Australian Dental Journal
The official journal of the Australian Dental Association

AUSTRALIAN DENTAL ASSOCIATION INC.

*Australian Dental Journal* 2013; 58: 350–357

doi: 10.1111/adj.12091

# Effect of non-surgical periodontal treatment on HbA1c: a meta-analysis of randomized controlled trials

AKC Liew,*† N Punnanithinont,* Y-C Lee,* J Yang*

*Harvard School of Public Health, Boston, Massachusetts, USA.
†Faculty of Dentistry, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia.

## ABSTRACT

***Background:*** A meta-analysis of randomized clinical trials (RCTs) was conducted to evaluate whether non-surgical periodontal treatment can reduce the HbA1c% level in type 2 diabetic patients. Recent accumulation of RCTs necessitates updating of the findings of previous reviews.
***Methods:*** A search of the literature on English publications was conducted in Cochrane CENTRAL, Medline and EMBASE (until 31 March 2012). An RCT was selected if the study population was type 2 diabetic patients (≥16 years old) diagnosed with periodontitis, and compared HbA1c% change with or without non-surgical periodontal treatment for at least three months of the study duration. Weighted mean differences for pooled data and antibiotic use strata were calculated. Heterogeneity and publication bias were explored.
***Results:*** A total of 358 articles were identified but only six were suitable. Compared to the control group, the pooled analysis (n = 422) showed −0.41% (95% CI: −0.73% to −0.09%, p = 0.013) absolute difference in HbA1c% with treatment. Studies without adjunctive antibiotic had HbA1c% change of −0.64% (95% CI: −1.06% to −0.23%, p = 0.002), but we could not conclude on the effect of adjunctive antibiotic use (p = 0.734). Publication bias was significant with Egger's test (p = 0.014) but not with Begg's test (p = 0.06).
***Conclusions:*** The meta-analysis suggested that non-surgical periodontal treatment was associated with a reduction in HbA1c%.

***Keywords:*** Periodontal debridement, HbA1c, diabetes mellitus type 2, dental scaling, root planing.

***Abbreviations and acronyms:*** HbA1c = glycated haemoglobin; MD = mean difference; RCT = randomized clinical trials; SE = standard error.

*(Accepted for publication 16 December 2012.)*

## INTRODUCTION

In recent years, the relationship between periodontal disease and systemic diseases such as diabetes mellitus has attracted the attention of researchers worldwide. Many reviews suggesting a two-way relationship between periodontitis and diabetes mellitus have been published.[1–5] Poor glycaemic control is associated with increased risk of developing periodontal disease,[6,7] more extensive and severe destruction of periodontal tissue[6,7] and alveolar bone loss.[8] Hence, it is commonly regarded as one of the risk factors of periodontal disease. Improved glycaemic control may alleviate periodontal disease.[9] In turn, control of periodontal disease was postulated to enhance glycaemic control in patients with type 2 diabetes.[9]

Periodontitis is diagnosed when there is gingival inflammation, connective tissue and alveolar bone loss, and apical migration of junctional epithelium.[11] Clinical signs include increased probing pocket depth or clinical attachment loss. Interventions for periodontitis range from oral hygiene instruction, scaling, root planing, antibiotics, chlorhexidine to surgical treatment, or a combination of these.

Chronic hyperglycaemia resulting from defects in insulin secretion and/or insulin action is typical for diabetic mellitus.[12] Possible long-term outcomes of this disease includes pathological and functional damages to various organs. Diabetes mellitus has a high prevalence worldwide, with an age-standardized adult prevalence of 9.8% in males and 9.2% in females in 2008.[13] Blood glucose control is crucial to prevent complications.[14–19] Glycated haemoglobin (HbA1c) is often used in clinical settings to monitor average blood glucose levels over the past few months, hence high HbA1c indicates poor glycaemic control.[20]

In 2010, a Cochrane review estimated a 0.4% reduction of HbA1c associated with periodontal treatment. However, the review also reported low quality of evidence and suggested more studies to be done.[21] Since then, several new controlled trials have emerged in publications.[22–26]

Therefore, it is timely to conduct a systematic review and meta-analysis to aggregate more evidence and enhance the knowledge of the potential effect of non-surgical periodontal treatment in glycaemic control. Answering this fundamental question will enable physicians and dentists to make evidence-based recommendations to diabetic patients.

