Published in final edited form as:

J Periodontol. 2013 April ; 84(4 0): S153–S169. doi:10.1902/jop.2013.1340017.

Evidence that periodontal treatment improves diabetes outcomes: a Systematic Review and Meta-analysis

S. Engebretson¹ and T. Kocher²

¹Department of Periodontology and Implant Dentistry, New York University, New York, NY, USA

²Unit of Periodontology, Department of Restorative Dentistry, Periodontology and Endodontology Dental School, University Medicine, Greifswald, Germany

Abstract

Context—The effect of periodontal therapy on diabetes outcomes has not been established.

Objective—This update examines the effect of periodontal treatment on diabetes outcomes.

Data Sources—Literature since October 2009 using MEDLINE.

Study eligibility criteria—Published RCTs including periodontal therapy for diabetic subjects, a metabolic outcome, an untreated control group, and follow up of 3 months.

Data Extraction—Predefined data fields, including study quality indicators were used.

Data Synthesis—A search revealed 56 publications of which 9 met inclusion criteria. Mean change of HbA1c from baseline was compared across treatment groups. Pooled analysis was based on random effects models.

Results—A meta analysis indicated a mean treatment effect of -0.36% HbA1c (CI -0.54 , -0.19) compared to no treatment after periodontal therapy ($p < 0.0001$). Heterogeneity tests revealed only minimal evidence of publication bias ($I^2 = 9\%$).

Limitations—Small sample size and high risk of bias remain problematic for studies of this type. Periodontal therapy varied considerably.

Conclusion—The modest reduction in HbA1c observed as a result of periodontal therapy in subjects with type 2 diabetes is consistent with previous systematic reviews. Despite this finding, multi-center trials of sufficient sample size are lacking.

Keywords

Diabetes; Diabetes Mellitus; Type 2; Periodontal Disease; Periodontitis; Glycosylated Hemoglobin; HbA1c

Corresponding Author: Steven P. Engebretson, DMD, MS Department of Periodontology and Implant Dentistry 345 East 24th Street New York University College of Dentistry New York, NY, 10010 USA Tel: 1-212-998-9640 Fax: 1-212 spe2002@nyu.edu.

Conflict of Interest The authors disclosed no conflicts of interest

Clinical Trials.gov: NCT00997178

Rationale

Type 2 diabetes is a major public health problem of global importance. Worldwide, about 347 million adults suffer from type 2 diabetes, corresponding to a global prevalence of about 10% in 2008 (Danaei et al., 2011). According to the World Health Organization current prevalence may double by the year 2030, and diabetes-related health care expenditures range from 2.5% to 15% of annual health care budgets (Zhang et al., 2009).

Hemoglobin A1c (HbA1c) reflects serum glucose levels during the 120-day life of the red blood cell, and is a robust measure of glycaemic control, (Engelgau et al., 1997, Selvin et al., 2004, Yale et al., 2001, Maggs et al., 1998, Hundal et al., 2002, 1998, Knowler et al., 2002) frequently used for treatment decision-making in clinical medicine. Elevated HbA1c has been linked to micro- and macro- vascular diabetes complications (Engelgau et al., 1997), (Knowler et al., 2002), (ADA, 2003).

Patients with diabetes are at two to three times the risk for developing chronic periodontitis (Taylor et al., 1996), and those with elevated HbA1c have a significantly higher prevalence of periodontitis and more tooth loss than those with better metabolic control (Seppala et al., 1993, Demmer et al., 2012, Tsai et al., 2002)

Acute and chronic infections may adversely influence glycaemic control (Sammalkorpi, 1989). Furthermore it has been established that HbA1c is adversely affected by systemic inflammation (Shoelson et al., 2006). In this context, and for the last several decades, a biologically plausible link between metabolic control and periodontitis has been investigated (Taylor, 2001). If effective treatment of periodontitis could modify glycaemic control, then periodontal therapy may contribute to a patient management program that incorporates life style changes and medications.

Several recent systematic reviews (Teeuw et al., 2010, Simpson et al., 2010) have been conducted to assess the evidence that periodontal treatment influences glycaemic control. The aim of this manuscript is to provide an update to account for recent findings.

Objectives

A structured approach was used to formulate the research question for this systematic review using five components commonly known by the acronym “PICOS” (O’Connor D, 2009): the patient population (P), the interventions (I), the comparison group (C), the outcome of interest (O), and the study design (S). The population under study was comprised of individuals, with diabetes, and periodontitis. The intervention chosen was periodontal therapy, either surgical or non-surgical, with or without the use of adjunctive antibiotics, antiseptics, or oral hygiene instruction. The comparison group chosen was an untreated group or ‘usual care’ group (that may or may not have received oral hygiene instruction and/or supragingival scaling). The outcome of interest was HbA1c, or fructosamine, or fasting glucose, or oral glucose tolerance test, and the study design of interest was randomized clinical trials with at least three months of follow up.

METHODS

Protocol and registration

This review is an update of two excellent systematic reviews that were conducted in 2010, due to an increase in clinical trials activity in this area. All previous studies used for analysis in those reviews were included in this one, except as noted, and additional studies meeting the required criteria have been added. In all, 5 new studies meeting the inclusion criteria established by the 2010 reviews resulted in a total of 9 randomized clinical trials for inclusion in this review.

Type of studies and participants

Further details of the PICOS questions: 1) Randomized clinical trials that included participants over the age of 18 with both diabetes and periodontitis were considered for inclusion and, 2) Studies that compared an intervention consisting of periodontal therapy, surgical or non-surgical, with a comparator group consisting of a non-treatment or delayed treatment group with at least 3 months of follow up and, 3) Studies that measured HbA1c, or fasting glucose, or OGTT, as a primary outcome. Both type 1 and type 2 diabetes were considered for inclusion, with separate analysis planned for each. Only published studies in the English language were considered for inclusion.

Type of interventions

Studies that reported periodontal therapy of any kind (non-surgical or surgical periodontal therapy with or without the use of adjunctive antibiotics, or other (anti-inflammatory) medication use) were initially considered for inclusion. Studies may or may not have included as part of therapy extraction of hopeless teeth and/or endodontic treatment if indicated.

