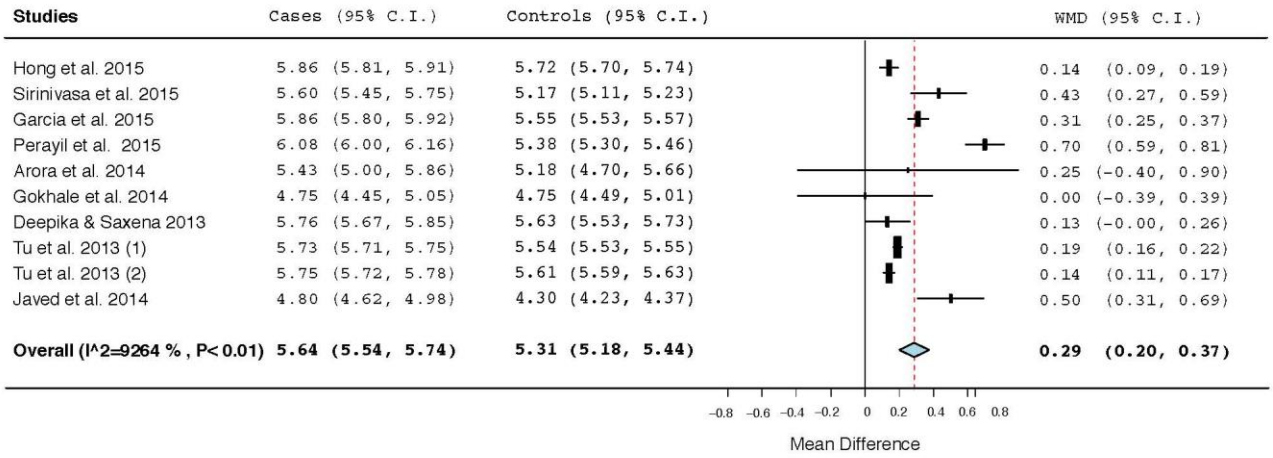


Table 2. Effect of Periodontal disease on metabolic control in subjects without diabetes. Articles in red have been included from Borgnakke et al. (Borgnakke et al. 2013)

Author Year Country Study Design BL DM Typer	**A) Subjects: a. Perio Cases b. Comparison groups B) Age C) Study Duration**	**EXPOSURE**	**OUTCOME**	**Effect on Metabolic Control? & Generalizable?**	**Effect size: Odds Ratio (OR), Trend, HR, HRR & Significance (95%CI)**	**Effect on Metabolic Control/Conclusion**	**Confunders Controlled**
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 generalizable	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							
Demmer et al. 2010 Germany (Pomerania)	A) N=2,793 (47%M+53%F) a1) 488 a2) 463	Perio Exam: Partial mouth* Tooth count:	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 (ptrend=0.84) 2) Those perio healthy at	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 cell count

Cohort No DM	a3) 479 a4) 241 b) 1,122 B) 48(+15)yrs [20-81yrs] C) 5yrs	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% Used 3 additional PD groupings based on: 1) BL PPD 2) BL # teeth 3) 5yr change in % sites w/CAL>5mm		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)		•fibrinogen hsCRP •sex region smoking •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

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 •eating btw. •meals •weight at BL •Multivariate

COMMENTS No examiner calibration; Dose-response effect stat. sign for trend; CPI is a poor measure of PD

Tu et al. 2013 Taiwan Cross -sectional NO DM	A) N= 33,740 (18,469 F + 15,271 M) Perio a1) 10381 b1) G=4729 b2) H=18536 B) CP: M= 53.22 yrs (dev.st 11.15) F= 54.15 yrs (dev.st 11.08) H: M=50.55 yrs (dev.st 12.93) F=49.96 yrs (dev.st 12.43) G: M=47.06 yrs (dev.st 11.78) F= 48.57 yrs (dev.st 11.48) C) NA	Gingivitis group: at least one tooth with the diagnosis of gingivitis but not periodontitis; Periodontitis group: at least one tooth with the diagnosis of periodontitis;	• FBG • PC • HbA1c (%) • Insulin resistance • Metabolic syndrome	• Yes, periodontal patients had statistically significant higher FBG, PC and HbA1c, compared to the reference control group. • Periodontitis is highly associated with insulin resistence and metabolic syndrome in female subjects. A weaker relation was noted for men (insulin resistance and periodontitis) Not generalizable	• <u>OR for MetS (significant only for Women)</u> Gingivitis 1.424 (1.301-1.559) p <0.001 Periodontitis 1.517 (1.413-1.628) p <0.001 • <u>OR for Insulin Resistance</u> <u>Women</u> Gingivitis 1.499 (1.368-1.643) p <0.001 Periodontitis 1.606 (1.494-1.726) p <0.001 <u>Men</u> Periodontitis 1.129 (1.039-1.227) p =0.004	Subject with periodontitis were characterized by higher level of Fasting glucose, postprandial glucose and HbA1c respect gingivitis and reference group. There is an increased prevalence of MetS in women affected by gingivitis and periodontitis. Effect even stronger in non smokers.	•Patients' occupations •Age •medications taken •major medical •conditions •smoking history (current, former or non-smokers) •number of cigarettes smoked per day
COMMENTS: no radiographs or periodontal charting was taken. No calibration reported. Only private patients coming from upper and middle class only.							
Xiong et al. 2013 USA Case-Control NO DM	A) N=39 Perio a1) 13 b1)26 B) prior GDM •<25 years old= 1	Full-mouth periodontal examination at six sites per tooth: • Probing depth (PD) • Gingival margin level • Clinical attachment loss (CAL) • Bleeding on probing (BOP)	• FBG • 1⁄2-hour glucose (mg/dL) • 1-hour glucose (mg/dL) • 2-hour glucose (mg/dL) • Fasting insulin (uU/mL) • 1⁄2-hour insulin (uU/mL) • 1-hour insulin (uU/mL) • 2-hour insulin (uU/mL) • HOMA-IR	Yes, worse blood glucose levels, 1-hour insulin and IS-SI were recorded in periodontal subjects Women with both prior GDM	• 1⁄2-hour glucose (mg/dL): 112.48 ± 1.25 (NPD) 138.41 ± 1.30 (PD) p<0.05 • 1-hour glucose (mg/dL): 91.62 ± 1.33 (NPD) 132.50 ± 1.34 (PD) <0.01 • 2-hour glucose (mg/dL): 90.66 ± 1.25 (NPD) 98.15 ± 1.41 (PD) NS	Periodontal disease alone is also associated (to a lesser extent) with lower insulin sensitivity, poorer b-cell function,and hyperglycemia. Even more significant if associate dwith history of GDM.	• Age • Race/ethnicity • Education • BMI