## METHODS

### Search strategy

Three databases, Cochrane CENTRAL, MEDLINE (via PubMed) and EMBASE, were systematically searched using the search terms as listed online (Supplementary Appendix 1) with the assistance of a reference librarian, from the inception of all databases to 31 March 2012. Systematic hand-searching was abandoned as the initial hunt could not identify relevant trials which went unrecorded in electronic databases. However, the reference lists of the retrieved publications were carefully cross-checked to avoid omission of relevant trials.

### Study selection criteria

To be included in the meta-analysis, the studies had to meet the following criteria: (1) study design: randomized controlled clinical trial (RCT); (2) population: diabetic patients (type 2 diabetes mellitus), at least 16 years old, diagnosed with periodontitis; (3) intervention: non-surgical periodontal treatment including mechanical instrumentation, ultrasonic debridement, supragingival irrigation, subgingival irrigation; with or without adjunctive use of local drug delivery and systemic antibiotics; a minimal follow-up period of three months; (4) comparator: control group with no periodontal treatment or delayed treatment; (5) outcome: mean change in HbA1c level; or pre- and post-treatment HbA1c levels; and (6) published in the English language.

The *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1.0) was used as a guideline for the selection process.[27] Four independent reviewers (AL, NP, YC and JY) evaluated all retrieved articles. Disagreements were resolved by consensus. The reasons for exclusion are listed in Fig. 1. As the databases were not mutually exclusive, replication of entries was removed.

After excluding articles ineligible for the study, the relevance of all articles from the titles and abstracts was evaluated. Full-text articles were reviewed while articles which were not in accordance with the pre-specified selection criteria were excluded.

### Methodological study quality assessment

The selected studies were assessed on the criteria of a randomized controlled trial, which were: (1) random sequence generation; (2) allocation concealment; (3) addressing incomplete outcome data; (4) blinding; and (5) intention-to-treat analysis.

### Data extraction

Four authors (AL, NP, YL and JY) independently extracted data from each RCT in pre-designed electronic forms. Any discrepancy was resolved by consensus. From all relevant studies, the key points including demographic characteristic of the population, study quality, intervention in the control and treatment groups, study duration and design, pre- and post-treatment and absolute change of HbA1c levels in each treatment arm were recorded.

When not reported, the absolute difference of HbA1c percentage was calculated by extracting the mean change of HbA1c in the control group and the mean change of HbA1c in the intervention group.

If the standard deviation was not reported, standard error (SE) was imputed first by the following formulas using the available *t*-value or *t*-value computed from *p*-value[27]:

$$\mathrm{SE} = \frac{\mathrm{MD}}{\mathrm{t}}$$

in which SE is the standard error, MD is the mean difference and t is the *t*-value. Using the SE, the standard deviation can be obtained by:[27]

$$\mathrm{SD} = \frac{\mathrm{SE}}{\sqrt{\frac{1}{\mathrm{N_I}} + \frac{1}{\mathrm{N_C}}}}$$

where $N_I$ and $N_C$ denote sample size for the intervention group and control group, respectively.

If the standard deviation was not reported, it was imputed by the following formulas:[27]

$$\mathrm{SD}_{change} = \sqrt{\mathrm{SD}^2_{baseline} + \mathrm{SD}^2_{final} - (2 \times \mathrm{Corr} \times \mathrm{SD}_{baseline} \times \mathrm{SD}_{final})}$$

in which Corr is the correlation coefficient and SD is the standard deviation. Correlation coefficient was set at 0.5, consistent with a previous review.[28]