Type of outcome measures

The primary outcome of interest for this review was a diabetes outcome consisting of a measure of glycaemic control. HbA1c, fructosamine, fasting glucose, or OGTT were considered for inclusion. Change in diabetes medication, or reduction in insulin utilization was also considered as a secondary outcome. Homeostasis model assessment was also considered for inclusion as a secondary outcome. The effect of periodontal therapy on lipids in subjects with diabetes is the topic of another recent systematic review and meta analysis and therefore not included here [Sgolastra, 2012 #456].

Information Sources/Search

MEDLINE was searched according to a method previously described by Teeuw et al (Teeuw et al., 2010), using identical search criteria and terms: ((periodontal disease) OR (periodont*[Text Word]) OR (periodontitis)) AND ((diabetes[Text Word]) OR (diabet*[Text Word]) OR (diabetic*[Title]) OR (diabetic patient*[Text Word]) OR (diabetes patient[Text Word]) OR (non insulin dependent diabetes) OR (niddm[Text Word]) OR (insulin dependent diabetes[Text Word]) OR (iddm[Text Word]) OR (type 1 diabetes) OR (t1dm) OR (type 2 diabetes) OR (t2dm)) AND ((therapy) OR (treatment) OR (intervention))

AND ((controlled clinical trial) OR (randomized clinical trial) OR (RCT)) AND (English[Language]) from October 2009 to the end of July 2012.

The search and inclusion criteria were for articles published since October 2009, the last date for inclusion in the previous systematic review (Teeuw et al., 2010, Simpson et al., 2010).

Study Selection

Eligibility assessment was by a single author (SE) and confirmed by the second author (TK). Titles and abstracts were scanned to rule out studies that did not meet inclusion criteria; because they were reviews, commentaries, case series, or case reports October 2009. A second level full text search was initiated on those studies that remained eligible. Of those studies, 5 met the criteria for inclusion in the meta-analysis. Reasons for exclusion are listed in the appendix.

Data Collection Process/Appraisal of DM outcomes

All studies that were included reported HbA1c values for each study group at baseline and after the intervention follow up period. For data extracted from systematic reviews, change from baseline of HbA1c for each treatment group is reported, along with standard deviation of the change. If not presented as change from baseline, the change from baseline was calculated for each group by subtracting the follow-up value from the baseline value. Standard deviation of the change in HbA1c from baseline to follow-up if not stated in the manuscript was calculated according to a method previously described (Teeuw et al., 2010). Data were extracted from the published results of each study included, using data collection forms as previously described in a Cochrane Review by Simpson et al (Simpson et al., 2010).

Assessment of the risk of bias in included studies

Risk of bias was assessed for each included study. The Cochrane risk bias tool was used to assess each study on five criteria sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting as previously described (Teeuw et al., 2010).

Summary Measures

Only the primary outcome of interest, the comparison of the effect of treatment vs. no treatment on HbA1c levels was submitted to meta-analysis. None of the included studies reported fructosamine. Fasting glucose, or OGTT values were reported by only one study and were therefore not included in the analysis. No studies of type 1 diabetes met inclusion criteria.

Synthesis of Results

Data were submitted to meta-analysis (Review Manager (RevMan) Version 5.1. for Mac OS, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) using the inverse variance method and random effects models showing mean difference and 95% CI in HbA1c from baseline to three months between treatment and non-treatment groups.

Forest plots showing the point estimate and confidence intervals for each study were created. The heterogeneity statistic, I^2 , and overall effect Z score with p value were calculated. Studies in which more than one treatment group was compared with a control were analyzed separately but control subjects were counted only once in the overall n as previously described (Higgins JPT, 2011).

Risk of Bias Across Studies

Funnel plots were constructed to evaluate the effect of publication bias according to a method described by Sutton (Sutton et al., 2000). The funnel plot reveals the relationship between the effect-size of each trial (change in HbA1c from baseline) with its corresponding standard error of the mean difference. The rationale being that with increased sample size, a reduced standard error of the effect size would be expected. The funnel plot was inspected visually for asymmetry, as asymmetry may reveal heterogeneity across studies. A symmetrical funnel plot is characteristic of studies with little or no publication bias. An asymmetrical funnel plot may indicate publication bias in that small trials with negative results are less likely to be published. Heterogeneity was tested using the Breslow-Day test, and using a method described by Higgins et al. (Higgins and Thompson, 2002) to measure percentage of total variation across studies due to heterogeneity of effects of periodontal therapy on HbA1c. Any resulting inconsistency is reported as the I^2 statistic which represents the percent of variability attributed to between-study variability. An I^2 of zero is interpreted as no heterogeneity between studies.

RESULTS

Study Selection

The initial search revealed 54 new records for further scrutiny (Figure 1). Titles and abstracts were scanned to rule out studies that did not meet inclusion criteria, (eg. reviews, commentaries, case series, or case reports October 2009). A second level full text search was initiated on those studies remaining. One study (Sun et al., 2010) was deemed a duplicate report. One study (Singh et al., 2008) not revealed by MEDLINE search was gleaned from the bibliography of a recent review.

4 studies were included in the present analysis which were also included for comparison in two previous systematic reviews (Jones et al., 2007a, Yun et al., 2007, Katagiri et al., 2009, Kiran et al., 2005), while two studies (Stewart et al., 2001, Promsudthi et al., 2005) that were included in one or the other recent systematic review (Teeuw et al., 2010)(Simpson et al., 2010) were excluded from the current analysis because neither were deemed a randomized clinical trial, and hence did not meet the inclusion criteria. One further study (Bharti et al., 2011) that otherwise met inclusion criteria was excluded on the basis that subjects not willing to participate in the treatment group were automatically included in the control group. As Simpson et al (Simpson et al., 2010) for similar reasons excluded another study (Promsudthi et al., 2005) as per Cochrane group protocol, our decision was also to exclude.

Thus, in addition to the 4 studies published prior to October 2009, 5 additional studies published since October 2009 met the criteria for inclusion in this meta-analysis for a total of 9 studies. In the 9 included studies there were 398 in the treated groups and 321 in the untreated control groups, for a total of 719 subjects (Table 1). Reasons for exclusion of other publications are listed in the appendix.