	•25-35 years old= 14 •>35 years old= 5 B2) no prior GDM •<25 years old= 2 •25-35 years old= 11 •>35 years old =6 C) not reported	26= Women without periodontal disease (NPD) 13= Women with periodontal disease (PD)	• Matsuda index (ISOGTT) • IGI/HOMA-IR • IS-SI	and periodontal disease had the most impaired glucose metabolism; Not Generalizable	• 1-hour insulin (uU/mL): 45.86 ± 1.64 (NPD) 73.83 ± 1.84 (PD) <0.01 • IS-SI: 620.61 ± 2.51 (NPD) 315.86 ± 3.51 (PD) P = 0.06		
COMMENTS: limited and peculiar sample (history of GDM: N=19 with a history of GDM , N=20 without GDM history), results hardly generalizable							
Arora et al. 2014 USA Cohort* NO DM	A) N= 1165 B) 30–80 years C) 1 year	Full-mouth examination 6 sites per tooth By a trained hygienist • PD • AL	• IFG or IGT • FPG • Two hour glucose (OGTT) (mg/dl) • Insulin levels (IU/ml) • HOMA-IR • HbA1c% (mmol/mol) Impaired fasting glucose (IFG) and Impaired glucose tolerance (IGT) IFG = fasting plasma glucose ≥100 mg/dl and <126 mg/dl; IGT = 2-h post-challenge glucose values ≥140 mg/dl and <200 mg/dl.	Yes, severe periodontitis was associated with a 93% increase in the odds of impaired glucose tolerance after multivariable adjustment. Findings were similar for mean PD. Associations between measures of periodontal infection and IFG were weak and not statistically significant. Genralizable	IGT prevalence: controls 12% cases 31% OR varied according to the model of adjustment from 1.75 (1.16–2.62) to 2.90 (1.80–4.68) highly significant. IFG prevalence controls 38% cases 59% OR varied according to the model of adjustment from 1.05 (0.56-1.99) to 2.01 (1.28–3.14). Only few models of adjustment reached significance Multivariable logistic regression models	Clinical measure of periodontal infections are associated with pre-diabetes	• Age • Race/ethnicity • Sex • Education • Physical activity level • Cigarette Smoking • Alcohol consumption Caloric intake • Height • Weight Blood pressure measures • BMI • Triglycerides Total cholesterol • HDL-cholesterol C-reactive protein (CRP) White blood cell count (WBC)

					• Periodontal status Mean PD ≥75th percentile: Isolated-IFG, OR= 0.91 [0.57, 1.45]; • Isolated-IGT, OR= 1.85 [0.73, 4.66]; • Combined IFG+IGT, OR= 2.06 [0.91, 4.66]; p= 0.05;		
COMMENTS: part of the NHANES, may be regarded as cross-sectional; Periodontal examination were made by trained, registered hygienist whose received intense training followed by periodic monitoring and recalibration against a reference examiner.							
Choi et al. 2014 USA Cross-sectional NO DM	A) N= 5,731 (2,575 M + 3,156 F) Periodontal quartiles: a1) Q1=1462 a2) Q2=1416 a3) Q2=1420 a4) Q2=1433 B) 20-65 yrs (43±16.9 yrs) C) 3 yrs	Periodontal examination (NHANES protocol) • CAL • PD measured at two sites (mid-buccal and mesiobuccal) on every tooth in each of two randomly chosen quadrants, one in the maxilla and the other in the mandible IgG antibodies to A. actinomycetemcomitans (cut off 156 EU) and P. gingivalis (cut-off 168) Median CAL: • Q1= 0.27 • Q2= 0.59 • Q3=1.00 • Q4= 2.19	Fasting plasma glucose (FPG) • normal; FPG <100 mg/dL (5.6 mmol/L) • prediabetes:100<FPG<126mg/dL (7.0 mmol/L), • diabetes: FPG >126 mg/dL or self-reported	Yes, there was a statistically significant association between IFG and diabetes with CAL, in particular Q3 and Q4; for what concerning PD, Q4 was associated with IFG and Q2, Q3 and Q4 were associated with diabetes.	Confounding Effect (OR [95% confidence interval]) of CRP and Antibodies on CAL and Prediabetes and Diabetes -Quartile for CAL IFG • Q2=0.97 (0.83 to 1.13)* ; 0.96 (0.83 to 1.13)**; 0.97 (0.83 to 1.13)***; 0.97 (0.83 to 1.13)**** • Q3=1.34 (1.25 to 1.44)*; 1.34 (1.25 to 1.43)**; 1.35 (1.26 to 1.45)***; 1.34 (1.25 to 1.43)**** • Q4=1.74 (1.62 to 1.86)*; 1.75 (1.64 to 1.87)**; 1.76 (1.65 to 1.88)***; 1.73 (1.62 to 1.85)**** DIABETES • Q2=1.22 (0.99 to 1.51)*; 1.28 (1.04 to 1.59)**; 1.22 (0.99 to 1.51)***; 1.20 (0.97 to 1.48)**** • Q3=1.43 (1.16 to 1.76)*;	A strong association was noted among periodontits and diabetes in individuals with high levels of CRP and P.gingivalis.	• Age • Sex • Education • Income • Race • Smoking • alcohol intake • missing teeth • frequency of dental visits • BMI • central adiposity • physical activity **Additionally adjusted for: • Inflammation history • CRP ***First model additionally adjusted for • A. actinomycetemcomitans ****First model additionally adjusted for

