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Periodontal treatment and glycaemic control in patients with diabetes and periodontitis: an umbrella review

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ABSTRACT

Background: Studies suggest that non-surgical periodontal treatment improves glycaemic control in patients with diabetes and periodontitis. The aim of this umbrella review is to summarize the effects of periodontal treatment on glycaemic control in patients with periodontitis and diabetes.
Methods: A systematic review of systematic reviews with or without meta-analysis published between 1995 and 2015 was performed. Three independent reviewers assessed for article selection, quality and data extraction.
Results: Thirteen (13) systematic reviews/meta-analysis were included for qualitative synthesis. A reduction (0.23 to 1.03 percentage points) in the levels of HbA1c at 3 months after periodontal intervention was found. This reduction was statistically significant in 10/12 meta-analysis. One review with sufficiently large samples found a non-significant reduction (−0.014 percentage points; 95% CI −0.18 to 0.16; p = 0.87). Only three studies separated the use of adjunctive antibiotics and found a reduction of 0.36 percentage points but the difference was not statistically significant.
Conclusions: Highly heterogeneous short-term studies with small sample size suggest that periodontal treatment could help improve glycaemic control at 3 months in patients with type 2 diabetes and periodontitis. However, longer term studies having sufficient sample size do not provide evidence that periodontal therapy improves glycaemic control in these patients.

Keywords: Diabetes, glycated haemoglobin, periodontal treatment, periodontitis, systematic review.

Abbreviations and acronyms: BOP = bleeding on probing; CAL = clinical attachment loss; HbA1c = glycated haemoglobin; LPS = lipopolysaccharide; RCT = randomized clinical trials; SRP = scaling and root planing.

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INTRODUCTION

Diabetes is an endocrine/metabolic disorder characterized by alterations in the metabolism of carbohydrates, proteins and lipids.[1] However, chronic hyperglycaemia underlies the incidence and the progression of diabetes related microvascular complications (retinopathy, nephropathy, neuropathy) as well as the main aetiopathogenic mechanism in periodontal disease.[2]

Periodontitis is an inflammatory chronic reaction to the biofilm accumulated around the tooth surfaces in the absence of proper oral hygiene in an especially susceptible host that leads to the loss of periodontal support until teeth are lost. The biofilm is composed by more than 1000 different species of microorganisms but some strictly anaerobic bacteria such as *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola* and *Aggregatibacter actinomycetemcomitans* are frequently associated with the initiation and perpetuation of periodontitis.[3] The inflammation induced by the biofilm, if not controlled, results in clinical attachment loss (CAL), pocketing, bleeding on probing (BOP) and bone loss.

The chronic state of the infection and inflammation accumulated over time has been associated with insulin resistance and worse glycaemic control in patients with type 2 diabetes and periodontitis.[1,4] The liberation of lipopolysaccharide (LPS) and the subsequent release of interleukin (IL)-1β, TNFα and IL-6 are included as possible mechanisms.[5] Consequently, it has been shown that if the infection and inflammation reduced, this may have a positive impact on glycaemic parameters (fasting plasma glucose and glycated haemoglobin (HbA1c)).[6,7]

Several randomized clinical trials (RCT) have shown that scaling and root planing (SRP) not only improves periodontal status in patients with type 2 diabetes and periodontitis, but also may help improve glycaemic control.[8,9] However, this finding was not

confirmed by other studies, in which metabolic improvement following SRP in similar groups of patients was not detected.[10,11]

Over the years, several systematic reviews have been published on the subject showing a consistent modest reduction in the levels of HbA1c after periodontal treatment at 3 months and thus creating controversy.[12,13] An umbrella review attempts to systematically review all the systematic reviews available, addressing the same question on a specific topic of study. This approach summarizes the evidence in order to understand its strength from more than one systematic review of the same or different intervention for a specific condition. In addition, umbrella reviews help to underline consistent or contradictory findings in consideration whether the independent systematic reviews assess the question and arrive at similar conclusions. The aim of this umbrella review is to summarize the effects of periodontal treatment on glycaemic control in patients with periodontitis and diabetes.

METHODS

The study protocol was registered at the International Prospective Register of Systematic Reviews – PROSPERO (CRD42015024551).

Focused question (PICOS) and inclusion criteria

The PICOS (patients, intervention, control, outcome and study design) strategy to formulate a focused question was used as follows: what is the effect of periodontal treatment on glycaemic control in patients with type 1 and 2 diabetes and periodontitis?

The articles were eligible for inclusion if they met the following criteria:

1. Systematic reviews with or without meta-analysis.
2. Articles that compared non-surgical periodontal therapy with or without antimicrobials with control, which included no treatment, delayed treatment or supragingival prophylaxis.
3. HbA1c as the primary outcome. Secondary outcomes included fasting glucose levels.
4. Changes in the primary outcome recorded at baseline and at least 3 months after interventions.
5. Articles written in English, Spanish or Portuguese.
6. Articles published between 1995 and July 2015.

Search strategy and data extraction

All procedures of search, data extraction and analysis of the systematic reviews were performed independently by three reviewers (JEB, CR, AAS) in Medline via Pubmed, EMBASE, Cochrane Database of Systematic Reviews, Science Direct, Google Scholar, SCOPUS and Scielo in order to include high impact journals as well as grey literature. The following keywords and the Boolean operators 'AND' and 'OR' were used to filter information: (systematic review [tiab] OR meta-analysis [tiab]) AND (non-surgical periodontal therapy OR non-surgical therapy OR periodontal therapy OR scaling and root planing) AND (diabetes [tiab] OR diabetes mellitus OR type 1 diabetes OR type 2 diabetes) AND (glycosilated haemoglobin OR glycated haemoglobin] OR HbA1C [tiab]) AND (fasting glucose OR glucose levels OR glycaemia) NOT (letter [tiab] OR newspaper article [tiab]). In the first round, the title and abstract were evaluated to define potential articles. After all duplicate references were excluded, the remaining articles were reviewed in full text. Any discrepancies were resolved by the consensus of all three reviewers. An update of the search for new articles published after July 2015 was performed in December 2015.