Study Characteristics

The studies included were all randomized controlled clinical trials published in the English language. The duration of the follow up period was at least 3 months, with one study (Jones et al., 2007a) including a 4-month follow-up. Although 2 studies were of 6-month duration (Koromantzios et al., 2011, Chen et al., 2012), only three or four month follow up data was included here. The inclusion criteria would have included studies of type 1 diabetes however, none were available that met the inclusion criteria, and hence all of the included studies were of subjects with type 2 diabetes. 7 studies were single center (Kiran et al., 2005, Moeintaghavi et al., 2012, Yun et al., 2007, Chen et al., 2012, Singh et al., 2008, Sun et al., 2011, Koromantzios et al., 2011), two were multi-centered (Katagiri et al., 2009) (Jones et al., 2007a). The largest in terms of sample size of the above data include Sun et al (Sun et al., 2011) with 157 participants and Jones et al (Jones et al., 2007b) with 154. These two studies report that as a result of periodontal therapy in type 2 diabetic subjects HbA1c were reduced by 0.36% and 0.16% over the control groups respectively. HbA1c reductions ranged from 1.11% (Kiran et al., 2005) to 0.05% (Katagiri et al., 2009), with a mean HbA1c reduction from baseline of -0.36 % 95% CI (-0.54, -0.19). 8 of 9 studies reported a decrease in mean HbA1c from baseline to three months for the treatment group. Of those studies, 5 of 8 were statistically significant decreases. Among the control groups receiving no periodontal treatment 5 of the 9 studies reported a decrease in HbA1c from baseline to three months but none of those decreases were statistically significant.

Treatment modalities

All treatment group interventions consisted of non-surgical periodontal therapy with or without adjunctive topical or systemic antibiotics, and/or topical antiseptics, while one study included surgical therapy. 7 studies were parallel arm two group studies, while 2 studies (Chen et al., 2012, Singh et al., 2008) included three treatment groups. Of the three group studies, Chen et al, reported that both treatment groups received scaling and root planing only, while in the Singh study (Singh et al., 2008) one group received scaling and root planing only and the second treatment group received scaling and root planing plus adjunctive systemic antimicrobial dose doxycycline. Of the two group studies, 3 studies' treatment included scaling and root planing only (Kiran et al., 2005, Moeintaghavi et al., 2012, Chen et al., 2012), 1 study (Koromantzios et al., 2011) called for scaling and root planing plus extraction of hopeless teeth. The remaining studies included adjunctive treatments. Jones et al (Jones et al., 2007a) treatment protocol called for scaling and root planing plus systemic antimicrobial dose doxycycline and 0.12% chlorhexidine rinse. Yun et al (Yun et al., 2007) included systemic antimicrobial dose of doxycycline in both treatment (scaling and root planing) and control (no scaling and root planing) groups. Sun et al (Sun et al., 2011) treatment included scaling and root planing and flap surgery ('when indicated'), extraction of hopeless teeth, occlusal adjustment, and systemic Tinidazole plus ampicillin

both pre- and post-operatively. One study, Katagiri et al (Katagiri et al., 2009), used topical minocycline as an adjunctive therapy to scaling and root planing

Risk of bias in included studies

The following measures of risk of bias were assessed for all included studies; the randomization scheme, allocation of treatment group concealment, masking of examiners, withdrawals and loss to follow-up. These measures were assessed by using a standardized form described by the Cochrane group [Simpson, 2010 #143].

Effects of interventions Results of Individual Studies

A statistically significant weighted mean difference of 0.36% [95% C.I. -0.54 to -0.19%] HbA1c reduction was seen in the treatment group. The effect of the interventions in the individual studies is seen in Table 2. The 'forest' plot describes the effect on HbA1c in terms of mean reduction from baseline, and standard deviation, as a comparison between treatment groups. An I^2 of 9% is an indication that minimal heterogeneity (different treatment effect) was observed across studies.

Risk of Bias Across Studies

To evaluate the effect of publication bias we used a method described by Sutton (Sutton et al., 2000) to create funnel plots. The funnel plot is a measure of effect size vs the standard error of the mean difference. If smaller non-significant studies are less likely to be published, then an asymmetry would be observed in the funnel plot. The funnel plot created was visually inspected and reveals minimal asymmetry (Figure 2) suggesting some evidence of publication bias.

Discussion

Summary of Evidence

This review is an update of two excellent systematic reviews that were conducted in 2010, due to an increase in clinical trials activity in this area. All previous studies used for analysis in those reviews were included in this one, except where noted, and additional studies meeting the required criteria have been added. In all, 5 new studies meeting the inclusion criteria established by the 2010 reviews resulted in a total of 9 randomized clinical trials for inclusion in this review. The studies included investigations with at least three months of follow-up of the effect of periodontal therapy on type 2 diabetes outcomes. It is noteworthy that the total number of subjects available for meta-analysis within the included studies now exceeds 700, nearly double the population of the 2010 Diabetes Care systematic review and meta-analysis by Teeuw et al (Teeuw et al., 2010). Equally noteworthy is that the effect size of -0.36% HbA1c (95% CI -0.66, -0.19) observed across all 9 studies, is comparable to the two most recent and extensive systematic reviews (-0.40% HbA1c, CI -0.77, -0.04 (Teeuw et al., 2010) and -0.40% HbA1c, CI -0.78, -0.01 (Simpson et al., 2010), and remains statistically significant. Hence conclusions made previously that periodontal therapy may improve metabolic parameters, as measured by HbA1c, as a result of periodontal therapy are consistent with the findings of the present meta analysis. Of note, a review and meta-analysis by Janket et al in 2005 [Janket, 2005 #390] reached a similar (albeit non-significant)

effect level (-0.38 %HbA1c, CI $-1.5, 0.7$) even though none of the studies in that review were part of the present analysis due to inclusion restraints. A major limitation, as before, is that no single randomized clinical trial reported here would be defined as a phase 3 (pivotal study), and hence, validation of these findings in a large clinical trial is needed. Results from one such study may be expected by early 2013 ([Clinical Trials.gov](#): NCT00997178).

