

Evidence that periodontal treatment improves diabetes outcomes: a systematic review and meta-analysis

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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: Pre-defined 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, there is limited confidence in the conclusion due to a lack of multi-centre trials of sufficient sample size are lacking.

Key words: diabetes; diabetes mellitus; glycosylated haemoglobin; HbA1c; periodontal disease; periodontitis; type 2

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Conflict of interest and source of funding statement

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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 preva-

lence 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).

Haemoglobin 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, Maggs et al. 1998, Yale et al. 2001, Hunsdal et al. 2002, Knowler et al. 2002, Selvin et al. 2004) 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, Tsai et al. 2002, Demmer et al. 2012).

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 programme that incorporates life style changes and medications.

Several recent systematic reviews (Simpson et al. 2010, Teeuw 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 et al. 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 3 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, five new studies meeting the inclusion criteria established by the 2010 reviews resulted in a total of nine 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 oral glucose tolerance test (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 (t1 dm) OR (type 2 diab) OR (t2 dm)) 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 (Simpson et al. 2010, Teeuw 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, five met the criteria for inclusion in the meta-analysis. Reasons for exclusion are listed in the Appendix S1.

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 *versus* no treatment on HbA1c levels was submitted to meta-analysis. None of the included studies reported fructosamine. Fasting glucose, or OGTT values, was 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 3 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 analysed separately but control subjects were counted only once in the overall n as previously described (Higgins & Green 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 & 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 per cent 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 (Fig. 1). Titles and abstracts were scanned to rule out studies that did not meet inclusion criteria, (e.g. 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.

Four studies were included in the present analysis which were also included for comparison in two previous systematic reviews (Kiran et al. 2005, Jones et al. 2007, Yun et al. 2007, Katagiri et al. 2009), whereas 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. 2013) 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 four studies published prior to October 2009, five additional studies published since October 2009 met the criteria for inclusion in this meta-analysis for a total of nine studies. In the nine 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.

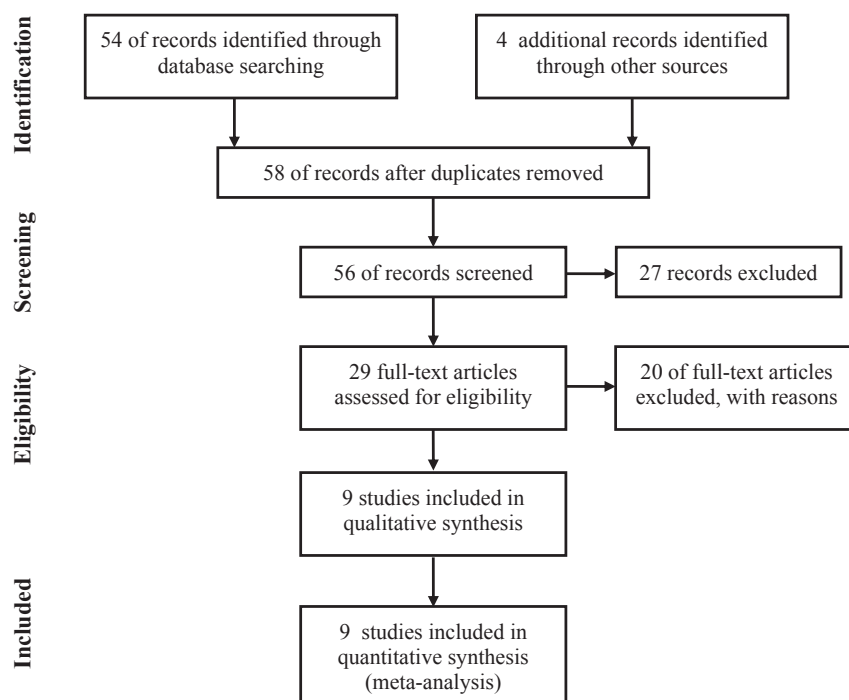


Fig. 1. Flow chart of manuscripts screened through the review process.