It was determined before the review to extract the following information: author name(s), year of publication, period during which the included original studies were published, sources searched, objectives, number of studies, number of participants, types of study design included, instrument of quality assessment used, interventions, control, method of analysis, heterogeneity, outcome and findings.

Quality assessment

Reviewers assessed the studies using the PRISMA checklist[14] for systematic reviews and then appraised for quality with the AMSTAR tool.[15] The AMSTAR tool (a measurement tool to assess systematic reviews) consists of 11 checklist items. Each item is given a score of 1 if the specific criterion is met, or a score of 0 if the criterion is not met, is unclear, or is not applicable. An overall score relating to review quality is then calculated (the sum of the individual item scores). AMSTAR characterizes quality at three levels: 8 to 11 is high quality, 4 to 7 is medium quality, and 0 to 3 is low quality. Low quality reviews were excluded. Any discrepancies were resolved by the consensus of all three reviewers.

Assessment of risk of bias

An assessment of the validity of the results presented in the systematic reviews is critical for the recommendations. The judgement for each study included in the systematic review/ meta-analysis involves assessing the risk of bias as 'low risk', as 'high risk, or as 'unclear risk', with the last category indicating either lack of information or uncertainty over the potential for bias. The systematic reviews/meta-analysis were assessed if they included an analysis of the risk of bias according

to a specified tool (Cochrane risk of bias tool, JADAD score, etc.) and how this analysis was used in the interpretation of the results. In addition, the rigor with which authors included/excluded studies and the tools used to combine the studies were used as a criterion for assessing the risk of bias of the systematic review.

Data analysis

All data extracted were analysed qualitatively and presented in narrative form. No attempt to perform a meta-analysis was done since several systematic reviews included some of the same studies and this would result in duplicated values. In addition, most of the studies were highly heterogeneous.

RESULTS

After all databases were searched, 83 relevant references were found. After duplicates were removed, 82 were analysed for title and abstract and 67 were excluded because they did not meet the inclusion criteria. The review by Engebretson and Kocher in 2013, although being published simultaneously in two different journals,[12,16] were considered as one review. Fifteen articles were revised in full text for eligibility and 1 was further excluded because it did not meet the inclusion criteria.[28] Fourteen systematic reviews/meta-analysis were included for qualitative analysis (Fig. 1).

The quality appraisal of the included systematic reviews is presented in Table 1. Eight reviews[12,13,17,18,21,22,24,80] were of high quality while 5 were of moderate quality.[19,20,23,25,26] One review[27] was of low quality due to several methodological inconsistencies and thus not considered. Thirteen systematic reviews were included for qualitative synthesis (Fig. 1). Heterogeneity of the studies included in the systematic reviews ranged from 0% to 89%. Only 3 reviews had low risk of bias[17,22,24] while 6 were unclear[12,13,18,20,21,80] and 5 had high risk of bias.[19,23,25–27] Inconsistencies in the reviews such as rigor in the search and inclusion of studies, errors found in the manuscript and the overall quality of the review accounted for bias.

Table 2 depicts the characteristics of systematic reviews included for qualitative synthesis. The systematic reviews analysed the changes in HbA1c in the test groups which received non-surgical periodontal therapy with or without antibiotics as compared to no treatment/delayed treatment in the control group. In two reviews, intervention included flap surgery.[12,80] Values reported correspond to reduction in actual HbA1c and are expressed as percentage points (Table 3). One of the reviews was qualitative and reported a significant reduction in HbA1c after periodontal therapy at 3 months.[19] A tendency for a reduction in the levels of HbA1c at 3 months after periodontal intervention in patients with type 2 diabetes was found in 12 systematic reviews after meta-analysis. The reduction values ranged from 0.23 to 1.03 percentage points. This reduction was statistically significant in 10/12 meta-analysis. Few reviews reported results after 6 months and the difference was not statistically significant. The review by Li *et al.*[17] in a separate analysis considered studies with sufficient large samples and found a non-significant reduction in patients with type 2 diabetes (−0.014 percentage points; 95% CI −0.18 to 0.16; p = 0.87). The review by Simpson *et al.*[80] found a reduction in HbA1c of −0.29 percentage points (95% CI: −0.48 to −0.10) at 3–4 months, which included a large sample study and mostly small sample studies. Three studies[24,26,80] separated the use of adjunctive antibi-