					1.48 (1.20 to 1.83)**; 1.48 (1.20 to 1.83)***; 1.40 (1.15 to 1.71)**** • Q4=3.65 (2.84 to 4.69)*; 3.86 (3.01 to 4.97)**; 3.98 (3.03 to 5.22)***; 3.46 (2.73 to 4.39)**** -Quartile for PPD: IFG • Q2=0.94 (0.79 to 1.10)*; 0.93 (0.79 to 1.10)**; 0.94 (0.79 to 1.10)***; 0.93 (0.79 to 1.10)**** • Q3=1.12 (0.93 to 1.35)*; 1.12 (0.93 to 1.35)**; 1.12 (0.93 to 1.35)***; 1.12 (0.93 to 1.35)**** • Q4=1.27 (1.12 to 1.45)*; 1.27 (1.12 to 1.46)**; 1.27 (1.12 to 1.45)***; 1.26 (1.10 to 1.44)**** DIABETES • Q2=1.66 (1.45 to 1.91)*; 1.61 (1.38 to 1.87)**; 1.64 (1.43 to 1.88)***; 1.63 (1.40 to 1.90)**** • Q3=1.28 (1.08 to 1.52)*, 1.27 (1.07 to 1.51)**; 1.29 (1.09 to 1.53)***; 1.25 (1.03 to 1.51)**** • Q4=1.66 (1.33 to 2.08)*; 1.61 (1.29 to 2.02)**; 1.66 (1.31 to 2.09)***; 1.53 (1.21 to 1.94)****	• P. gingivalis
COMMENTS: Limitation of the NHANES in terms of oral measurement; calibration not reported							
El-Beshbishy et al. 2014 Saudi Arabia Cross-Sectional NO DM	A) N=60 a1) 5 periodontitis systemically healthy a2) 13 periodontitis + acute myocardial	Presence of Periodontitis	% of diabetes cases	% of diabetes was higher in PD affected subjects no statistical difference was reported.	% of diabetes: 13.3 % NO PD vs 20% PD 5.9% (AMI NO PD), vs 38.5%(AMI+PD)	Among AMI patients, the % diabetes is higher in people affected by periodontitis	None

	infarction (AMI) b1) H=25 perio and systemically healthy b2) H+ AMI= 17 perio and AMI B) 35-70 yrs C)NA				Not generalizable		

COMENTS: limited sample, no statistical analysis in metabolic outcome, no adjustments. No information on periodontal examination.

Flores et al. 2014 Brazil Cross-sectional NO DM	A) N=93 (57 M; 63F) a1) 51 previous myocardial infarction a2) 42 other major cardiovascular events B) 63.5±9.8 yrs C) NA	Full mouth Periodontal examination at six sites per tooth: • VP • GR • PPD • BOP	• FPG • HbA1c	Statistically significant differences for FPG between periodontitis and controls; No statistically significant differences for HbA1c Not generalizable	• FPG=126.8±48.4 (P); 109.8±37.5 (NO-P), p=0.03 • HbA1c= 7.2±2.3 (P); 6.4±1.1 (NO-P), p=0.17	Patients affected by periodontitis were characterized by higher level of fasting plasma glucose	• Sex • Age • Smoking exposure • Diabetes status • Toothbrushing frequency • Dental visits • CRP • triglycerides (TGs) • very-low-density • lipoprotein cholesterol

COMMENTS: Limited sample on cardio-vascular subjects. Two trained and calibrated examiners, but calibration modalities are not reported.

Gokhale et al. 2014 India Case-control DM 1 + DM 2	A) N=60 (24 M, 36F) Perio a1) DMCP=15 a2) CP=15 b1) DMPH=15 b2) H =15 B) 36-60 yrs (44.2 yrs) C) 2 months	Full mouth Periodontal examination (4 sites/tooth) Periodontal clinical examination • GI • PD Radiographic evidence of bone loss Periodontitis= GI >1, >3 teeth with PD> 5mm, BOP+RX bone loss	• RBS • glycated hemoglobin (HbA1c) Diabetes= HbA1c>6,5 %, RBS >200 mg/dL	No statistically significant differences for HbA1c and RBS between periodontitis and no periodontitis in systemically healthy patients Not generalizable	Consolidated Pairwise Comparison (P value) Among H vs CP for: RBS: p= 0.9993 HbA1c: p= 1.0000 One-way analysis of variance and Tukey multiple post hoc procedures	The presence of periodontitis in healthy patients, did not statistically influenced glycaemic control	None to assess metabolic control
COMMENTS: Limited sample; limited sample; Performed to analyze the resistin level; Examiner calibration not reported; Type of perio exam: not reported							
Javed et al. 2014 Pakistan Cross-sectional NO DM	A) N=88 (M) a1) 28 patients with CP and prediabetes a2) 30 patients with CP and without prediabetes a3) 30 controls B) 39-51 yrs C) NA	Periodontal clinical parameters: • plaque index • bleeding on probing • probing depth • attachment loss • number of missing teeth Radiological parameter: • marginal bone loss CP was defined as clinical AL ≥ 3 mm,25,26 PD ≥ 5 mm,25,26 and MBL ≥ 3 mm 6,27 in > 30% of the sites.	• Fasting blood glucose (FBG) • hemoglobin A1c (HbA1c) prediabetes= fasting blood glucose [FBG] 100-125 mg/dL [5.6-6.9 mmol/L] and hemoglobin A1c [HbA1c] 5.7%-6.4% Health was self-reported	No effect was noted Not generalizable;	•FBG (mg/dL): CP= 80.1 ± 3.5; NO CP= 75.3 ± 2.2 •HbA1c (%): CP=4.8 ± 0.5; NO CP= 4.3 ± 0.2; Not significant	No effected noted.	None
COMMENTS: Study conducted only in male subjects; Trained and calibrated examiner but calibration modalities are not reported. Digital panoramic radiographs were viewed on a calibrated computer screen using a software program for analysis of MBL.							
Kapellas et al. 2014 Australia Cross-sectional	A) N=310 a1) S-PD=83 a2) M-PD= 188	Partial Periodontal examination: -For 6 index teeth:	No. self-reported diabetes	Yes, there are statistically significant differences for self reported diabetes,	No. self-reported diabetes – (Yes) p<0.01 • Non-cases:0 • M-PD= 21 (11.2) • S-PD= 20 (24.4)	Participants with severe periodontal disease were more likely to be self –report diabetes	None