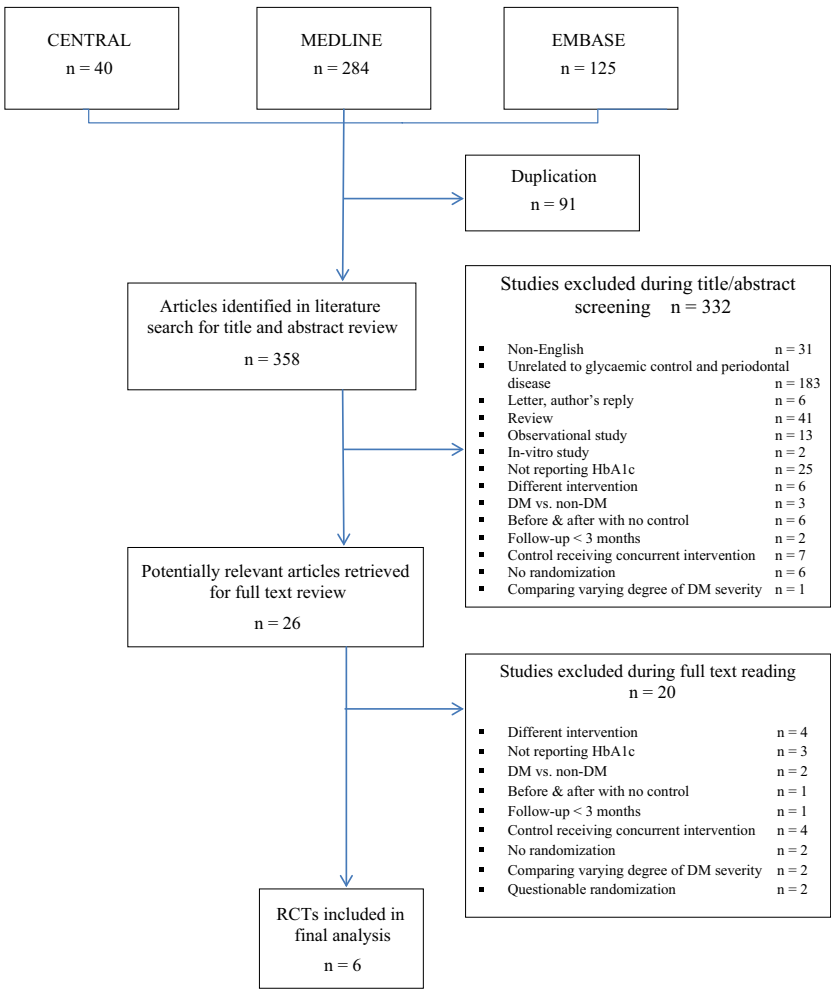


**Fig. 1** QUORUM flowchart.

### Statistical analysis

All numerical data for meta-analysis were entered in STATA 11.0 (Texas, USA). A meta-analysis was conducted, comparing the intervention group which received periodontal treatment and the control group with no periodontal treatment.

For a particular multi-arm study, the intervention group fulfilling the inclusion criteria for pair-wise comparison would be considered.[27] Thus, only the intervention group and control group contrasting non-surgical periodontal treatment (with/without adjunctive antibiotic) versus no treatment/delayed treatment/usual care will be used for data analysis.

Weighted mean difference was estimated using a random-effect model (DerSimonian-Laird method) from the selected RCTs. In addition, the presence of significant heterogeneity was evaluated by chi-square test for homogeneity (Cochran Q-statistic and *p*-value), as well as the I-squared statistic and 95% CI of the $I^2$. Stratification was done for studies with and without antibiotic use. Publication bias was assessed by Begg's test, Egger's test and funnel plot.

## RESULTS

The literature search from the three databases yielded a total of 358 articles, after removal of duplications. The titles and abstracts of these articles were screened for relevance, and the reasons for exclusion are listed in Fig. 1. Of these articles, only 26 were qualified for full-text reading. In the end, only six RCTs fulfilled the pre-specified inclusion criteria.

Singh *et al.* mentioned that the subjects in their study were randomized,[29] but the randomization process such as sequence generation and allocation concealment methods were not described. Hence, the study was excluded from this meta-analysis. No additional studies were identified by cross-referencing the bibliographies of relevant and included articles.