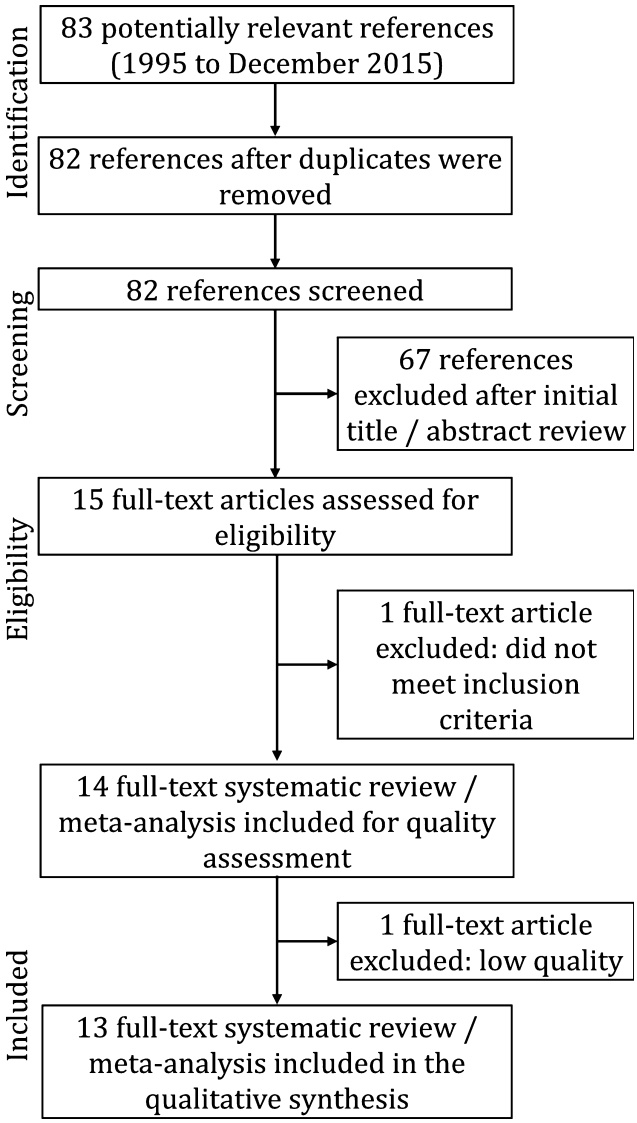

Fig. 1 Flow chart of study selection.

Table 1. Quality appraisal and summary of the systematic reviews

Author/year	Appraisal rating (PRISMA)	AMSTAR Score	Quality	Heterogeneity	Risk of bias	Comments
Simpson *et al.*[80] 2015	27/27	11	High	High (I^2 = 53%)	Unclear	An update on a previous systematic review (Simpson *et al.*[24] 2010). The analysis may be biased since the authors included mostly low quality and heterogeneous studies. The authors included information from an abstract and not a full-published study available for assessment. It is not possible to confirm the information for this study and hence adds bias to the analysis.
Li *et al.*[17] 2015	23/27	8	High	Mod (I^2 = 41.7%)	Low	An update on a previous systematic review (Sgolastra *et al.*[22] 2013). Moderate heterogeneity between studies that should be considered when analysing the results.
Wang *et al.*[18] 2014	23/27	9	High	High (I^2 = 68–89%)	Unclear	A systematic review and meta-analysis that complied with PRISMA guidelines. High risk of publication bias and heterogeneity between studies, which may have affected the results.
Mauri-Obradors *et al.*[19] 2014	15/27	5	Mod	High	High	A heterogeneous narrative systematic review. The majority of studies included support a reduction in the levels of HbA1c presumably in type 2 diabetes subjects. Evidence for type 1 diabetes patients is scarce and inconclusive
Sun *et al.*[13] 2014	21/27	8	High	High (I^2 = 85.4%)	Unclear	High heterogeneity between studies was found. Inadequate methods to combine and analyse the included studies. Meta-analysis included 2 non-RCT. Results should be interpreted carefully.
Wang *et al.*[20] 2014	21/27	7	Mod	Low (I^2 = 0%)	Unclear	The authors included a study which was classified as a RCT (Gaikwad *et al.*[31] 2013) but after careful reading of the article, it was found that it did not register a clinical trials number and did not present a randomization sequence.
Corbella *et al.*[21] 2013	23/27	8	High	High (I^2 = 40–69%)	Unclear	Different levels of heterogeneity were found between studies. Sources of variability between studies included definition of well and poorly controlled diabetes, mixed inclusion of type 1 and 2 diabetes subjects, definition of periodontitis, definition of periodontal treatment.
Engebretson and Kocher[12] 2013	24/27	8	High	Low (I^2 = 9%)	Unclear	An update of a previous systematic review (Simpson *et al.*[24] 2010). Although heterogeneity between included studies was low, publication bias may have occurred. There is no stratification according to the intervention and hence is not possible to conclude on the effects of antimicrobials or other means of therapy.
Sgolastra *et al.*[22] 2013	25/27	11	High	Low (I^2 = 0–30%)	Low	Carefully performed systematic reviews that used appropriate methods for meta-analysis. However, due to the risk of bias found in the studies included in the meta-analysis, results should be interpreted with caution.
Liew *et al.*[23] 2013	22/27	7	Mod	High (I^2 = 57.8%)	High	A systematic review that showed significant publication bias due to small sizes studies that could have affected the results of the meta-analysis. The authors included a non-RCT in the meta-analysis. Heterogeneity was high between studies. Results should be interpreted with caution.
Simpson *et al.*[24] 2010	27/27	11	High	High (I^2 = 0–57%)	Low	A detailed systematic review with appropriate methods for meta-analysis. Due to the small amount of studies, publication bias analysis was not conducted and hence uncertainty remains. Heterogeneity was high between studies.
Teeuw *et al.*[25] 2010	20/27	5	Mod	High (I^2 = 23.7–59.5%)	High	Inadequate methods to combine and analyse the included studies. Meta-analysis consisted of a mix of 3 RCT and 2 non-RCT that may have affected the results and produced high bias.
Darre *et al.*[27] 2008	11/27	3	Low	Low (Q = 12.23, df = 8, P = 0.14)	High	Inadequate methods to combine and analyse the included studies. Inclusion criteria for studies are not clear and several non-RCT that could have produced bias in the results.
Janket *et al.*[26] 2005	22/27	7	Mod	Low (Q = 0.18–0.32: P = 0.99)	High	Inadequate methods to combine and analyse the included studies. There was a mix of mostly non-RCT and 2 RCT with contrasting study designs that could have produced high bias.