DM	b1) 39=non cases B) 22-73 yrs C)NA	• Oral plaque score • Dental calculus -At 4 sites for every other tooth: • PPD • GR • CAL • Moderate Periodontitis: >2 interprox sites with CAL>4mm, or >2 sites with PD>5 mm • Severe Periodontitis: >2 interprox sites with CAL>6mm and >1 site with PD>5 mm		among different periodontal groups sample of Indigenous Australian adults Not generalizable			
COMMENTS: Calibrated examiners, but calibration modalities are not specified							
Longo et al. 2014 Brazil Case-Control DM	A) N=42 (23 M, 19 F) Perio a1) P=6 (5 M, 5 F) a2) DMI+P=10 (4M, 6 F) a3) DMA+P=10 (6M, 4 F) b1) H=6 (2M, 4F) b2) DMPH=10 (6M, 4 F) B) B) >35 yrs C) 15 months	Full mouth Periodontal examination (6 sites/tooth) • PI • Ging/BOP • PPD • CAL Periodontitis (American Academy of Periodontology, 1998) >30% of sites with PD >4 mm + BOP	HbA1c	No, there were no statistically significant differences for HbA1c %	HbA1c % • H=5.18±0.60 • P=5.43±0.54 mean±standard deviation	The presence of periodontitis in healthy patients, did not statistically influenced glycaemic controls	None
COMMENTS: Underpowered sample per comparison; Intraexaminer reliability for detecting PDs within 1 mm was >90%.							
Perayil et al. 2014	A) N=60 (26 M + 34 F)		HbA1c level	Yes, there were significant	HbA1c level of group PD (6.08% ±0.23%) was higher	HbA1c level was higher in PD group	None

India Case-control NO DM	a1) PD=30 b1) H=30 B) 35 -65 yrs c)	Full mouth periodontal assessment on 6 sites • oral hygiene index simplified(OHI-S) score • gingival index (GI) • probing depth (PD) • clinical attachment level (CAL) Periodontitis: PD ≥5 mm and CAL >3 mm in ≥5 teeth		differences between group H and group PD in regard to baseline OHI-S, GI, PD, and HbA1c (P <0.05). Not Generalizable	than that of group H (5.38% ±0.22%), (P <0.001)		
COMMENTS: Single, trained examiner, but calibration modalities are not reported.							
Rao Deepika & Saxena 2013 India Case-Control NO DM	N=60 a1) PD=30 b1) H=60 3 months 35-65 yrs	Examiner trained and calibrated CAL,BOP, PD · PD= CAL >30% + BOP in more than 30% sites · Controls: PPD<4 mm + BOP< 15%, no previous PD treatment, no CAL	HbA1c level	There was a slight increase of HbA1c level in periodontitis group (5,76%) in comparison to controls (5,63%), p=0,071 Among women, HbA1c was statistically significant higher (p=0,024) in cases (5,81%) vs controls (5,54%) Not generalizable	significant (p=0.01) positive correlation (r=0,349) between HbA1c and the plaque scores of the entire sample.	the level of HBA1Ac was not statistically significant between PD and controls	None
COMMENTS: Undajusted data. No info on calibration of the examiners.							
Banu et al. 2015 India Case-Control	A) N=60 (23 M + 37 F) a1) 40 CP b1) 20 H B) 40-65 yrs C) 15 months	Periodontal examination: • PI • PPD Bitewing radiographs: • interproximal bone loss	• FPG • IU	No statistically significant differences among H and CP for FBG and Insulin level The differences in	• FPG (mg/dl): H=88.75±7.05; CP=89.70±6.56; p=0.662 • IU: H=5.90±1.70; CP=7.16±5.92: p=0.367	The presence of periodontitis did not statistically influenced glycaemic controls	None

		from the cemento-enamel junction of the tooth to the bone crest for each patient Chronic periodontitis • radiographic evidence of interproximal bone loss (>50% alveolar bone loss in >2 quadrants of the dentition • >4 teeth should be involved in each jaw, >5mm PD, >4 mm clinical attachment level, and 80% BOP of the proximal sites.		Not generalizable	continuous variables between groups were compared by the use of Kruskal–Wallis test.		
COMMENTS: Examiners number not specified and calibration modalities are not reported							
Garcia et al. 2015 USA Cohort DM & NO DM	A) N=7,042 (3506 M; 3536 F) Perio a1) PD=3161 a2) PD+DM=707 b1) H=2860 b2) DM=314 B) 52yrs (30- 80 yrs) C) 3 yrs	Periodontal examination based on the FMPE protocol Total number of teeth	DM status as self-reported DM glycemic control was stratified using Hb1AC cut- off points of 7.0%, 7.5%, 8.0%, 8.5%, and 9.0%.	Yes, there was a statistically significant association between Hb1AC level and periodontitis in United States adults ages ‡30 years Generalizable	Periodontitis Status by Self-Reported DM Status and Glycemic Control Adjusted OR for Periodontal Status By Hb1AC cut-off: 1) DM<7,0%=0,98 (0,70-1,361); DM> 7,0%=1,33 (1,01-1,750) 2) DM<7,5%=0,96 (0,71-1,29); DM> 7,5%=1,58 (1,10-2,28) 3) DM<8,0%=1,00 (0,75-1,32); DM> 8,0%=1,65 (1,17-2,33) 4) DM<8,5%=0,98 (0,75-1,29); DM> 8,5%=2,17 (1,52-3,11) 5) DM<9,0%=1,00 (0,77-1,32); DM> 9,0%=2,22 (1,41-3,51) Glycoemoglobin % OR=1,14 (1,08-1,22)	The mean Hb1AC levels for individuals with and without periodontitis were 5.9% and 5.6%, respectively	Demographic factors: • Age • Gender • Educational Level • Marital Status, • Race/Ethnicity • Smoking Status • Federal Poverty Level, Number of Teeth Behavioral and dental • BMI • Smoking status