### Study characteristics

The characteristics of the six studies are summarized in Table 1. All studies were reported as randomized controlled trials.[22,23,30–33] The mean age per study ranged

## Table 1. Study characteristics

| Study | Year | Country | Number (n) | | | | Interventions | Mean age–years (SD) *Male%* | | | Mean baseline HbA1c% (SD) | | | Follow-up time (months) | Study design and details |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total | C | Tx1 | Tx2 | | C | Tx1 | Tx2 | C | Tx1 | Tx2 | | |
| Kiran *et al.*[30] | 2005 | Turkey | 44 | 22 | 22 | | Control: delayed treatment<br>Tx1: oral hygiene instruction/advices, scaling, root planing/ curettage/debridement | 52.82 (12.27)<br>*36* | 55.95 (11.21)<br>*45* | | 7.0 (0.72) | 7.31 (0.74) | | 3 | RCT<br>Single centre<br>Blinding of assessor |
| Promsudthi *et al.*[31] | 2005 | Thailand | 52 | 25 | 27 | | Control: no treatment<br>Tx1: oral hygiene instruction/advices, scaling, root planing/ curettage/ debridement, removal of supra and subgingival calculus | 61.64 (5.81)<br>*40.74* | 61.11 (5.83)<br>*32* | | 9.17 (1.02) | 8.98 (0.88) | | 3 | ?RCT<br>Single center |
| Jones *et al.*[32] | 2007 | US | 154 | 80 | 74 | | Control: delayed treatment<br>Tx1: scaling, root planing/curettage/ debridement, antibiotic, chlorhexidine | 60<br>*94* | 59<br>*100* | | 10.22 (1.29) | 9.9 (1.28) | | 4 | RCT<br>Multi-centre, veterans intention-to-treat analysis.<br>Blinding of assessor<br>C:19% smoker, Tx1:29% smoker |
| Katagiri *et al.*[33] | 2009 | Japan | 49 | 17 | 32 | | Control: delayed treatment<br>Tx1: Oral hygiene instruction/advices, root planing/curettage/ debridement, antibiotic | 59 (4.8)<br>*54.55* | 60.3 (9.9)<br>*65.63* | | 6.9 (0.9) | 7.2 (0.9) | | 6 | RCT<br>Multi-centre |
| Chen *et al.*[23] | 2012 | China | 134 | 44 | 45 | 45 | Control: no treatment<br>Tx1: local treatment (e.g. caries, restoration, root canal tx, extraction), scaling, root planing/curettage/ debridement<br>Tx2: supragingival prophylaxis | 63.2 (8.51)<br>*41.5* | 59.86 (9.48)<br>*54.8* | 57.91 (11.35)<br>*60.5* | 7.25 (1.49) | 7.31 (1.23) | 7.29 (1.55) | 6 | RCT<br>Single centre |
| Moeintaghavi *et al.*[22] | 2012 | Iran | 40 | 18 | 22 | | Control: delayed treatment<br>Tx1: scaling, root planing/curettage/ debridement | N/A<br>*61.1* | N/A<br>*40.9* | | 8.72 (2.22) | 8.15 (1.18) | | 3 | RCT<br>Single centre<br>Blinding of assessor |

from 53.8 to 63.2 years. Although smoking is an important risk factor of both periodontal disease[34] and diabetes mellitus,[35] only Jones *et al.* reported the percentage of smokers in each arm.[32] All studies described study populations having type 2 diabetes mellitus and were diagnosed with chronic periodontitis.[22,23,30–33]

Scaling and root planing/curettage/debridement were prescribed as the basic non-surgical periodontal intervention for the treatment group in all studies.[22,23,30–33] In Chen *et al.*, Group 2 (n = 45) was not included for meta-analysis because only supragingival prophylaxis was given at three-month follow-up.[23] Variation existed with regards to adjunctive therapy, including the prescription of chlorhexidine and antibiotic.

### Methodological study quality assessment

The studies varied in terms of quality and were inadequate in many ways (Table 2). In particular, reporting of the allocation concealment, assessment of loss-to-follow-up and blinding was limited in these studies. Only Jones *et al.* reported conducting intention-to-treat analysis.[32] Blinding was not reported in many studies.[23,31–33]

### Pooled analysis

A significant difference in HbA1c (%) change was evident in the pooled analysis (Fig. 2) between the treatment and control groups (p = 0.037), with an effect size of −0.41% (95% CI: −0.73% to −0.09%).

### Exploration of heterogeneity

Heterogeneity among studies was significant ($\chi^2$ = 11.85, p = 0.037) when evaluated by the Q statistic. $I^2$ was estimated at 57.8%, which suggested moderate heterogeneity.