Table 2. Characteristics of included systematic reviews

Author	Search period	Number of studies/ participants	Participant characteristics	Types of studies included	Instrument of quality assessment	Interventions
Simpson *et al.*[80] 2015	up to December 2014	35/2565	Type 1 and 2 diabetes and periodontitis	RCT	Risk of Bias Tool (Cochrane Handbook)	Interventions: mechanical debridement, surgical treatment and antimicrobial therapy Control: no active intervention/usual care, alternative periodontal therapy
Li *et al.*[17] 2015	up to April 2015	9/1082	Type 2 diabetes and periodontitis	RCT	Risk of Bias Tool (Cochrane Handbook)	Intervention: non-surgical periodontal treatment Control: no periodontal treatment, delayed treatment
Wang *et al.*[18] 2014	up to January 2014	10/1135	Type 1 and 2 diabetes and periodontitis	RCT	Risk of Bias Tool (Cochrane Handbook)	Intervention: non-surgical periodontal treatment with or without antimicrobial therapy Control: no periodontal treatment, delayed treatment
Mauri-Obradors *et al.*[19] 2014	January 2001 to October 2012	13/866 8/520	Type 1 and 2 diabetes and periodontitis	RCT non-RCT	Jadad score	Intervention: non-surgical periodontal treatment with or without antimicrobial therapy Control: no periodontal treatment
Sun *et al.*[13] 2014	January 1980 to 31 July 2012	8/515	Type 2 diabetes and periodontitis	RCT/ non-RCT	Risk of Bias Tool (Cochrane Handbook)	Intervention: periodontal treatment with or without adjunctive antimicrobial therapy Control: no periodontal treatment
Wang *et al.*[20] 2014	up to January 2014	4/143	Type 2 diabetes and periodontitis	RCT/ non-RCT	Risk of Bias Tool (Cochrane Handbook)	Intervention: non-surgical periodontal treatment with or without antimicrobial therapy Control: no periodontal treatment
Corbella *et al.*[21] 2013	1970 to October 2012	14/933	Type 1 and 2 diabetes and periodontitis	RCT	Risk of Bias Tool (Cochrane Handbook)	Intervention: non-surgical periodontal treatment with or without antimicrobial therapy Control: no periodontal treatment
Engebretson and Kocher[12] 2013	October 2009 to July 2012	9/689	Type 1 and 2 diabetes and periodontitis	RCT	Risk of Bias Tool (Cochrane Handbook)	Intervention: non-surgical or surgical periodontal therapy with or without the use of adjunctive antibiotics, or other (anti-inflammatory) medication use Control: no periodontal treatment
Sgolastra *et al.*[22] 2013	1970 to May 2012	5/315	Type 2 diabetes and periodontitis	RCT	Consolidated Standards of Reporting Trials (CONSORT) statement	Intervention: non-surgical periodontal treatment with or without antimicrobial therapy Control: no periodontal treatment, coronal scaling, mechanical tooth cleaning
Liew *et al.*[23] 2013	up to March 2012	6/422	Type 2 diabetes and periodontitis	RCT/ non-RCT	Risk of Bias Tool (Cochrane Handbook)	Intervention: non-surgical periodontal treatment with or without antimicrobial therapy Control: no periodontal treatment, delayed treatment
Simpson *et al.*[24] 2010	up to March 2010	7/490	Type 1 and 2 diabetes and periodontitis	RCT	Risk of Bias Tool (Cochrane Handbook)	Intervention: non-surgical periodontal treatment with or without antimicrobial therapy Control: no periodontal treatment/usual treatment
Teeuw *et al.*[25] 2010	up to March 2009	5/371	Type 1 and 2 diabetes and periodontitis	RCT/ non-RCT	Risk of Bias Tool (Cochrane Handbook)	Intervention: non-surgical periodontal treatment Control: no periodontal treatment
Janket *et al.*[26] 2005	January 1980 to January 2005	2/143 8/295	Type 1 and 2 diabetes and periodontitis	RCT non-RCT	Author's Quality Assessment Rubric	Intervention: non-surgical periodontal treatment with or without antimicrobial therapy Control: no periodontal treatment, self as control, historical control.

Table 3. Principal findings of the included systematic reviews (changes in HbA1c are expressed as percentage points)