Another finding that deserves mention is the range of standard deviations of the change from baseline of HbA1c ranging in the present analysis from 0.57 to 2.87. This finding is consistent with an earlier review and meta-analysis by Janket et al (Janket et al., 2005).

Risk of bias in small studies also continues to be a problem for generalizability to other populations. Randomization groups across all studies comprised only 15-82 subjects per group. Nonetheless, the 9 studies investigated here represent subjects from a broad range of ethnic and geographic origins. Subjects lived in China (N=206), Japan (N=49), India (n=45), Iran (n=40), Turkey (n=44), Greece (n=60) and the US (n=165). These widespread locations also reflect a wide diversity of health care systems, and therefore support the generalizability of this treatment approach.

Several of the included studies have followed subjects for more than three months. In addition to Jones et al (Jones et al., 2007a) reporting on a four month follow up study, three of the included studies have reported six month and longer outcomes. These longer-term follow up studies will be the focus of a future review and are not reported here.

A number of well-conducted clinical trials were excluded from this analysis because of the lack of a non-treatment group for comparison. Until it is established in larger clinical trials that non-surgical periodontal therapy does or does not improve metabolic parameters in people with diabetes, small studies that compare different treatment methods to this aim, do not contribute to the central study question. Nonetheless, should future studies confirm the findings of this and other systematic reviews on the topic, there will doubtless be fruitful ground for further research as to which periodontal therapy is most effective in this regard.

Also of importance (stated succinctly by Armitage (Armitage, 2008)), is that while periodontal therapy across studies included in this analysis were fairly uniform, the issue of treatment to a clinical endpoint goal has not yet been addressed. In 2 out of these 9 studies periodontal conditions did not change significantly, whereas in 7 out of these 9 studies statistically significant periodontal treatment effects were observed. To what extent these treatment effects can be considered clinically relevant for diabetes outcomes can not be determined, because the authors reported mean values for clinical attachment loss and probing depths and these types of values may be open to interpretation from a clinical perspective (Armitage, 2008).

Another critical issue concerns the definition of periodontitis in studies aimed at affecting diabetes outcomes, for can it be expected that change in HbA1c will occur if mild or periodontitis cases (or gingivitis) are treated? Since there is no general agreement in the scientific community as to what constitutes a periodontal case, and since very different inclusion criteria have been used in the studies reviewed here, the authors of this review took the liberty to assign case definitions of the included studies. Based on our interpretation

of the reviewed publications, 3 studies included cases with gingivitis or mild periodontitis, 3 studies cases with mild to moderate periodontitis, and 3 studies cases with moderate to severe periodontitis. Kiran et al (Kiran et al., 2005) stated: "Considering that the patients did not have any deep pockets, the effect on the metabolic control is actually a consequence of a decrease in gingivitis". The finding that mild periodontitis impacts HbA1c level appears to be at odds with the intuitive picture of the association between periodontal disease and systemic disease as discussed by Offenbacher (Offenbacher, 1996). Most researchers with a periodontal background have considered advanced periodontal disease with deep pockets as the sine qua non of *exposure* to periodontal infections. However, data from several populations have broadly defined periodontal disease as that which is characterized by only a few sites of advanced periodontal breakdown while the majority of sites have little pocketing (Holtfreter et al., 2009, Albandar, 1990). Future studies should include individuals with a wide range of periodontal inflammation and infection in order to determine whether control of gingivitis or mild periodontitis, or the reduction of deep periodontal pockets are necessary to impact metabolic control.

This raises the issue of adjunctive treatments and their contribution to periodontal therapy endpoints. Pivotal trials have demonstrated the clinical benefit of adjunctive systemic, or topical antimicrobials in periodontal disease management. Intake of systemic antibiotics could potentially mask the effect of scaling and root planing on HbA1c, because it may also act on non-oral sources of infection. Thus the observed reduction in HbA1c levels may not be solely attributable to the local reduction in the periodontal infectious burden (Jones et al 2007, Yun et al 2007, Singh et al 2008). While three of the studies did use such adjunctive therapies, there were not sufficient numbers in these trials to perform a meaningful subgroup analysis. The role of other host modulating agents in this regard has not been fully explored, although non-steroidal anti-inflammatory drugs have been shown to be useful in both periodontal disease (Williams et al., 1989) and diabetes management (Goldfine et al., 2010). Subantimicrobial doxycycline likewise is an effective adjunct to scaling and root planing (Caton et al., 2000), but has had only limited use as an adjunctive agent to scaling and root planing in trials of periodontal therapy and diabetes outcomes (Engelbreton and Hey-Hadavi, 2011).

Clinically significant reductions in HbA1c have been the basis for approval of new products for the treatment of diabetes because reducing HbA1c may prolong the onset of diabetes complications. The Diabetes Control and Complications Trial (DCCT) (DCCT, 1993, UKPDS, 1998), United Kingdom Prospective Diabetes Study (UKPDS) and other studies have shown that reductions in HbA1c decrease the risk of developing diabetic retinopathy, nephropathy, and neuropathy. However, there is currently no evidence of a "threshold" for the benefit of reducing HbA1c. Hence, any reduction in HbA1c might be expected to decrease the risk of diabetic complications regardless of the baseline HbA1c. Regarding the clinical relevance of periodontal treatment on the metabolic control, it must be understood, that the dental treatment is an add-on therapy to pharmacotherapy, and lifestyle changes. Metformin is often used as the drug of first choice in the treatment of type 2 diabetic patients (Nathan et al., 2009). Around 50% of all type 2 diabetes patients are treated with further antidiabetic drugs besides metformin in order to achieve metabolic control. Thus to weigh

the clinical relevance of any “dental” HbA1c reduction we have to compare its effect with a second drug in addition to metformin. As add-on treatment to metformin several agents can be used depending on the metabolic control (Nathan et al., 2009). The additional reduction of HbA1c besides the monotherapy with metformin was 0.85%, 0.61%, 0.42% respectively for sulphonylureas, α -glucosidase inhibitors and thiazolidinediones (Monami et al., 2008). Thus if periodontal scaling and root planing can improve the metabolic control by 0.4 to 0.5%, then its effect may be comparable to the effect of additional pharmacotherapy and therefore may find its place in the treatment of diabetic patients. Future studies should include patients with different diabetic treatment approaches to find out, if periodontal treatment works equally well in all diabetic patients irrespective of drugs used or better in subjects with certain glucose lowering interventions.