Since antibiotic use was identified *a priori* as a potential source of heterogeneity, subgroup analysis was done accordingly. Non-surgical periodontal treatment without adjunctive antibiotic showed a significant improvement (p = 0.002) of HbA1c level [−0.64% (95% CI: −1.06% to −0.23%)]. Also, the heterogeneity among studies was moderate ($\chi^2$= 5.35, p = 0.148, $I^2$ = 43.9%). However, this improvement was not significant (p = 0.734) with antibiotic use.

### Publication bias

Publication bias existed as the funnel plot (Fig. 3) displayed an asymmetrical distribution. In Egger's test, the intercept value was negative (−4.54). The publication bias was statistically significant in Egger's test (p = 0.014), therefore the null hypothesis of no small-study effects was rejected. However, Begg's test was marginally significant (p = 0.06).

## DISCUSSION

The selected studies showed reasonable comparability in terms of population characteristics as well as baseline HbA1c levels within the study. Population comparability between studies was also satisfactory, except Jones *et al.* which had a high percentage of males as the study was conducted among veterans.[32] The research quality was far from ideal. For instance, per protocol analysis was done in Promsudthi *et al.*,[31] Chen *et al.*[22] and Moeintaghavi *et al.*[23] This could jeopardize the purpose of randomization.

Furthermore, the reporting of study methods was not comprehensive, making it difficult to inspect for heterogeneity due to study quality. The duration of treatment ranged from three to six months; treatment and reassessment cycles were also differential. Although all studies provided mechanical instrumentation as intervention, Jones *et al.* prescribed additional systemic doxycycline 100 mg by mouth daily for 14 days,[32] whereas Katagiri *et al.* provided topical minocycline 10 mg for all periodontal pockets at the end of every visit.[33]

Despite this, it was evident that non-surgical periodontal treatment is beneficial in glycaemic control, as there was an overall 0.41% reduction in HbA1c level with intervention. This was similar to the findings of the two reviews in 2010 by Simpson *et al.* and Teeuw *et al.*, which reported a 0.40% reduction of HbA1c

**Table 2. Quality measure of included studies in the meta-analysis**

| | Adequate sequence generation? | Allocation concealment? | Incomplete outcome data addressed? | Blinded clinical operator? | Masking of laboratory assessment? | Masking of periodontal outcome assessor? | Intention-to-treat analysis done? |
|---|---|---|---|---|---|---|---|
| Kiran | + | ? | + | + | + | + | ? |
| Promsudthi | + | + | ? | ? | ? | ? | - |
| Jones | + | + | + | + | + | + | + |
| Katagiri | + | + | - | ? | ? | ? | ? |
| Chen | + | + | + | - | ? | ? | - |
| Moeintaghavi | + | ? | + | + | ? | + | - |