Author	Objectives	Method of analysis	Outcome assessed	Findings
Simpson *et al.*[80] 2015	To investigate the effect of periodontal therapy on glyaemic control in people with diabetes mellitus.	Meta-analysis	Change in HbA1c between baseline and endpoint in response to periodontal intervention	Mean percentage reduction in HbA1c of −0.29% (95% CI: −0.48 to −0.10) at 3–4 months for periodontal treatment vs. no treatment. No evidence that one treatment is more effective in controlling glycaemia in patients with diabetes. No evidence for the use of adjunctive antimicrobials
Li *et al.*[17] 2015	To investigate whether non-surgical periodontal treatment can reduce the haemoglobin A1c (HbA1c) % level in type 2 diabetic patients	Meta-analysis	Change in HbA1c between baseline and endpoint in response to periodontal intervention	Pooled analysis of all studies: reduction in HbA1c of −0.27 (95% CI: −0.46 to −0.07, p = 0.007) after intervention at 3 months in type 2 diabetes patients Sufficient sample studies: reduction in HbA1c of −0.014 (95% CI: −0.18 to 0.16, p = 0.87) after intervention at 3 months in type 2 diabetes patients
Wang *et al.*[18] 2014	To evaluate the effect of periodontal treatment on glycaemic control of diabetic patients.	Meta-analysis	Change in HbA1c between baseline and endpoint in response to periodontal intervention. Secondary outcomes changes in pocket probing depth and clinical attachment level	Reduction in HbA1c at 3 months in type 2 diabetes patients (–0.36, 95% CI: –0.52 to –0.19, P = 0.0001) Reduction in HbA1c at 6-months in type 2 diabetes patients (–0.30, 95% CI: –0.69 to 0.09, P = 0.13)
Mauri-Obradors *et al.*[19] 2014	To determine whether non-surgical periodontal treatment is able to reduce serum glycated haemoglobin (HbA1c) levels in patients with diabetes mellitus	Qualitative	Change in HbA1c between baseline and endpoint in response to periodontal intervention	Fourteen studies reported a significant decrease in HbA1c levels (p < 0.05) after periodontal treatment in type 2 diabetes patients. The findings are insufficient and inconclusive to in patients with type 1 diabetes
Sun *et al.*[13] 2014	To identify the effects of periodontal treatment on glycaemic control sustained for 6 months in a randomized controlled study group of type 2 diabetic patients with periodontal disease.	Meta-analysis	Change in HbA1c between baseline and endpoint in response to periodontal intervention. Secondary outcome fasting plasma glucose	HbA1c differences from baseline to 3 months between the intervention and control group in type 2 diabetes patients: 1.03 (95% CI: 0.36 to 1.70) FPG differences from baseline to 3 months between the intervention and the control group in type 2 diabetes patients: 0.69 mg/dl (95% CI: −0.27 mg/dl, 1.66 mg/dl)
Wang *et al.*[20] 2014	To evaluate the reported effects of periodontal therapies on metabolic control in T2DM patients with PD	Meta-analysis	Differences in HbA1c values between pre- (baseline) and post-treatment/ intervention (at final visit) in the included studies	HbA1c results between the periodontal treatment group and control group in type 2 diabetes patients (HbA1c −0.23, 95% CI: −0.61 to 0.14; P = 0.21)
Corbella *et al.*[21] 2013	To investigate whether non-surgical periodontal treatment reduces glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels in diabetic patients	Meta-analysis	Change in HbA1c between baseline and endpoint in response to periodontal intervention	HbA1c differences from baseline to 3–4 months between the intervention and control group: −0.38 (95% CI: −0.23 to −0.53) HbA1c differences from baseline to 6 months between the intervention and control group: −0.31 (95% CI: 0.11 to −0.74) FPG differences from baseline to 3–4 months between the intervention and the control group: −9.01 mg/dl (95% CI: −2.24 mg/dl to −15.78 mg/dl) FPG differences from baseline to 6 months between the intervention and the control group: −13.62 mg/dl (95% CI: 0.45 mg/dl to −27.69 mg/dl) In participants treated with adjunctive antimicrobials, a non-significant increase of HbA1c was observed 3 months after treatment

(*continued*)

Table 3 *continued*

Author	Objectives	Method of analysis	Outcome assessed	Findings
Engebretson and Kocher[12] 2013	To examine the effect of periodontal treatment on diabetes outcomes in type 2 diabetes subjects	Meta-analysis	Changes in glycaemic control: HbA1c, fructosamine, Oral Glucose Tolerance Test (OGTT) and fasting glucose. Secondary outcomes: Homeostasis model assessment (HOMA)	A mean reduction in HbA1c −0.36 (CI −0.54 to −0.19) compared to no treatment after periodontal therapy ($p < 0.0001$) at 3 months in type 2 diabetes patients
Sgolastra *et al.*[22] 2013	To assess whether SRP, compared to non-treatment, coronal scaling, or mechanical tooth cleaning, can improve metabolic and glycaemic control in patients with both CP and DM2	Meta-analysis	Changes in HbA1c and fasting plasma glucose (FPG)	Reduction of HbA1c 0.65 (95% CI: 0.43 to 0.88; $P < 0.05$) and FPG 9.04mg/dL; 95% CI: 2.17 to 15.9; $P < 0.05$) after non-surgical periodontal therapy at 3 months in type 2 diabetes patients
Liew *et al.*[23] 2013	To evaluate whether non-surgical periodontal treatment can reduce the HbA1c% level in type 2 diabetic patients	Meta-analysis	Change in HbA1c between baseline and endpoint in response to periodontal intervention	Pooled analysis: reduction in HbA1c in the intervention group: −0.41 (95% CI: −0.73 to −0.09, $p = 0.013$) at 3 months in type 2 diabetes patients Studies without adjunctive antibiotic had HbA1c change of −0.64 (95% CI: −1.06 to −0.23, $p = 0.002$) at 3 months in type 2 diabetes patients The use of antibiotics was inconclusive in type 2 diabetes patients
Simpson *et al.*[24] 2010	To investigate the relationship between periodontal therapy and glycaemic control in people with diabetes and to identify the appropriate future strategy for this question.	Meta-analysis	Change in HbA1c between baseline and endpoint in response to periodontal intervention	Change in HbA1c for scaling/root planing and oral hygiene with or without antibiotic therapy as compared to no treatment/usual treatment after 3/4 months in type 2 diabetes patients was −0.40 (95% CI: −0.78 to −0.01; $P = 0.04$) Change in HbA1c for scaling/root planing without adjunctive antibiotics after 3/4 months in type 2 diabetes patients −0.80 (95% CI −1.73 to 0.13; $P = 0.09$) Change in HbA1c for scaling/root planing with adjunctive antibiotics in the test group after 3/4 months in type 2 diabetes patients −0.36 (95% CI: −0.83 to 0.11; $P = 0.14$) Change in HbA1c for scaling/root planing with adjunctive antibiotics in both test and control groups after 3/4 months in type 2 diabetes patients −0.15 (95% CI: −1.04 to 0.74; $P = 0.74$)
Teeuw *et al.*[25] 2010	To explore the robustness of observations that periodontal therapy leads to the improvement of glycaemic control in diabetic patients	Meta-analysis	Change in HbA1c between baseline and endpoint in response to periodontal intervention and fasting plasma glucose	A mean reduction in HbA1c after therapy of −0.40 (95% CI −0.77 to −0.04, $P = 0.03$) favouring periodontal intervention in type 2 diabetic patients at 3 months
Janket *et al.*[26] 2005	To quantify the effects of periodontal treatment on HbA1c level among diabetic patients, to explore possible causes for the discrepant reports, and to make recommendations for future studies	Meta-analysis	Change in HbA1c between baseline and endpoint in response to periodontal intervention	Reduction of HbA1c all studies = −0.4 (95% CI: −1.5 to 0.7) Reduction of HbA1c type 2 diabetes only = −0.7 (95% CI: −2.2 to 0.9) Reduction of HbA1c with only non-surgical therapy = −0.4 (95% CI: −2.1 to 1.3) Reduction of HbA1c with only non-surgical therapy plus antimicrobials = −0.7 (95% CI: −2.3 to 0.9)