Another issue faced by clinicians is that both periodontal and diabetic intervention depend on patient compliance (Asche et al., 2011, Renz and Newton, 2009). For most individuals with type 2 diabetes, lifestyle interventions fail to achieve or to maintain the metabolic targets. The role of daily oral hygiene and supportive periodontal therapy on diabetes outcomes has not been determined.

Potential biases and limitations in the review process

There are several limitations to this review. We chose to search a single database, MEDLINE, using a previously published search strategy (Teeuw et al., 2010). While the PubMed database is widely regarded and used as an authoritative representation of the biomedical literature, several studies were added to the review that were not indexed in MEDLINE. Another limitation is the use of a single author (SE) to screen potential studies. We cannot rule this out as a potential source of bias, however, the search strategy and methods used in this systematic review were essentially duplication of work done previously. This strategy has served the purpose of making the present review comparable to the previous ones, a useful strategy for future reviewers.

Authors' conclusions

On the basis of this and previous systematic reviews and meta-analysis, that compare the effects of periodontal therapy on diabetes outcomes, it may be concluded that a consistent albeit moderate treatment effect size on HbA1c has been observed across studies as a result of periodontal therapy in subjects with type 2 diabetes. This analysis of newly available data has demonstrated a statistically significant effect of periodontal therapy on HbA1c similar to that observed in past systematic reviews.

Recommendations to clinicians however are not yet warranted since large prospective clinical trials have not yet been completed, and hence the generalizability of the present systematic review findings are limited. Also, it should be kept in mind that meta-analyses of small trials do not always predict the outcome of large trials (LeLorier et al., 1997). A 1997 study by LeLorier et al examined the outcome of 12 large randomized controlled trials which had been preceded by meta-analyses of small trials. They found that the outcome of these large trials were not predicted accurately 35% of the time by the meta-analyses.

With regard to the continued conduct and publication of underpowered studies, it may be more productive for clinical investigators to pool resources and to conduct larger more generalizable clinical trials than to perform small studies in isolation. The resultant data is at high risk for bias, and the benefits to the profession and the public are questionable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

SE is supported by NIH/NIDCR Grant U01 DE018902

TK is supported by an educational grant from GABA (Switzerland) and by the research project Greifswald Approach to Individualized Medicine (GANI_MED), the GANI_MED consortium is funded by the Federal Ministry of Education and Research and the Ministry of Cultural Affairs of the Federal State of Mecklenburg – West Pomerania (03IS2061A)

Grant Support: SE was supported by NIH/NIDCR Grant U01 DE018902, TK was supported by BMBF grant 03IS2061A and by an educational grant from GABA, Switzerland.

References

- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998; 352:837–853. [PubMed: 9742976]
- ADA. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003; 26(Suppl 1):S5–20. [PubMed: 12502614]
- Albandar JM. A 6-year study on the pattern of periodontal disease progression. *J Clin Periodontol*. 1990; 17:467–471. [PubMed: 2403413]
- Armitage GC. Effect of periodontal therapy on general health--is there a missing component in the design of these clinical trials? *J Clin Periodontol*. 2008; 35:1011–1012. doi:10.1111/j.1600-051X.2008.01327.x. [PubMed: 19040576]
- Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clinical therapeutics*. 2011; 33:74–109. doi:10.1016/j.clinthera.2011.01.019. [PubMed: 21397776]
- Bharti P, Katagiri S, Nitta H, Nagasawa T, Kobayashi H, Takeuchi Y, Izumiyama H, Uchimura I, Inoue S, Izumi Y. Periodontal treatment with topical antibiotics improves glycaemic control in association with elevated serum adiponectin in patients with type 2 diabetes mellitus. *Obesity Research & Clinical Practice*. 2011
- Caton JG, Ciancio SG, Blieden TM, Bradshaw M, Crout RJ, Hefti AF, Massaro JM, Polson AM, Thomas J, Walker C. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. *J Periodontol*. 2000; 71:521–532. doi: 10.1902/jop.2000.71.4.521. [PubMed: 10807113]
- Chen L, Luo G, Xuan D, Wei B, Liu F, Li J, Zhang J. Effects of non-surgical periodontal treatment on clinical response, serum inflammatory parameters, and metabolic control in patients with type 2 diabetes: a randomized study. *J Periodontol*. 2012; 83:435–443. doi:10.1902/jop.2011.110327. [PubMed: 21859323]
- Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, Rao M, Ali MK, Riley LM, Robinson CA, Ezzati M. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet*. 2011; 378:31–40. doi:10.1016/S0140-6736(11)60679-X. [PubMed: 21705069]

- DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993; 329:977–986. [PubMed: 8366922]
- Demmer RT, Holtfreter B, Desvarieux M, Jacobs DR Jr, Kerner W, Nauck M, Volzke H, Kocher T. The Influence of Type 1 and Type 2 Diabetes on Periodontal Disease Progression: Prospective results from the Study of Health in Pomerania (SHIP). *Diabetes Care*. 2012 doi:10.2337/dc11-2453.
- Engebretson SP, Hey-Hadavi J. Sub-antimicrobial doxycycline for periodontitis reduces hemoglobin A1c in subjects with type 2 diabetes: a pilot study. *Pharmacological research : the official journal of the Italian Pharmacological Society*. 2011; 64:624–629. doi:10.1016/j.phrs.2011.06.024. [PubMed: 21782948]
- Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, Badran A, Sous ES, Ali MA. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. *Diabetes Care*. 1997; 20:785–791. [PubMed: 9135943]
- Goldfine AB, Fonseca V, Jablonski KA, Pyle L, Staten MA, Shoelson SE. The effects of salsalate on glycaemic control in patients with type 2 diabetes: a randomized trial. *Annals of internal medicine*. 2010; 152:346–357. doi:10.1059/0003-4819-152-6-201003160-00004. [PubMed: 20231565]
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine*. 2002; 21:1539–1558. doi:10.1002/sim.1186. [PubMed: 12111919]
- Higgins, JPT.; S., G., editors. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration; 2011.
- Holtfreter B, Schwahn C, Biffar R, Kocher T. Epidemiology of periodontal diseases in the Study of Health in Pomerania. *J Clin Periodontol*. 2009; 36:114–123. doi:10.1111/j.1600-051X.2008.01361.x. [PubMed: 19207886]
- Hundal RS, Petersen KF, Mayerson AB, Randhawa PS, Inzucchi S, Shoelson SE, Shulman GI. Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. *J Clin Invest*. 2002; 109:1321–1326. [PubMed: 12021247]
- Janket SJ, Wightman A, Baird AE, Van Dyke TE, Jones JA. Does periodontal treatment improve glycaemic control in diabetic patients? A meta-analysis of intervention studies. *J Dent Res*. 2005; 84:1154–1159. [PubMed: 16304446]
- Jones JA, Miller DR, Wehler CJ, Rich SE, Krall-Kaye EA, McCoy LC, Christiansen CL, Rothendler JA, Garcia RI. Does periodontal care improve glycaemic control? The Department of Veterans Affairs Dental Diabetes Study. *J Clin Periodontol*. 2007a; 34:46–52. doi:10.1111/j.1600-051X.2006.01002.x. [PubMed: 17137468]
- Jones JA, Miller DR, Wehler CJ, Rich SE, Krall-Kaye EA, McCoy LC, Christiansen CL, Rothendler JA, Garcia RI. Does periodontal care improve glycaemic control? The Department of Veterans Affairs Dental Diabetes Study. *Journal of Clinical Periodontology*. 2007b; 34:46–52. doi: 10.1111/j.1600-051X.2006.01002.x. [PubMed: 17137468]
- Katagiri S, Nitta H, Nagasawa T, Uchimura I, Izumiyama H, Inagaki K, Kikuchi T, Noguchi T, Kanazawa M, Matsuo A, Chiba H, Nakamura N, Kanamura N, Inoue S, Ishikawa I, Izumi Y. Multi-center intervention study on glycohemoglobin (HbA1c) and serum, high-sensitivity CRP (hs-CRP) after local anti-infectious periodontal treatment in type 2 diabetic patients with periodontal disease. *Diabetes research and clinical practice*. 2009; 83:308–315. doi:10.1016/j.diabres.2008.10.016. [PubMed: 19168253]
- Kiran M, Arpak N, Unsal E, Erdogan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. *J Clin Periodontol*. 2005; 32:266–272. doi:10.1111/j.1600-051X.2005.00658.x. [PubMed: 15766369]
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346:393–403. [PubMed: 11832527]
- Koromantzou PA, Makrilakis K, Dereka X, Katsilambros N, Vrotsos IA, Madianos PN. A randomized, controlled trial on the effect of non-surgical periodontal therapy in patients with type 2 diabetes. Part I: effect on periodontal status and glycaemic control. *J Clin Periodontol*. 2011; 38:142–147. doi:10.1111/j.1600-051X.2010.01652.x. [PubMed: 21114680]

- LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *The New England journal of medicine*. 1997; 337:536–542. doi:10.1056/NEJM199708213370806. [PubMed: 9262498]
- Maggs DG, Buchanan TA, Burant CF, Cline G, Gumbiner B, Hsueh WA, Inzucchi S, Kelley D, Nolan J, Olefsky JM, Polonsky KS, Silver D, Valiquett TR, Shulman GI. Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1998; 128:176–185. [PubMed: 9454525]
- Moeintaghavi A, Arab HR, Bozorgnia Y, Kianoush K, Alizadeh M. Non-surgical periodontal therapy affects metabolic control in diabetics: a randomized controlled clinical trial. *Australian dental journal*. 2012; 57:31–37. doi:10.1111/j.1834-7819.2011.01652.x. [PubMed: 22369555]
- Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. *Diabetes research and clinical practice*. 2008; 79:196–203. doi:10.1016/j.diabres.2007.08.024. [PubMed: 17931733]
- Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2009; 52:17–30. doi:10.1007/s00125-008-1157-y. [PubMed: 18941734]
- O'Connor D, GS.; Higgins, JPT. Chapter 5: Defining the review question and developing criteria for including studies. In: S., G.; Higgins, JPT., editors. *Cochrane handbook for systematic reviews of interventions version 5.0.0*. The Cochrane Collaboration; 2009.
- Offenbacher S. Periodontal diseases: pathogenesis. *Annals of periodontology / the American Academy of Periodontology*. 1996; 1:821–878. [PubMed: 9118282]
- Promsudthi A, Pimapsri S, Deerochanawong C, Kanchanasavita W. The effect of periodontal therapy on uncontrolled type 2 diabetes mellitus in older subjects. *Oral Dis*. 2005; 11:293–298. doi:10.1111/j.1601-0825.2005.01119.x. [PubMed: 16120115]
- Renz AN, Newton JT. Changing the behavior of patients with periodontitis. *Periodontology*. 2009; 51:252–268. 2000. doi:10.1111/j.1600-0757.2009.00314.x.
- Sammalkorpi K. Glucose intolerance in acute infections. *J Intern Med*. 1989; 225:15–19. [PubMed: 2645379]
- Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004; 141:421–431. [PubMed: 15381515]
- Seppala B, Seppala M, Ainamo J. A longitudinal study on insulin-dependent diabetes mellitus and periodontal disease. *J Clin Periodontol*. 1993; 20:161–165. [PubMed: 8450080]
- Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *The Journal of clinical investigation*. 2006; 116:1793–1801. doi:10.1172/JCI29069. [PubMed: 16823477]
- Simpson TC, Needleman I, Wild SH, Moles DR, Mills EJ. Treatment of periodontal disease for glycaemic control in people with diabetes. *Cochrane database of systematic reviews*. 2010:CD004714. doi:10.1002/14651858.CD004714.pub2. [PubMed: 20464734]
- Singh S, Kumar V, Kumar S, Subbappa A. The effect of periodontal therapy on the improvement of glycaemic control in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. *International journal of diabetes in developing countries*. 2008; 28:38–44. doi: 10.4103/0973-3930.43097. [PubMed: 19902046]
- Stewart JE, Wager KA, Friedlander AH, Zadeh HH. The effect of periodontal treatment on glycaemic control in patients with type 2 diabetes mellitus. *J Clin Periodontol*. 2001; 28:306–310. [PubMed: 11314885]
- Sun WL, Chen LL, Zhang SZ, Ren YZ, Qin GM. Changes of adiponectin and inflammatory cytokines after periodontal intervention in type 2 diabetes patients with periodontitis. *Arch Oral Biol*. 2010; 55:970–974. doi:10.1016/j.archoralbio.2010.08.001. [PubMed: 20889139]
- Sun WL, Chen LL, Zhang SZ, Wu YM, Ren YZ, Qin GM. Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis. *Internal medicine*. 2011; 50:1569–1574. [PubMed: 21804283]

- Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. *BMJ*. 2000; 320:1574–1577. [PubMed: 10845965]
- Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. *Ann Periodontol*. 2001; 6:99–112. [PubMed: 11887478]
- Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ. Severe periodontitis and risk for poor glycaemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol*. 1996; 67:1085–1093. [PubMed: 8910827]
- Teeuw WJ, Gerdes VE, Loos BG. Effect of periodontal treatment on glycaemic control of diabetic patients: a systematic review and meta-analysis. *Diabetes Care*. 2010; 33:421–427. doi:10.2337/dc09-1378. [PubMed: 20103557]
- Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. *Community Dent Oral Epidemiol*. 2002; 30:182–192. [PubMed: 12000341]
- UKPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998; 352:837–853. [PubMed: 9742976]
- Williams RC, Jeffcoat MK, Howell TH, Rolla A, Stubbs D, Teoh KW, Reddy MS, Goldhaber P. Altering the progression of human alveolar bone loss with the non-steroidal anti-inflammatory drug flurbiprofen. *J Periodontol*. 1989; 60:485–490. [PubMed: 2677301]
- Yale JF, Valiquett TR, Ghazzi MN, Owens-Grillo JK, Whitcomb RW, Foyt HL. The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2001; 134:737–745. [PubMed: 11329231]
- Yun F, Firkova EI, Jun-Qi L, Xun H. Effect of non-surgical periodontal therapy on patients with type 2 diabetes mellitus. *Folia medica*. 2007; 49:32–36. [PubMed: 18018467]
- Zhang Y, Dall TM, Mann SE, Chen Y, Martin J, Moore V, Baldwin A, Reidel VA, Quick WW. The economic costs of undiagnosed diabetes. *Population health management*. 2009; 12:95–101. [PubMed: 19361252]

Figure 1.
Flow Chart of manuscripts screened through the review process

Figure 2.
Funnel plot of comparison: Periodontal Therapy outcome: Change in HbA1c (%HbA1c).

Table 1

Country	Number of subjects	Perio	Method	Baseline	Change in CAL, PD,	Diabetic	Comment:	Comment:
Single vs multicenter	Inclusion	don'tis	for	and follow	BOP (mean)	medication at	periodontitis	diabetes
HbA1c inclusion	criteria	criteria	evaluation	up HbA1c		baseline		
Treatment in test	Reviewers	“case	of	values		Change in		
and	definition”	definition”	periodonti	(mean)		diabetic		
control group			tis			medication		
						during trial		
(Jones et al., 2007a)	US	8 teeth	PD, BOP,	Tx: 9.9%	emergency	Oral medication: 77	no	In 16% of
	165 T2DM male	CPTN 3 in		9.3%	treatment not	Insulin: 47	periodontal	subjects
	subjects	sextants		Ctr: 10.2%	reported	Oral medication and	treatment	insulin dose
	RCT	Gingivitis,		9.6%	Tx: PD 2.5 -	Insulin: 37	effect	was
	multicenter	and			CAL 3.2 -	Change in insulin		increased
	Tx: scaling +	moderate			BOP 14.3	medication		
	doxycycline +	periodontitis			Ctr: PD 2.4 -			
	CHX rinse	PD > 5 mm			CAL 3.1 -			
	Ctr: usual care	2.6%			BOP 13.2 -			
	HbA1c > 8.5%							
Moeintaghavi et al 2012	Iran	Not reported	PD, CAL,	Tx: 8.15%	emergency	Oral medication	Periodontal	Metabolic
	40 T2DM,	Gingivitis	PI, GI	7.41%	performed	No insulin	conditions	control
	RCT,	and		Ctr: 8.72%	Tx: PD 2.31 2.21	Change not	improved in	improved
	single center	moderate		8.97%	CAL 3.14 2.80	reported	Tx group	Tx 11/22
	Tx: scaling	periodontitis			BOP --			Ctr: 5/18
	Ctr: no Tx, OH	all sites with			Ctr: PD 2.06 2.33			
	HbA1c > 7%	PD < 5mm			CAL 3.1 3.47			
					BOP --			
Yun et al 2007	China,	14 teeth,	PD,CAL,	Tx: 8.26%	Emergency Tx	Baseline	no	Unclear if
	46 T2DM,	PD 5mm <	PI, BOP	7.49%	performed	medication not	periodontal	subjects
	RCT	8mm in at		Ctr: 8.22%	Tx: PD 3.86 3.42	reported	treatment effect	were on
	single center	least 4 teeth,		7.64%	CAL 4.3 4.11	Change not reported	In both	diabetes
	HbA1c not reported	2 quadrants			BOP 71.5 42.5		groups	drugs
	Newly diagnosed	Moderate			Ctr: PD 3.77 3.61		antibiotics	Trial not
	diabetes	periodontitis			CAL 4.25 4.2		=<	optimal for
	Tx: scaling +				BOP: 70.7 58.2		improvement	research
	doxycycline						of	question
	Ctr: no scaling +						perio	because both
	doxycycline						condition	groups
								received
								antibiotics.
Chen 2012	China	1mm mean	PD, CAL, PI,	Tx1: 7.31%	Emergency Tx not	Diet control: 4	Periodontal	Metabolic
	134 T2DM,	CAL,	BOP	7.30%	reported	Oral	conditions	status
	RCT,	16 teeth		Tx2: 7.29%	Tx1: PD 2.66 2.27	medication: 109	improved in	did not improve
	Single center	Moderate		7.43%	CAL 3.57 2.28	Insulin: 13	Tx1 Tx2	in any group
	HbA1c not reported	periodontitis		Ctr: 7.25%	BOP 37.4 13.6	Change in		
	Tx-1 scaling+rescale	about 4% of		7.59%	Tx2 PD 2.57 2.20	medication not		
	at 3	sites 6mm			CAL 2.95 2.55	reported		
	mo				BOP 32.4 12.1			
	Tx-2 scaling + supra				Ctr: PD 2.47 2.38			
	at 3 mo				CAL 3.37 3.29			
					BOP: 34.0 28.5			