COMMENTS: Full mouth periodontal examination data from NHANES 2009-2012. Examiner calibration not reported. Definition of total periodontitis from the American Academy of Periodontology (AAP)							
Islam et al. 2015 South Korea Cohort DM + NO DM	A)N=19122 (8248 M + 10874 F) a1) CP=5070 a2) CP+DM=922 b1) H=12108 b2) DM= 1022 B)>20yrs C)3 yrs	Partial mouth CPI normal (CPI=0), gingival bleeding (CPI=1), calculus (CPI=2), a shallow periodontal pocket of 3.5~5.5 mm (CPI=3) or a deep periodontal pocket of 5.5 mm or more (CPI=4). PD=CPI ≥ 3.	• glucose • insulin resistance • HbA1c IFG diabetes mellitus was defined based on physician diagnosis or those with a fasting blood glucose ≥ 126 mg/dL, taking insulin or antidiabetic medication.	No, there were no statistically significant differences (p=0,172) although higher levels of HbA1c were found in periodontitis participants as compared to those without In logistic regression analysis periodontitis showed a significant association with IFG as an independent variable after adjustment for potential confounding factors in every model (p<0.001).	HbA1c, %b : • No Periodontitis=7.3±1.6 • Periodontitis= 7.4±1.6 NS Adjusted ORs and 95% CIs of prevalence of IFG for periodontitis among participants without diabetes • Model-1:(OR, 1.302; 95% CI,1.199~1.413); p<0.001 • Model-2:(OR, 1.282; 95% CI, 1.180~1.393); p<0.001 • Model-3: (OR, 1.301; 95% CI,1.193~1.418); p<0.001	Higher mean HbA1c levels were found in periodontitis patients rather than subjects without periodontitis, although the result was statistically insignificant. In patients without diabetes, the prevalence of IFG was higher in periodontitis patients as compared to subjects without periodontitis (28.5% vs. 17.7%).	• Model-1 for: Age, Sex, BMI • Model-2 for: Model 1 + SBP •T-chol • Model-3: Model 2+ region smoking •alcohol consumption •exercise
COMMENTS: no info on calibration of the examiner; CPI is a poor measure of PD							
Lee et al. 2015 Korea Cross-Sectional NO DM	A=941 (590 M+ 351 F) a1) Code CPI 0 (N = 579) a2) Code 1 (N = 125) a3) Code 2 (N = 228) B) 12-18 yrs C) 1 year	Partial mouth Periodontal examination CPI • 0=healthy • 1=bleeding following probing • 2=presence of dental calculus • 3=4 >PD<5 mm • 4=PD ≥6 mm Subjects divided in healthy gingiva and gingivitis (CPI ≥1)	FBG (mg/dL) Risk of MetS: three or more of these parameters: abdominal obesity; FPG ≥110 mg/dl; elevated blood pressure including treatment for hypertension; hypertriglyceridemia: serum triglyceride level ≥110 mg/dl; and low HDL cholesterol: serum HDL cholesterol ≤40 mg/dl.	No statistically significant differences for fasting blood glucose (mg/dl) among the CPI groups Not generalizable (adolescents)	FBG: 89.19±0.29 md/dl (no gingivitis); 88.82±0.45 md/dl (gingivitis), p=0.526 OR for gingivitis for High fasting glucose: crude=0.07 (0.01–0.70); adjusted= 0.07 (0.00–0.81)	The presence of periodontitis did not statistically influence glycaemic control, nor risk of MetS	•age •gender •income •dental check-up •frequency of brushing •frequency of eating between meals •physical activity

COMMENTS: Trained and calibrated examiner. Conducted in adolescents cohort. Only 8 subjects with FBG ≥ 110 mg/dl. CPI is a poor measure of PD.							
Srinivasa 2015 India Case-control General population	A)N=40 (22 M + 18F) a1) severe PD=20 b1) H=20 B1)H= 40.1±14.4 yrs B2) PD= 38.9±13.4 yrs	Clinical parameters: • PPD • BoP • CAL H = PDs ≤4 mm and BoP ≤15% and no CAL Severe PD = at least five teeth with PD ≥5 mm, BOP and CAL>1 mm on >5 teeth or radiographic bone loss	HbA1c	Yes, there were statistically significant differences (p = 0.003) for HbA1c between the two groups Not generalizable	HbA1c (%)Mean: Periodontitis=±SD 5.66±0.35 %; No Periodontitis= 5.17±0.3 %; p=0.003*	HbA1c levels were slightly elevated in chronic periodontitis cases than in controls.	None
COMMENTS: limited sample. No adjustment. Not specific data about the periodontal examination and calibration modalities are not reported							
Chang et al. 2016 Taiwan Chronic Kidney Disease Cohort	A) N=2831 B) 53.1± 8.4 C) 2.4 – 7.3 yrs	PD The 2015 updated classifications from the American Academy of Periodontology, periodontal diseases are classified into gingivitis and periodontitis	• fasting blood glucose, • HbA1c	Yes, patients with higher periodontal pocket depth (>4.5 mm) showed FBG and and HbA1c Not generalizable	Bivariate Correlation Coefficients Between Baseline Periodontal Pocket Depth and: • fasting blood glucose=0.28, p<0.01 • hemoglobin A1c (HbA1c)=0.26, p<0.01	Patients affected by periodontitis were characterized by higher level of FBG and HbA1c	• age •sex •diabetes mellitus •PPD • hypertension •smoke •betel nut • albuminuria •creatinine
COMMENTS: Subjects with chronic kidney disease; Not specific data about the periodontal examination and calibration modalities are not reported							
Hong et al. 2016 Republic of Korea Cross-sectional DM + NO DM	A) N= 9977 a1) CP=2728 b1) H=7249 B) 19 yrs C)NA	CPI Full mouth Periodontal Examination Periodontitis (CP) was defined as a community periodontal index score of ≥ 3	• NFG • IFG • HbA1c (%) • Anti-diabetes medication (%) • Diabetes (%) • NFG 1hrs (<90 mg/dL) • NFG 2hrs (90–99 mg/dL) • IFG 1hrs (100–110 mg/dL) • IFG 2hrs (111–125 mg/dL), and diabetes (>126 mg/dL)	Statistically significant differences among CP and NO CP for FPG and HbA1c and diabetes prevalence Not generalizable	• FBG mg/dL: H=96.8 (96.3–97.3); CP=100.4 (99.0–101.8), p<0.001 • HbA1c (%): H=5.72 (5.70–5.74); CP=5.86 (5.81–5.91), p<0.001 • Anti-diabetes medication (%): H=4.9 (4.3–5.4); CP=6.2 (4.9–7.4), p=0.072 • Diabetes (%): H=7.60	People affected by periodontitis were characterized by higher level of HbA1c and FPG	age, sex, smoking history, heavy alcohol drinking, college graduation, household income, waist circumference, serum TG level, serum HDL-cholesterol level, and the presence of hypertension