Table 4. List of cited studies across the included systematic reviews

Author	Study	Journal	Simpson *et al.* 2015	Li *et al.* 2015	Sun *et al.* 2014	Mauri-Obradors *et al.* 2014	Wang *et al.* 2014	Wang *et al.* 2014	Corbella *et al.* 2013	Sgolastra *et al.* 2013	Liew *et al.* 2013	Engebretson and Kocher 2013	Simpson *et al.* 2010	Teeuw *et al.* 2010	Janket *et al.* 2005
*Calbacho *et al.*[82]	RCT	J Dent Res	X												
Haerian Ardakani *et al.*[83]	RCT	J Shahid Sadoughi U Med Sci and Health	X												
*Kothiwale *et al.*[84]	RCT	Diabetes	X												
Macedo *et al.*[85]	RCT	Lasers Med Sci	X												
Li *et al.*[86]	RCT	J Pek U Health Sci	X												
Madden *et al.*[87]	RCT	J Contemp Dent Pract	X												
Miranda *et al.*[88]	RCT	J Clin Periodontol	X												
Pradeep *et al.*[89]	RCT	J Periodontol	X												
Santos *et al.*[90]	RCT	J Periodontal Res	X												
Santos *et al.*[91]	RCT	J Clin Periodontol	X												
Skaleric *et al.*[92]	RCT	J Int Acad Periodontol	X												
Tsalikis *et al.*[93]	RCT	J Clin Periodontol	X												
Raman *et al.*[9]	RCT	BMC Oral Health	X	X											
Gay *et al.*[11]	RCT	J Clin Periodontol	X	X											
Engebretson *et al.*[10]	RCT	JAMA	X	X				X							
Zhang *et al.*[29]	RCT	J Dent Science	X	X				x							
Botero *et al.*[8]	RCT	J Periodont Res						X							
Telgi *et al.*[30]	RCT	J Periodontal Implant Sci						X							
Gaikwad *et al.*[31]	non-RCT	J Periodontal Implant Sci					X								
Gilowski *et al.*[32]	RCT	Oral Dis	X				X								
Auyeung *et al.*[33]	non-RCT	J Periodontol				X									
Moientaghavi *et al.*[34]	RCT	Aust Dent J	X	X	X	X		X	X	X	X	X			
Chen *et al.*[35]	RCT	J Periodontol	X	X		X		X	X	X	X	X			
Lin *et al.*[36]	RCT	Clin Oral Invest				X									
Sun *et al.*[37]	RCT	Intern Med	X		X	X		X	X			X			
Calabrese *et al.*[38]	non-RCT	Diabetes Metab				X									
Koromantzos *et al.*[39]	RCT	J Clin Perio	X	X	X	X		X	X	X		X			

(*continued*)

Table 4 *continued*

Author	Study	Journal	Simpson *et al.* 2015	Li *et al.* 2015	Sun *et al.* 2014	Mauri-Obradors *et al.* 2014	Wang *et al.* 2014	Wang *et al.* 2014	Corbella *et al.* 2013	Sgolastra *et al.* 2013	Liew *et al.* 2013	Engebretson and Kocher 2013	Simpson *et al.* 2010	Teeuw *et al.* 2010	Janket *et al.* 2005
Ou and Li[40]	non-RCT	Chin Med J				X									
Engebretson and Hey-Hadavi[41]	RCT	Pharmacol Res	X						X						
Khader *et al.*[42]	RCT	J Periodont Res			X										
Kardesler *et al.*[43]	non-RCT	J Periodontol				X									
Santos *et al.*[44]	non-RCT	J Periodontol	X			X									
Katagiri *et al.*[45]	RCT	Diabetes Res Clin Pract	X			X		X	X		X	X		X	
Al-Zahrani *et al.*[46]	RCT	J Periodontol	X			X	X		X						
Singh *et al.*[47]	RCT	Int J Diabetes Dev Ctries	X	X				X	X	X		X			
Llambes *et al.*[48]	RCT	Clin Oral Invest	X						X						
O'Connell *et al.*[49]	RCT	J Periodontol	X			X	X		X						
Navarro-Sanchez *et al.*[50]	non-RCT	J Clin Perio				X									
Yun *et al.*[51]	RCT	Folia Medica	X									X	X		
Jones *et al.*[52]	RCT	J Clin Perio	X			X			X		X	X	X	X	
Kiran *et al.*[53]	RCT	J Clin Perio	X	X	X	X		X	X	X	X	X	X	X	
Promsudthi *et al.*[54]	non-RCT	Oral Dis			X	X					X			X	
Hong *et al.*[55]	RCT	Chines J Geriatr			X										
Rodrigues *et al.*[56]	RCT	J Periodontol	X			X			X				X		X
Al-Mubarak *et al.*[57]	RCT	J Clin Perio							X				X		
Stewart *et al.*[58]	non-RCT	J Clin Perio			X	X								X	X
Rocha *et al.*[59]	RCT	J Periodontol	X			X							X		
Iwamoto *et al.*[60]	non-RCT	J Periodontol													X
Christgau *et al.*[61]	non-RCT	J Clin Perio													X
Grossi *et al.*[62]	RCT	J Periodontol	X										X		X
Westfelt *et al.*[63]	non-RCT	J Clin Perio													X
Smith *et al.*[64]	non-RCT	J Periodontol													X