+ adequate, ? unclear, - inadequate

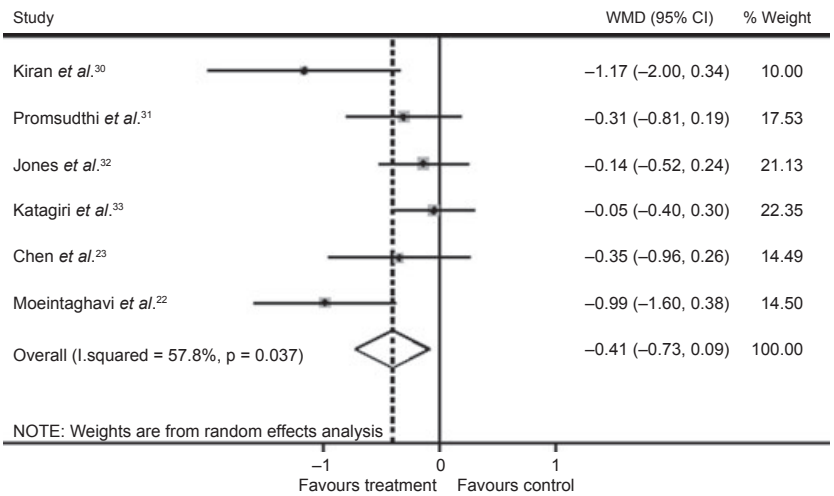


**Fig. 2** Pooled analysis.

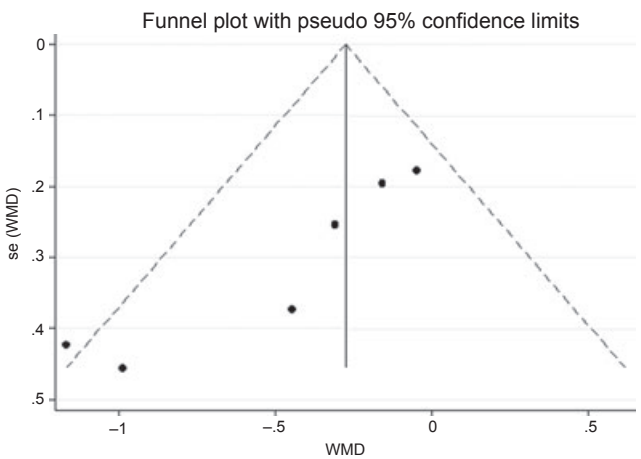


**Fig. 3** Funnel plot. Assymetrical distribution, suggesting small study effect.

compared to the control group.[21,28] However, caution is warranted in interpreting these data as the heterogeneity among studies was significant ($p = 0.037$).

When stratified by antibiotic use, the analysis confirmed that mechanical instrumentation alone could indeed improve glycaemic control, reducing 0.64% unit of HbA1c level compared to no treatment. The subgroup analysis of non-surgical periodontal treatment without antibiotic showed greater effect size, but this could be due to the exaggeration driven by small studies ($n < 100$).

In contrast, studies using adjunctive antibiotic, whether systemic or topical, suggested that the overall effect was non-significant. Interestingly, recent studies have shown otherwise. Sub-antimicrobial level was found to be beneficial for periodontal control[36] and glycaemic control[37] in diabetic patients. Biological plausibility and pharmacological mechanism could not be established at this point. Also, only two trials used adjunctive pharmacological therapy. Therefore, more research is needed in this area.

Despite the promising outcome, our study showed there was a significant publication bias resembling 'small-study effects'. Small studies with findings favouring the intervention of interest were more likely to be published in journals, and vice versa.[38] In this meta-analysis, four out of six studies had a small sample size ($n < 100$). However, language restrictions in the study selection could have omitted published negative findings in other languages. Alternatively, it was likely that the current attention on oral systemic health association had encouraged researchers and reviewers on publishing concurring results.

The percentage reduction of HbA1c associated with non-surgical periodontal treatment was modest. Still, its clinical importance could not be denied. Since type 2 diabetes mellitus is a multifactorial disease, glycaemic control requires effective management of these risk factors.[39,40] Hence, despite the small effect size, treatment of periodontal diseases contributes to the overall picture of better general health outcome.

However, monitoring and controlling glycated haemoglobin for type 2 diabetes mellitus should be individualized for each diabetic patient, as disease duration, pre-existing macrovascular conditions, hypoglycaemic unawareness, comorbidities and frailty varied among patients,[41] and there was limited evidence of improved mortality with HbA1c reduction.[42,43] Recommendations of healthy eating habits, healthy lifestyle, physical activities and weight management remained as essential.[44]

Also, HbA1c should not be the sole indicator of glycaemic control, as confounders such as haemolytic anaemia, red-cell survival, extracellular-intracellular glucose balance and non-glycaemic genetic determinants of haemoglobin glycation may hinder accurate diagnosis.[37] Future research about the association between periodontal treatment and glycaemic control should utilize a combination of conventional measures

of blood glucose (e.g. fasting plasma glucose[22,23,30,31] and post-prandial glucose[30]) to improve validity.

The strengths of this meta-analysis were the restriction to only randomized controlled trials and the inclusion of additional studies since the publication of the two reviews in 2010. Effort was made to systematically and thoroughly search the literature. The findings suggested the need to better understand the interaction of antibiotic and non-surgical periodontal treatment, as well as the significant presence of publication bias.

However, limitations in the robustness of the results were recognized, including the scarcity of RCTs, small sample size within the study, as well as variation in intervention within and across studies. This meta-analysis also did not include non-English publications, which might be systematically different.