							(6.90–8.30); CP=12.0 (10.3–13.7), p <0.001 OR for FBG 111-125 mg/dl 1.33 (1.01-1.75) p=0.044 in periodontitis subjects		

COMMENTS: Oral examination of periodontal health was conducted by trained dentists; CPI is a screening test of PD.

AMI= acute myocardial infarction; BP, Blood Pressure; BOP= Bleeding on Probing; BPE=Basic Periodontal Examination; CKD, chronic kidney disease; C-PPD, cumulative periodontal probing depth; CPI,Community Periodontal Index; CRAE/CRVE, Central retinal arteriolar/venular equivalents; 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; DMCP=Diabetes + chronic periodontitis; DMA+P= Diabetics with periodontitis and adequate glycaemic control DMI+P= Diabetics with periodontitis and inadequate glycaemic control; DMG=Diabetes+ Gingivitis; DMPH= Diabetes+periodontal health; F, Female; FBG= Fasting Blood Glucose; FU, Follow-Up/End of Study Period; G= gingivitis; GR= gingival recession; GT, Glucose Tolerance; H= Systemic and periodontal healthy; HbA1c, Glycosylated(Glycated) Haemoglobin; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; hr,hour; HR, Hazard Ratio; hrs=hours hsCRP, high-sensitivity C-reactive protein; IGI/HOMA-IR: insulin secretion Index; IGT, Impaired Glucose Tolerance; IU: Insuline; M, Male; MBL=marginal bone loss; MGI= Modified Gingival Index; MI= myocardial infarction; M-PD=moderate periodontitis; NFG, normal fasting glucose; NGT, Normal Glucose Tolerance; NHANES, National Health and Nutrition Examination Survey; OGTT, Oral Glucose Tolerance Test; OR, Odds Ratio; Perio/PD, PC, post-challenge glucose; Periodontal Disease; PI= Plaque index; PPD, Periodontal Probing (Pocket) Depth; RBS=Random blood sugar; R-DM2=retinopathy+ diabetes; RR, Risk Ratio; RX= X rays; SBP, systolicblood pressure; S-PD= severe periodontitis; Stat. sign., statistically significant; T-chol, total cholesterol; VP= visible plaque; vs., versus; yr(s), Year(s).

Appendix. Tab. S1 NOS scale for quality rating of Case-Control Study

Author, Year	A) SELECTION (Max. 4 Stars)				B) COMPARABILITY (Max. 2 Stars)	C) EXPOSURE: PERIODONTAL DISEASE (Max. 3 Stars)			TOTAL OF STAR
	Is the case definition adequate? (Max 1 Star)	Representativeness of the cases (Max 1 Star)	Selection of Controls (Max 1 Star)	Definition of Controls (Max 1 Star)	Comparability of cases and controls on the basis of the design or analysis (Max 2 Stars) a) Study controls for age (= most important factor) b) Study controls for smoking (=additional	Ascertainment of Exposure (Max 1 Star) a) Secure record, e.g. surgical/dental records/oral clinical examination b) Structure interview where blind to case/control status (self-reported periodontal disease) c) Interview not blinded to	Same method of ascertainment for cases and controls (Max 1 Star)	Non-response rate (Max 1 Star)	

					important factor)	**case/control status** **d) Written self-report or medical/dental record only** **e) No description**			
Rao Deepika et al.2013	★	★	★	★	★★	★	★	★	9
Xiong et al. 2013	★		★	★		★	★	★	6
El-Beshbishy et al. 2014					★			★	2
Srinivasa et al. 2015	★	★		★	★	★	★	★	7

Appendix. Tab. S2 NOS scale for quality rating of Cross-Sectional Study

Author, Year	**A) SELECTION (Max. 4 Stars)** **(Max. 4 Stars)**				**B) COMPARABILITY (Max. 2 Stars)**	**C) OUTCOME (max 1 star)**	**TOTAL OF STAR**
	Representativeness of the exposed subjects (Periodontal infection/Periodontitis) (Max 1 Star)	**Selection of non-exposed subjects (No/Only mild periodontal infection/periodontitis) (Max 1 Star)**	**Ascertainment of exposure (Periodontal infection/Periodontitis) (Max 1 Star)**	**Ascertainment of outcome (Glycemic control/Diabetes) (Max 1 Star)**	**Comparability of exposed & non-exposed groups on the basis of the design or analysis (Max 2 Stars)** **a) Study controls for age (= most important factor)** **b) Study controls for smoking (=additional important factor)**	**Assessment of outcome (Glycemic control/Diabetes) (Max 1 Star)**	
Arora et al. 2014	★	★	★	★		★	5

Choi et al. 2014	★	★		★	★★	★	6
Flores et al. 2014	★	★	★	★	★★	★	7
Gokhale et a. 2014	★	★	★	★	★	★	6
Javed et al. 2014	★	★	★	★	★★	★	7
Kapellas et al. 2014	★	★	★	★	★	★	6
Banu et al. 2015	★	★	★	★	★★	★	7
Garcia et al. 2015	★	★	★	★	★★	★	7
Islam et al. 2015	★	★		★	★★	★	6
Lee et al. 2015	★	★	★		★	★	5
Hong et al. 2016	★	★		★	★★	★	6
Chang et al. 2017	★	★	★	★	★★		6