(*continued*)

otics and found a reduction of 0.36 to 0.70 percentage points but the difference was not statistically significant (Table 3).

In the same manner, a reduction in the fasting plasma glucose levels ranging from 0.69 to 9.04 mg/dL was observed at 3 months after periodontal intervention in patients with type 2 diabetes in 3/12 meta-analysis and this difference was statistically significant in 2 of them. Data from 6-month follow-up was scarce (Table 3).

Table 4 shows the studies that were cited in the systematic reviews. Fifty-five studies comprising 39 RCTs and 16 non-RCTs have been included in systematic reviews since 2005. Of all reviews, 13 have been published in medical journals and 42 in periodontics/dental journals. It can be observed how the authors selected the studies for inclusion in their systematic reviews and compared between reviews over the years. The most cited study is by Kiran *et al.*[53] with 11 citations followed by Moientaghavi *et al.*[34] with 9 citations and Chen *et al.*[35] and Koromantzos *et al.*[39] with 8 citations. Table 4 shows discrepancies in the way studies should be selected for analysis in systematic reviews and thus corresponding with the controversies found around the subject.

DISCUSSION

The premise that periodontal non-surgical periodontal treatment could help to improve glycaemic control in patients with type 2 diabetes and periodontitis was supported by 10/12 systematic reviews with meta-analysis. Whether the reduction in actual HbA1c values (0.23 to 1.03 percentage points) is significant for type 2 diabetes treatment and control remains yet to be answered. However, it has been observed that for every percentage point decrease in HbAlc (e.g. 9% to 8%), there is a 35% reduction in the risk of complications.[68] The main objective of non-surgical periodontal treatment is infection control and reduction in periodontal inflammation. It is considered that these mechanisms could have an impact in the metabolic control of glucose.[1,5] Due to the chronic nature of periodontal disease, healing and the establishment of balance between the host and the subgingival microbiota after treatment would take time. Therefore, the benefits of the periodontal treatment would be reflected in the quality of life of the patients with type 2 diabetes in the long term. In addition, it is necessary to consider that other factors such as medications, physical activity and diet that are under the control of the patient being studied may have accounted for part of the results observed in the RCTs. The impact of periodontal treatment in patients with type 1 diabetes and the use of adjunctive antimicrobials remain inconclusive to this date.

Table 4 *continued*

Author	Study	Journal	Simpson *et al.* 2015	Li *et al.* 2015	Sun *et al.* 2014	Mauri-Obradors *et al.* 2014	Wang *et al.* 2014	Wang *et al.* 2014	Corbella *et al.* 2013	Sgolastra *et al.* 2013	Liew *et al.* 2013	Engebretson and Kocher 2013	Simpson *et al.* 2010	Teeuw *et al.* 2010	Janket *et al.* 2005
Aldridge *et al.*[65]	non-RCT	J Clin Perio													X
Seppala and Ainamo[66]	non-RCT	J Clin Perio													X
Miller *et al.*[67]	non-RCT	J Periodontol													X

*Indicates reference from abstract and not a full-text publication. Green = randomized clinical trial. Orange = non-randomized clinical trial.

Most of the systematic reviews included in this umbrella review performed meta-analyses to combine the evidence. Nonetheless, this analysis could be jeopardized by publication bias. In addition, other sources of bias could also affect the meta-analysis such as: publication time lag (studies with negative results take longer to be published or not published at all), language bias (articles written exclusively in English) and selective outcome reporting.[69] Additionally, there is a small-study effect in which studies with small samples tend to give exaggerated results and higher risk estimates than large studies. Authors use a funnel plot to estimate the effect of individual studies on a specific outcome. Small sample studies scatter widely at the base while large sample studies scatter narrowly at the top.[70] Most studies included in the systematic reviews had insufficient samples that could have affected the results. Only one RCT has included a large sample and found no significant differences in the levels of HbA1c between intervention and control.[10] Large-scale multi-centre RCTs produce results that are more generalizable to the population.[71] Nonetheless, the large-sample trial by Engebretson *et al.*[10] has been criticized.[72,73] However, readers should carefully make their own decisions about this trial after considering evidence from the trial itself,[10] the authors response to criticism[74] and factors associated with the clinical response to periodontal therapy in the trial.[75] All these factors should be considered when appraising the results of a systematic review as the results of small sample studies may be biased. For example, the review by Li *et al.*[17] showed that overall the reduction in HbA1c is statistically significant but when large sample studies are only considered, the reduction is not statistically significant. The most recent review[80] reported a reduction in HbA1c of 0.29 percentage points (95% CI: −0.48 to −0.10), which included the study by Engebretson *et al.*[10] After careful analysis, the authors considered that the results from the study were consistent and did not need a further *post hoc* sensitivity analysis. In contrast, the RCT by Engebretson *et al.*[10] was not included in three systematic reviews,[13,19,20] all published in 2014 with contrasting results with the review by Li *et al.*[17] in 2015. Sun *et al.*[13] and Mauri-Obradors *et al.*[19] searched up until 2012 but were only published almost 2 years later, reflecting publication time lag. Wang and coworkers[20] searched for RCTs up until January 2014, but failed to find the study by Engebretson *et al.*[10] and thus adding bias to the results and conclusions of the review.