Thus, recommendations for future research examining this association are to: (1) have adequate randomization; (2) reduce within study heterogeneity by giving standardized treatment without topical or systemic antibiotic use, as well as standardized control of delayed treatment; (3) have a follow-up duration of at least three months; (4) examine fasting blood glucose level concurrently; (5) perform intention-to-treat analysis; (6) have thorough reporting of methods and measured outcomes.

More importantly, biological plausibility of the effect of non-surgical periodontal treatment and change in glycated haemoglobin level should be explored. In view of the lack of evidence, we also urge researchers to embark on studies comparing scaling and root planing only (control) versus scaling, root planing and adjunctive antibiotic (treatment). Researchers should be aware of the presence of publication bias in this area, and should not be discouraged to publish negative findings.

Finally, it is hoped that with more high-quality research, evidence-based guidelines could be formulated in the future, to guide physicians and dentists in the management of periodontal disease in diabetic patients.

## CONCLUSIONS

This meta-analysis found there was a small beneficial effect of non-surgical periodontal treatment in glycaemic control. However, the effect of adjunctive antibiotic usage in this association remained inconclusive to date.

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Appendix 1.** Search strategies.

## REFERENCES


1. Lakschevitz F, Aboodi G, Tenenbaum H, Glogauer M. Diabetes and periodontal diseases: interplay and links. Curr Diabetes Rev 2011;7:433–439.
2. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. Nat Rev Endocrinol 2011;7:738–748.
3. Bascones-Martinez A, Matesanz-Perez P, Escribano-Bermejo M, *et al.* Periodontal disease and diabetes–review of the literature. Med Oral Patol Oral Cir Bucal 2011;16:e722–729.
4. Gurav A, Jadhav V. Periodontitis and risk of diabetes mellitus. J Diabetes 2011;3:21–28.
5. Santacroce L, Carlaio RG, Bottalico L. Does it make sense that diabetes is reciprocally associated with periodontal disease? Endocr Metab Immune Disord Drug Targets 2010;10:57–70.
6. Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. J Periodontol 2006;77:1289–1303.
7. Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. Comm Dent Oral Epid 2002;30:182–192.
8. Taylor GW, Burt BA, Becker MP, *et al.* Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. J Periodontol 1996;67(Suppl 10):1085–1093.
9. Costa FO, Miranda Cota LO, Pereira Lages EJ, *et al.* Progression of periodontitis and tooth loss associated with glycemic control individuals under periodontal maintenance therapy: a 5-year follow-up study. J Periodontol 2013;84:595–605.
10. Bascones-Martinez A, Matesanz-Perez P, Escribano-Bermejo M, González-Moles M-Á, Bascones-Ilundain J, Meurman J-H. Periodontal disease and diabetes–review of the literature. Med Oral Patol Oral Cir Bucal 2011;16:e722–729.
11. Armitage GC. Periodontal diagnoses and classification of periodontal diseases. Periodontol 2000 2004;34:9–21.
12. World Health Organization. Definition, diagnosis and classification of diabetes mellitus. URL: 'http://www.staff.ncl.ac.uk/philip.home/who_dmc.htm'. Accessed April 2012.
13. Danaei G, Finucane MM, Liu Y, *et al.* 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.
14. 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;12;352:837–853.
15. Ohkubo Y, Kishikawa H, Araki E, *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–117.
16. 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.
17. Abbate M, Cravedi P, Iliev I, Remuzzi G, Ruggenenti P. Prevention and treatment of diabetic retinopathy: evidence from clinical trials and perspectives. Curr Diabetes Rev 2011;7:190–200.
18. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124–136.
19. Bañón S, Isenberg D. Rheumatological manifestations occurring in patients with diabetes mellitus. Scand J Rheumatol 2013;42:1–10.