Kiran 2005	<p>Ctrl no supragingival Tx, no OH</p> <p>Turkey 44 DM 2, RCT</p> <p>single center</p> <p>HbA1c 6%-8%</p> <p>Tx: scaling</p> <p>Ctrl: no scaling</p>	<p>Not reported moderate periodontitis</p>	<p>PD, CAL, GR, PI, GI, BOP</p>	<p>Tx: 7.31% 6.51% Ctrl: 7.00% 7.31%</p>	<p>Emergency Tx performed Tx: PD 2.29 1.80 CAL 4.3 4.11 BOP 54.4 23.9 Ctrl: PD 2.24 2.26 CAL 2.92 2.87 BOP: 50.5 51.9</p>	<p>Diet control: 3 Oral medication: 30 Insulin: 4 Insulin + oral: 7 Change in medication not reported</p>	<p>Periodontal conditions improved in Tx group</p>	<p>Some subjects with HbA1c 6-6.5% should be regarded as well controlled HbA1c improvement due to gingivitis control</p>
Koromantzios 2011	<p>Greece 60 T2DM, RCT</p> <p>single center</p> <p>HbA1c 7% - 10%</p> <p>Tx: scaling</p> <p>Ctrl: OH supragingival scaling</p>	<p>16 teeth PD: 8 sites 6mm CAL 4 sites 5mm, affected at least 2 quadrants Moderate to severe periodontitis</p>	<p>PD, CAL, BOP, GI</p>	<p>Tx: 7.87% 7.19% Ctrl: 7.59% 7.51%</p>	<p>Emergency Tx performed Tx: BOP 71.55 33.43 Ctrl: BOP: 69.27 64.92</p>	<p>Oral medication 48 Insulin 19 Change in medication reported</p>	<p>Periodontal conditions improved in Tx group</p>	
Katagiri 2009 2	<p>Japan 49 T2DM, RCT</p> <p>multicenter</p> <p>HbA1c 6.5% - 10%</p> <p>Tx: scaling + topical minocycline</p> <p>Ctrl: OH</p>	<p>11 teeth 2 sites with PD 4mm, Mild to moderate periodontitis</p>	<p>PD, BOP</p>	<p>Tx: 7.2% 7.0%² Ctrl: 6.9% 6.9%</p>	<p>Emergency Tx not reported Tx: PD 3.3 2.3 CAL -- BOP 46.6 17.4 Ctrl: PD 2.8 2.6 CAL -- BOP: 24.9 20.1</p>	<p>Diet control: 3 Oral medication: 27 Insulin: 19 Diabetes medication not changed during trial</p>	<p>Periodontal conditions improved in Tx group Topical application of minocycline may impact perio Tx effect</p>	<p>Tx subgroup analysis: HbA1c improvement only in subgroup where elevated CRP level decreased</p>
Singh 2008	<p>India 45 T2DM RCT</p> <p>single center</p> <p>HbA1c not reported</p> <p>Tx: scaling</p> <p>Tx-2: scaling systemic doxycycline</p> <p>Ctrl: no supragingival Tx, no OH</p>	<p>30% all teeth PD 4mm Moderate to severe periodontitis</p>	<p>PD, CAL; GI, PI</p>	<p>Tx1: 7.9 7.3 Tx2: 8.3 7.5 Ctrl: 8.1 8.1</p>	<p>Emergency Tx performed Tx-1: PD 2.67 2.33 CAL 3.44 3.14 BOP -- Tx-2: PD 2.52 2.14 CAL 3.22 3.14 BOP -- Ctrl: PD 2.44 2.40 CAL 2.78 2.83 BOP: 24.9 20.1</p>	<p>Diabetes medication reported Change in medication not reported</p>	<p>Periodontal conditions improved in both Tx groups No OH Adjunctive doxycycline > scaling Tx</p>	
Sun 2011	<p>China 106 T2DM RCT</p> <p>HbA1c 6.5% - 7.5%</p> <p>Tx: scaling, flap when</p>	<p>20 teeth PD>5mm and CAL 4mm On 30% sites Or</p>	<p>PD, CAL, BOP, PI, GI</p>	<p>Tx: 7.1% 6.6% Ctrl: 7.1% 7.2%</p>	<p>Emergency treatment performed Tx-3 PD 4.28 2.53 CAL 4.45 3.71 BOP: 93.6 48.8</p>	<p>Diet or oral medication Change in medication not reported</p>	<p>Periodontal conditions improved in Tx group</p>	

indicated, antibiotics for 3 PD > 4mm
indicated, antibiotics for 3 and CAL
(tinidazole ampicillin) >3mm on 60%
sites
Ctr: OH

Ctr³: PD 4.28 4.10
CAL 4.45 4.33
BOP: 93.6 93.1

Emergency treatment: extraction, endodontic treatment, restoration

OH oral hygiene

+ 6 mo results, 3 mo results not reported

2 not reported in table, extrapolated from a graph

** treatment period continued for 6 months, Tx 1 and Tx 2 only differs during the 3 to 6 months period, thus they can be both viewed as the same treatment modality,

*** study period extended over 4 months

³ Data reporting not distinct

PD: pocket depth, CAL: clinical attachment loss, BOP: bleeding on probing, Pl: plaque index, GI: gingival index, GR: gingival recession,