The duration of the follow-up period was at least 3 months, with one study (Jones et al. 2007) including a 4-month follow-up. Although two studies were of 6-month duration (Koromantzos et al. 2011, Chen et al. 2012), only 3 or 4-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. Seven studies were single centre (Kiran et al. 2005, Yun et al. 2007, Singh et al. 2008, Koromantzos et al. 2011, Sun et al. 2011, Chen et al. 2012, Moeintaghavi et al. 2012), two were multi-centred (Katagiri et al. 2009) (Jones et al. 2007). 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. 2007) 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 $-0.54, -0.19$). Eight of nine studies reported a decrease in mean HbA1c from baseline to 3 months for the treatment group. Of those studies, five of eight were statistically significant decreases. Among the control groups receiving no periodontal treatment five of the nine studies reported a decrease in HbA1c from baseline to 3 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. Seven studies were parallel arm two group studies, while two studies (Singh et al. 2008, Chen et al. 2012) 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, three studies' treatment included scaling and root planing only (Kiran et al. 2005, Chen et al. 2012, Moeintaghavi et al. 2012), one study (Koromantzos 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. 2007) 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% CI -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.

Table 1. Summary: Clinical studies of periodontal therapy and glycaemic control to date

	Country	Inclusion criteria	Method evaluation	HbA1c (%) (mean) at baseline and at 3 months	CAL (in mm), PD (in mm), BOP (in%) at baseline and at 3 months	Number of subjects with diabetic medication at baseline	Comment: periodontitis	Comment: diabetes
Kiran et al. 2005	Turkey 44 DM2 single center HbA1c 6%–8% tx: scaling ctr: no scaling	Not reported Very moderate periodontitis	PD, CAL, GR, PI, GI, BOP	Tx: 7.31% $\geq$ 6.51% Sctr: 7.00% $\geq$ 7.31%	emergency tx performed tx: PD 2.29 $\geq$ 1.80 CAL 4.30 $\geq$ 4.11 BOP 54.4 $\geq$ 23.9 ctr: PD 2.24 $\geq$ 2.26 CAL 2.92 $\geq$ 2.87 BOP 50.5 $\geq$ 51.9	Diet control: 3 Oral medication: 30 Insulin: 4 Insulin + oral: 7 Change in medication not reported	Periodontal conditions improved in tx group	Some subjects with, HbA1c 6%–6.5% should be regarded as well controlled due to gingivitis control
Jones et al. 2007 [†]	US 165 DM2 male subjects multicenter HbA1c > 8.5% tx: scaling + doxycycline + CHX rinse; usual care	$\geq$ 8 teeth with CPITN $\geq$ 3 gingivitis, and very moderate periodontitis (PD > 5 mm 2.6% of all teeth)	PD, BOP	tx: 9.9% $\geq$ 9.3% ctr: 10.2% $\geq$ 9.6%	emergency tx not reported tx: PD 2.5 $\geq$ nr CAL 3.2 $\geq$ nr BOP 14.3 $\geq$ nr ctr: PD 2.4 $\geq$ nr CAL 3.1 $\geq$ nr BOP 13.2 $\geq$ nr	Oral medication: 77 Insulin: 47 Oral medication and insulin: 37 Change in insulin medication	no periodontal treatment effect	In 16% of subjects insulin dose was increased