Appendix. Tab. S3 NOS scale for quality rating of Cohort Studies

Author, Year	A) SELECTION (Max. 4 Stars) (Max. 4 Stars)				B) COMPARABILITY (Max. 2 Stars)	C) OUTCOME (max 3 star)			TOTAL OF STAR
	Representativeness of the exposed cohort (Max 1 Star)	Selection of non-exposed cohort (Max 1 Star)	Ascertainment of exposure (Max 1 Star)	. Demonstration that outcome was not present at start of study (Max 1 Star)	Comparability of cohorts on the basis of the design or analysis (Max 2 Stars) Study controls for age (= most important factor) Study controls for smoking (=additional important factor)	Assessment of outcome (Max 1 Star) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (X-rays, medical/dental records, etc.) Record linkage Self-report only (no confirmation by secure records) No description	Was follow-up long enough for outcomes to occur (Max 1 Star)	Adequacy of follow-up of cohorts (ensuring losses are not related to exposure or outcome) (Max 1 Star)	
Morita et al. 2010	★	★		★	★★	★	★	★	8
Demmer et al. 2010	★	★	★	★	★★	★	★	★	9
Saito et al. 2004	★	★	★	★	★★	★	★	★	9

E2. 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?

Findings of New Evidence

Current evidence on the influence of periodontal disease on the risk of developing (incident) type 2 diabetes is based only on few studies that analyzed specified populations. The included study were predominantly conducted in Japan (3 out of 4 studies) for a total of 22,230 individuals (Saito et al. 2004, Demmer et al. 2010b, Ide et al. 2011, Morita et al. 2012). An increased risk of developing DMT2 was noted in subjects with poorer periodontal health was thoroughly noted, as measured by increase in PPD, and remained after adjustment in the majority of the study (Saito et al. 2004, Demmer et al. 2008a, Morita et al. 2012) . The presence of PD showed increased odds for developing diabetes of 50% (Demmer et al. 2008a).

Additional evidence are gathered form two Taiwanese studies involving a total of 50486 participants followed for 5 (Chiu et al. 2015a) and 13-years (Lin et al. 2014a). In both cases an increased risk to develop diabetes was registered in PD-affected subjects. Over 5-year, young adults (aged 35-44 years) with community periodontal index score of at least 3 presented a 33 % increased risk of incident hyperglycemia (including diabetes) [adjusted hazard ratio (aHR) = 1.33 (95 % CI 1.09–1.63)] after controlling for potential confounding factors. A larger retrospective study on 22299 PD-affected subjects and 22302 periodontally healthy subjects found that DMT2 incidence, over 13-year period, was 1.24-fold higher in the PD cohort than in the control group, with an adjusted hazard ratio of 1.19 (95% confidence interval = 1.10 to 1.29). Interestingly, patients requiring periodontal surgery, i.e. probable higher severity of PD, showed a higher risk in the first 6 year.

Although the majority of the included studies have been conducted on Asiatic populations, results appear robust enough to state that subjects affected by PD show a higher chance to develop diabetes when compared to non-PD affected ones. The meta-analytic data for adjusted hazard ratio shows a value of 1.29 (95% CI 1,11-1-46, $p<0.0001$).

Quality assessment

The quality of the included study is depicted in the Table S4. Five of the six studies included in the study have been conducted in Asia: 3 in Japan (Saito et al. 2004, Ide et al. 2011, Morita et al. 2012) and 2 in Taiwan (Lin et al. 2014b, Chiu et al. 2015b). The other study have been conducted in USA (Demmer et al. 2008b). Consequently results are not generalizable despite the selected participants were representative of the general population. One study was of retrospective design. In one study periodontitis was measured with Community Periodontal Index (Chiu et al. 2015a) or computerized medical notes (Lin et al. 2014a).

These large cohort studies of high quality according to the NOS scale.

Fig.3. Forest plot from random effects of meta-analysis evaluating the aHR (adjusted Hazard Ratio) among periodontitis cases in terms of incident diabetes/hyperglycemia as gathered from longitudinal observational studies (weighted mean difference (WMD), 95% Confidence Interval (C.I.)).

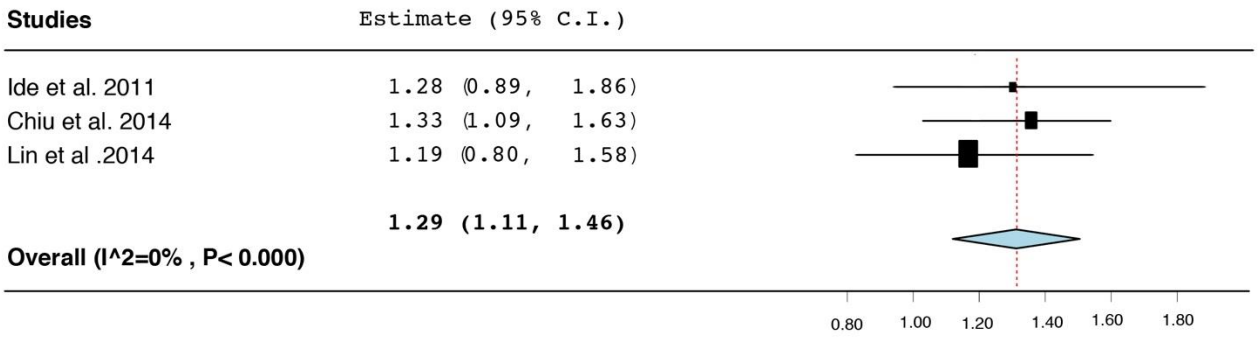


Table 3. Effect of Periodontal disease on the risk of incident diabetes

Author Year Country Study Design BL DM Typer	**A)Subjects: a. Perio Cases b. Comparison groups B) Age C) Study Duration**	**EXPOSURE**	**OUTCOME**	**Effect on Metabolic Control? & Generalisable?**	**Effect size: Odds Ratio (OR), Trend, HR, HRR & Significance (95%CI)**	**Effect on Metabolic Control/Conclusion**	**Confunders Controlled**
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 corresponded 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) a4) 759 (2.45-5.07) a5) 760 (5.08-8.0)	NHANES I protocol gingival inflammation extent presence or absence of periodontal pockets tooth mobility PDGroups@BL PD-1#(PI): "Periodontal	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) a3) 2.08(1.51-2.87) a4) 1.71(1.19-2.45) a5) 1.50(0.98–2.27)	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-	age sex race education smoking status BMI subscapular skinfold physical activity hypertension total cholesterol total caloric intake total protein