20. Zhang X, Gregg EW, Williamson DF, *et al.* A1c level and future risk of diabetes: a systematic review. Diabetes Care 2010;33:1665–1673.
21. Simpson TC, Needleman I, Wild SH, Moles DR, Mills EJ. Treatment of periodontal disease for glycaemic control in people with diabetes. Cochrane Database Syst Rev 2010;(5):CD004714.
22. Moeintaghavi A, Arab HR, Bozorgnia Y, Kianoush K, Alizadeh M. Non-surgical periodontal therapy affects metabolic control in diabetics: a randomized controlled clinical trial. Aust Dent J 2012;57:31–37.
23. Chen L, Luo G, Xuan D, *et al.* 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.
24. Darré L, Vergnes J-N, Gourdy P, Sixou M. Efficacy of periodontal treatment on glycaemic control in diabetic patients: a meta-analysis of interventional studies. Diabetes Metab 2008;34:497–506.
25. Calabrese N, D'Aiuto F, Calabrese A, *et al.* Effects of periodontal therapy on glucose management in people with diabetes mellitus. Diabetes Metab 2011;37:456–459.
26. Lin S-J, Tu Y-K, Tsai S-C, Lai S-M, Lu H-K. Non-surgical periodontal therapy with and without subgingival minocycline administration in patients with poorly controlled type II diabetes: a randomized controlled clinical trial. Clin Oral Invest 2012;16:599–609.
27. Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. URL: 'http:// www.cochrane-handbook.org'. Accessed April 2012.
28. Teeuw WJ, Gerdes VEA, Loos BG. Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. Diabetes Care 2010;33:421–427.
29. Singh S, Kumar V, Kumar S, *et al.* The effect of periodontal therapy on the improvement of glycemic control in patients with type 2 diabetes mellitus: a randomized controlled clinical trial. Int J Diabetes Dev Ctries 2008;28:38–44.
30. 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.
31. Promsudthi A, Pimapansri S, Deerochanawong C, Kanchanavasita W. The effect of periodontal therapy on uncontrolled type 2 diabetes mellitus in older subjects. Oral Dis 2005;11:293–298.
32. Jones JA, Miller DR, Wehler CJ, *et al.* Does periodontal care improve glycemic control? The Department of Veteran Affairs Dental Diabetes Study. J Clin Periodontol 2007; 34:46–52.
33. Katagiri S, Nitta H, Nagaswas T, *et al.* 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 Res Clin Pract 2009;83:308–315.
34. Laxman VK, Annaji S. Tobacco use and its effects on the periodontium and periodontal therapy. J Contemp Dent Pract 2008;9:97–107.
35. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. Br Med J 1995;310:555–559.
36. Deo V, Gupta S, Bhongade ML, Jaiswal R. Evaluation of subantimicrobial dose doxycycline as an adjunct to scaling and root planing in chronic periodontitis patients with diabetes: a randomized, placebo-controlled clinical trial. J Contemp Dent Pract 2010;11:009–016.
37. Engebretson SP, Hey-Hadavi J. Sub-antimicrobial doxycycline for periodontitis reduces hemoglobin A1c in subjects with type 2 diabetes: a pilot study. Pharmacol Res 2011;64:624–629.
38. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, 1996. URL: 'http://onlinelibrary.wiley.com/doi/10.1002/14651858.MR000006.pub3/abstract'. Accessed November 2012.
39. Pratley RE, Gilbert M. Clinical management of elderly patients with type 2 diabetes mellitus. Postgrad Med 2012;124:133–143.
40. Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roqué I Figuls M, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database Syst Rev 2008;(3):CD003054.
41. Herman WH, Cohen RM. Racial and ethnic differences in the relationship between hba1c and blood glucose: implications for the diagnosis of diabetes. JCEM 2012;97:1067–1072.
42. Hamet P. What matters in ADVANCE and ADVANCE-ON. Diabetes Obes Metab 2012;14:20–29.
43. Dailey G. Overall mortality in diabetes mellitus: where do we stand today? Diabetes Technol Ther 2011;13(Suppl 1):S65–S74.
44. Colagiuri S. Optimal management of type 2 diabetes: the evidence. Diabetes Obes Metab 2012;14(Suppl 1):3–8.

*Address for correspondence:*
*Dr Amy Liew Kia Cheen*
*Faculty of Dentistry*
*Universiti Kebangsaan Malaysia*
*Jalan Raja Muda Abdul Aziz*
*50300 Kuala Lumpur*
*Malaysia*
*Email: amyliew@dental.ukm.my*