Yun et al. 2007	China 46 DM2 single center HbA1c not reported Newly diagnosed diabetes tx: scaling + doxycycline ctr: no scaling + doxycycline	$\geq$ 14 teeth, with PD $\geq$ 5 mm <8 mm in at least four teeth, in two quadrants moderate periodontitis	PD, CAL, PI, BOP	tx: 8.26% $\geq$ 7.49% ctr: 8.22% $\geq$ 7.64%	emergency tx performed tx: PD 3.86 $\geq$ 3.42 CAL 4.3 $\geq$ 4.11 BOP 71.5 $\geq$ 42.5 ctr: PD 3.77 $\geq$ 3.61 CAL 4.25 $\geq$ 4.20 BOP 70.7 $\geq$ 58.2	Baseline medication not reported Change not reported	no periodontal treatment effect in both groups antibiotics	Unclear if subjects were on diabetes drugs Trial not optimal for research question because both groups received antibiotics
Singh et al. 2008	India 45 DM2 single center HbA1c not reported tx-1: scaling tx-2: scaling systemic doxycycline ctr: no supragingival tx, no OH	$\geq$ 30% all teeth with PD $\geq$ 4 mm moderate to severe periodontitis	PD, CAL, GI, PI	tx-1: 7.9% $\geq$ 7.3% tx-2: 8.3% $\geq$ 7.5% ctr: 8.1% $\geq$ 8.1%	emergency tx performed tx-1: PD 2.67 $\geq$ 2.33 CAL 3.44 $\geq$ 3.14 BOP nr $\geq$ nr tx-2: PD 2.52 $\geq$ 2.14 CAL 3.22 $\geq$ 3.14 BOP nr $\geq$ nr ctr: PD 2.44 $\geq$ 2.40 CAL 2.78 $\geq$ 2.83 BOP 24.9 $\geq$ 20.1	Diabetes medication not reported Change in medication not reported	Periodontal conditions improved in both tx group no OH adjunctive doxycycline > scaling tx	
Katagiri et al. 2009 ²	Japan 49 DM2 multicenter HbA1c 6.5%–10% tx: scaling + topical minocycline ctr: OH	$\geq$ 11 teeth with $\geq$ 2 sites with PD $\geq$ 4 mm mild to moderate periodontitis	PD, BOP	tx: 7.2% $\geq$ 7.0%* ctr: 6.9% $\geq$ 6.9%	emergency tx not reported tx: PD 3.3 $\geq$ 2.3 CAL nr $\geq$ nr BOP 46.6 $\geq$ 17.4 ctr: PD 2.8 $\geq$ 2.6 CAL nr $\geq$ nr BOP 24.9 $\geq$ 20.1	Diet control: 3 Oral medication: 27 Insulin: 19 Diabetes medication not changed during trial	Periodontal conditions improved in tx group Topical application of minocycline may impact perio tx effect	Tx subgroup analysis: HbA1c improvement only in subgroup where elevated CRP level decreased
Koromantzios et al. 2011	Greece 60 DM2 single center CAL: 4 sites $\geq$ 5 mm, HbA1c 7%–10% tx: scaling ctr: OH supragingival scaling	$\geq$ 16 teeth PD: 8 sites $\geq$ 6 mm CAL: 4 sites $\geq$ 5 mm, affected at least 2 quadrants moderate to severe periodontitis	PD, CAL, BOP, GI	tx 7.87% $\geq$ 7.19% ctr: 7.59% $\geq$ 7.51%	Emergency tx performed tx: BOP 71.6 $\geq$ 33.4 ctr: BOP: 69.3 $\geq$ 64.9	Oral medication 48 Insulin 19 Change in medication reported	Periodontal conditions improved in tx group	

Table 1. (continued)