	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]	Index"(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		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)	2) with incident diabetes was found also in normo-weight andin never-smoking partecipants	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*							
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 gammaglutamyl-transpeptidase
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							

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)							
Lin et al. 2014 Taiwan Retrospective cohort study 13 years DM-2	A) N=44601 a1) S-PD=22299 a2) M-PD=22302 B) age>40 yrs, mean 53.0 yrs C) 5.47 ± 3.54 years	Periodontitis Needing Surgical Treatment (YES or NOT)	• Incidence of DM2= patients who have been diagnosed with ICD- 9-CM codes 250 at least two times and concomitantly received antidiabetes medications.	Incidence of DM2 was 1.24-fold higher in the periodontitis cohort than in the control cohort, with an adjusted hazard ratio of 1.19 (95% confidence interval = 1.10 to 1.29); The elevated risk disappeared after being followed up for 6 years. Not generalizable	Diabetes Compared Between Periodontitis Cohorts With and Without Surgical Treatment: • IRR=1.24 (1.18 to 1.30) • aHR=1.19 (1.10 to 1.29)	Patients with periodontitis needing dental surgery have increased risk of future diabetes within 2 years compared with those participants with periodontitis not requiring dental surgery.	• Age • Sex • Urbanization • Income • Comorbidity • Hypertension • Hyperlipidemia • coronary artery disease • Obesity
COMMENTS: diagnosis according to ICD-9 codes. Comparison is among difference type of periodontits cohorts (no periodontally healthy controls)							
Chiu et al 2015 Taiwan Cohort	A) N= 5,885 a1) 1341 b1) 4033 B) 35–44 yrs C) 5 yrs	- CPI - PD= CPI ≥3	• FPG • 8 hr FBG	The cumulative incidence rates of hyperglycemia show that PD with CPI > 3 led to a dramatic increase in the risk of	•aHR of incident hyperglycemia (including diabetes)= 1.33 (95 % CI 1.09–1.63	Periodontal disease increases the risk (33%) of hyperglycemia	• Demographic features • Life style (betel quid chewing, smoking, and drinking), • Personal, and family disease history (DM2, hypertension,

	incident hyperglycemia compared with CPI <3 Not generalizable		cardiovascular and cerebrovascular disease, hyperlipidemia, and stroke) • Anthropometric measurements: tape measure, and weight scales. • Waist size • BP • Frequency of the dietary pattern classified into 5 levels: never or seldom, 1–2, 3–4, 5–6, and more than 7 times/per week over the past 6 months • TG • TC • HDL

COMMENTS: calibrated examiners. No HR for diabetes only presented.

Appendix. Tab. S4 NOS scale for quality rating of Cohort Studies

Author, Year	A) SELECTION (Max. 4 Stars) (Max. 4 Stars)				B) COMPARABILITY (Max. 2 Stars)	C) OUTCOME (max 3 star)			TOTAL OF STAR
	Representativeness of the exposed cohort (Max 1 Star)	Selection of non-exposed cohort (Max 1 Star)	Ascertainment of exposure (Max 1 Star)	. Demonstration that outcome was not present at start of study (Max 1 Star)	Comparability of cohorts on the basis of the design or analysis (Max 2 Stars) Study controls for age (= most important factor) Study controls for smoking (=additional important factor)	Assessment of outcome (Max 1 Star) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (X-rays, medical/dental records, etc.) Record linkage Self-report only (no confirmation by secure records) No description	Was follow-up long enough for outcomes to occur (Max 1 Star)	Adequacy of follow-up of cohorts (ensuring losses are not related to exposure or outcome) (Max 1 Star)	
Saito et al. 2004	★	★		★	★★	★	★	★	8
Demmer 2008	★	★	★	★	★★	★	★	★	9
Ide et al. 2011	★	★		★	★★	★	★		7
Morita 2012	★	★	★	★	★★	★	★	★	9
Lin et al. 2014	★	★	★	★	★★	★	★		8
Chiu et al. 2015	★	★	★	★	★★	★	★	★	9

Discussion

Summary of the evidence

- The available evidence suggests that:
- Subjects affected by periodontal disease and not affected by diabetes are associated to higher level of HB1Ac, fasting blood glucose or pre-diabetes/diabetes prevalence. In particular, these subjects show a statistically significant increase of 0.29 % of Hb1AC (0.20-0.37 %, 95% C.I.).
- Subjects affected by periodontal disease show a 29% significant higher risk (adjusted hazard ratio 1.29 95% CI 1,11-1-46) of developing incident diabetes when affected by severe periodontitis compared to periodontal healthy subjects.

Limitations

Most studies suffered of intrinsic limitations that render the overall applicability of the results. Samples were sometimes limited and not generalizable. Most importantly, some of the evidence was indirectly drawn from manuscripts which primary intention was not to assess the effect of periodontal disease on glycaemic control. Heterogeneity in terms of adjustment was important and, in multifactorial pathologies such as the ones we are dealing with, it might have an impact. Another limitation is that only article in English were searched and publication bias cannot be excluded.

Conclusions

Periodontal disease has a negative influence on glycaemic control of people with not known diabetes; in particular subjects affected by severe periodontitis are characterized by higher level of HB1Ac, fasting blood glucose and present a 29 % higher risk of developing diabetes, respect those people with healthy periodontium.

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