	Country	Inclusion criteria	Method evaluation	HbA1c (%) (mean) at baseline and at 3 months	CAL (in mm), PD (in mm), BOP (in%) at baseline and at 3 months	Number of subjects with diabetic medication at baseline	Comment: periodontitis	Comment: diabetes
Sun et al. 2011	China 106 DM2 HbA1c 6.5%–7.5% tx: scaling, flap when indicated, antibiotics for 3 d (tinidazole ampicillin) ctr: OH	≥ 20 teeth PD > 5 mm and CAL ≥ 4 mm on ≥ 30% sites Or PD > 4 mm and CAL ≥ 3 mm on ≥ 60% sites severe periodontitis	PD, CAL, BOP, PI, GI	tx: 7.1% ≥ 6.6% ctr: 7.1% ≥ 7.2%	emergency treatment performed tx [§] : PD 4.28 ≥ 2.53 CAL 4.45 ≥ 3.71 BOP 93.6 ≥ 48.8 ctr [§] : PD 4.28 ≥ 4.10 CAL 4.45 ≥ 4.33 BOP 93.6 ≥ 93.1	Diet or oral medication Change in medication not reported	Periodontal conditions improved in tx group	
Chen et al. 2012	China [†] 134 DM2 Single center HbA1c not reported tx-1: scaling + rescale at 3 months tx-2: scaling + supragingival at 3 months ctr: no supragingival tx, no OH	≥ 1 mm mean CAL, ≥ 16 teeth about 4% of sites ≥ 6 mm moderate periodontitis	PD, CAL, PI, BOP	tx-1: 7.31% ≥ 7.30% tx-2: 7.29% ≥ 7.43% ctr: 7.25% ≥ 7.59%	emergency tx not reported tx-1: PD 2.66 ≥ 2.27 CAL 3.57 ≥ 2.28 BOP 37.4 ≥ 13.6 tx-2: PD 2.57 ≥ 2.20 CAL 2.95 ≥ 2.55 BOP 32.4 ≥ 12.1 ctr: PD 2.47 ≥ 2.38 CAL 3.37 ≥ 3.29 BOP 34.0 ≥ 28.5	Diet control: 4 Oral medication: 109 Insulin: 13 Change in medication not reported	Periodontal conditions improved in tx-1 and in tx-2 group	Metabolic status did not improve in any group
Mohtaghavi et al. 2012	Iran 40 DM2 single center HbA1c > 7% tx: scaling ctr: no tx, OH	not reported all sites with PD < 5 mm gingivitis and very moderate periodontitis	PD, CAL, PI, GI	tx: 8.15% ≥ 7.41% ctr: 8.72% ≥ 8.97%	emergency performed tx: PD 2.31 ≥ 2.21 CAL 3.14 ≥ 2.80 BOP nr ≥ nr ctr: PD 2.06 ≥ 2.33 CAL 3.1 ≥ 3.47 BOP nr ≥ nr	Oral medication No insulin Change not reported	Periodontal conditions improved in tx group	Metabolic control improved [†] tx in 11/22 ctr in 5/18

PD, pocket depth; CAL, clinical attachment loss; BOP, bleeding on probing; PI, plaque index; GI, gingival index; GR, gingival recession; nr, not reported; OH oral hygiene

Emergency treatment: extraction, endodontic treatment, restoration

+6 months results, 3 months results not reported

*not reported in table, extrapolated from a graph

†treatment period continued for 6 months, tx 1 and tx2 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

§Data reporting not distinct

Table 2. Forest plot of comparison: Periodontal Therapy outcome: Change in HbA1c (%HbA1c) at 3 months.

Study or Subgroup	Treatment			Control			Mean difference		Mean difference IV, Random, 95% CI (%HbA1c)
	Mean (%HbA1c)	SD (%HbA1c)	Total	Mean (%HbA1c)	SD (%HbA1c)	Total	Weight	IV, Random, 95% CI (%HbA1c)	
Moeintaghavi 2012	-0.74	1.67	22	0.25	2.87	18	1.3%	-0.99 (-2.49, 0.51)	
Yun 2007	-0.77	2	23	-0.58	2.77	23	1.5%	-0.19 (-1.59, 1.21)	
Chen 2012 B	0.14	2.18	41	0.34	2.14	41	3.3%	-0.20 (-1.14, 0.74)	
Chen 2012 A	-0.01	1.94	42	0.34	2.14	41	3.7%	-0.35 (-1.23, 0.53)	
Kiran 2005	-0.8	0.77	22	0.31	1.83	22	4.1%	-1.11 (-1.94, -0.28)	
Singh 2008 B	-0.8	0.92	15	0.02	1.02	15	5.8%	-0.82 (-1.52, -0.12)	
Singh 2008 A	-0.6	0.92	15	0.02	1.02	15	5.8%	-0.62 (-1.32, 0.08)	
Koromantzos 2011	-0.73	0.91	30	-0.18	0.82	30	13.4%	-0.55 (-0.99, -0.11)	
Jones 2007	-0.65	1.21	74	-0.49	1.22	80	16.8%	-0.16 (-0.54, 0.22)	
Katagiri 2009	-0.14	0.63	32	-0.09	0.57	17	19.7%	-0.05 (-0.40, 0.30)	
Sun 2011	-0.5	0.99	82	-0.14	0.94	75	24.5%	-0.36 (-0.66, -0.06)	
Total (95% CI)			398			377	100.0%	-0.36 (-0.54, -0.19)	

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 11.01$, $df = 10$ ($p = 1.36$); $I^2 = 9\%$.

Test for overall effect: $Z = 4.13$ ($p < 0.0001$).

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 versus 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 (Fig. 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, five new studies meeting the inclusion criteria established by the 2010 reviews resulted in a total of nine randomized clinical tri-

als for inclusion in this review. The studies included investigations with at least 3 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 nine 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. 2005 (Janket et al. 2005) 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

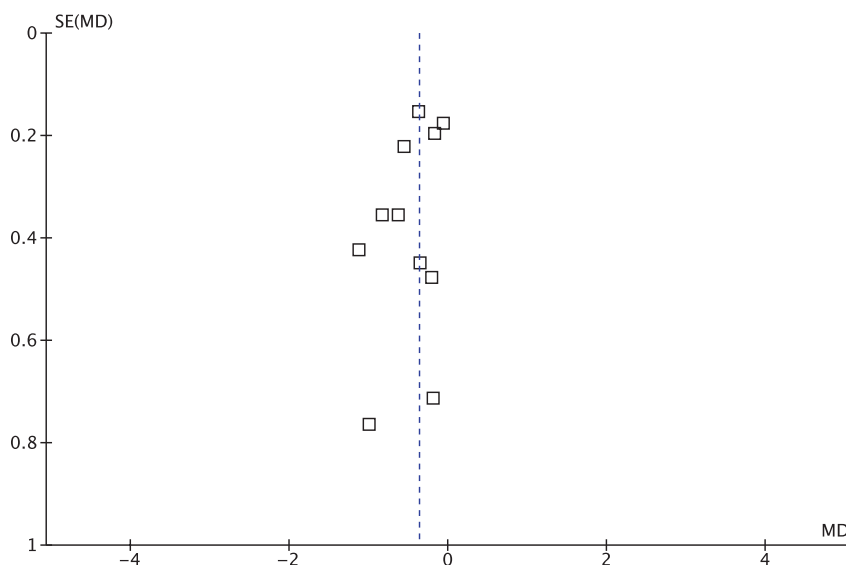


Fig. 2. Funnel plot of comparison: periodontal therapy outcome: change in HbA1c (%HbA1c).

trial is needed. Results from one such study may be expected by early 2013 (ClinicalTrials.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 nine 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 United States ($n = 165$). 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 3 months. In addition to Jones et al. (Jones et al. 2007) reporting on a 4-month follow-up study, three of the included studies have reported 6 months 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 end-

point goal has not yet been addressed. In two of these nine studies periodontal conditions did not change significantly, whereas in seven of these nine studies statistically significant periodontal treatment effects were observed. To what extent these treatment effects can be considered clinically relevant for diabetes outcomes cannot 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 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, three studies included cases with gingivitis or mild periodontitis, three studies cases with mild to moderate periodontitis and three 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 (Albandar 1990, Holtfreter et al. 2009). 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). Although 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 & 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 anti-diabetic drugs besides metformin 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 (Renz & Newton 2009, Asche et al. 2011). 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). Although the PubMed database is widely regarded and used as an authoritative repre-

sentation 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 are at high risk for bias, and the benefits to the profession and the public are questionable.

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Supporting Information

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

Appendix S1. Characteristics of included studies.

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Clinical Relevance

Scientific rational for the study: Systematic reviews and meta analysis have demonstrated significant reductions in Haemoglobin A1c following periodontal therapy in subjects with type 2 diabetes when compared with untreated control

subjects. However, recently published studies necessitated the need for an updated systematic review.

Principal findings: A statistically significant difference for change in Haemoglobin A1c from baseline level in favour of the periodontal therapy groups was found.

Practical implications: Recommendations to clinicians 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.