Another critical issue that affects a systematic review is heterogeneity between the included studies. This means that studies present different diagnostic definitions, patient characteristics, inclusion criteria, intervention protocols, primary outcome and reporting results. Systematic reviewers test for heterogeneity (I^2, X^2, Cochran's Q test) in which a value ≥50% indicates significant heterogeneity. In order to be combined, studies should be as homogeneous as possible. According to the heterogeneity tests, reviewers use either a fixed-effect or a random-effect model to analyse the combined studies. The systematic reviews summarized here reported high levels heterogeneity and this should be carefully considered when interpreting the robustness of the combined results. In addition, it can be observed in Table 4 that there are differences in how reviewers appraise for the inclusion criteria of studies.

The quality of each systematic review was assessed with the AMSTAR tool. High quality systematic reviews were generally very detailed while moderate quality reviews had unclear parts. It is possible to observe that the first systematic reviews had moderate quality and the most recently published have high quality. Factors that usually affected quality were inadequate reporting of included/excluded studies and the process of combining the included studies in the meta-analysis. These quality tools help the reader to assess critical components that a systematic review should include in order to appropriately interpret the results and its implications.

In addition to quality assessment, this umbrella review appraised each systematic review for its risk of bias. Reviewers are encouraged to perform a risk of bias analysis for each RCT included in a systematic review using available tools (JADAD score, Cochrane risk of bias tool). We considered the risk of bias in this review based on the quality, the rigor with which authors included/excluded studies and the tools used to combine the studies. It was observed that systematic reviews with high risk of bias included non-RCT studies and had high heterogeneity. Reviews with low risk of bias were very strict with the process of selecting and analysing RCT studies. Perhaps the most comprehensive systematic review is by Simpson *et al.*[80] in 2015. Nonetheless, they included in the meta-analysis information from an abstract. The review states that they contacted the respective authors of the abstract by email in 2013 and provided some information but there is no full-text publication of this study that can be adequately appraised by the scientific community. In addition, the review states that the information provided was of high risk and randomization not clearly explained. It is not clear how Simpson and coworkers[80] applied the quality assessment to this information and finally decided to include this study in the meta-analysis with only 24 subjects and several systematic flaws with evident low quality that would not have been appropriate for

analysis. It has been shown that the information from conference abstracts is significantly different from subsequent full publication in peer-reviewed journals.[81] On the other hand, the review by Li *et al*.[17] published in 2015 had a stricter method of study selection and shows the difference in results when large and small study samples are considered. Although bias will always be present, reviewers should consider all possible measures to lower the risk of bias. A detailed review protocol registration and adequate analysis methods are essential to control for bias.

The results of the systematic reviews and quality were clearly affected by the studies included instead of the systematic review protocol by itself. In the first systematic reviews,[26,27] non-RCT and other low quality studies available until 2008 were possibly considered appropriate for that time and hence were included (Table 4). The recommendation now is to include large scale RCT with the highest quality.

Another lesson learned is the necessity of appropriate systematic review protocols. Most systematic reviews did not report a registration number in database that can be reviewed to search for duplicate reviews. This reduces the production of repeated systematic reviews in the topic of interest. It is worth noting that overlapping of the same original studies within the many meta-analysis occurred. The majority of systematic reviews assessed here were published between 2013 to 2014 with contrasting results that could be attributed to differences in inclusion criteria, disease definition, primary outcome, intervention and controls. A detailed definition of the search protocol should be available for review in order to assess the quality of the systematic reviews and reduce bias and heterogeneity.

Since this is the first review of its kind addressing the question whether periodontal treatment could improve glycaemic control in subjects with diabetes and periodontitis, the following limitations should be considered. This review gathered the available information that has been reported on the subject based on a search strategy that may have limitations by itself. Publications in different languages and systematic reviews yet to be published may have been omitted. Nonetheless, we attempted to perform as wide a search as possible to include high impact journals as well as grey literature. Data extraction was limited to the information reported in the systematic reviews and therefore we only include one outcome (HbA1c). Other outcomes such as inflammatory markers could be important for subsequent reviews.

Patients with diabetes and periodontitis are complex. In order to evaluate the condition of patients with diabetes, the clinician must remember the signs and symptoms of diabetes and the relationship between the disease and oral infections. Periodontitis is common in patients with diabetes and therefore a full periodontal examination is mandatory.[76,77] As studies suggest,[78,79] poorly controlled diabetes patients show an association between high levels of glycaemia and periodontal attachment loss. For this matter, clinicians should review the patient's medical chart, dietary habits, oral hypoglycaemic agents, insulin use and past history of complications. In addition, laboratory tests including glycated haemoglobin (HbA1c) and fasting prepandrial glycaemia to corroborate glucose control are necessary. Only when the physician controls the condition can elective dental treatment be performed safely.[76,77] Achieving proper oral hygiene and reducing periodontal inflammation is a benefit by itself, but as shown in this review, studies only provide evidence that periodontal therapy can improve the control of type 2 diabetes at 3 months. A large sample trial that followed patients for 6 months did not demonstrate any effect of non-surgical periodontal therapy on glucose control. Further long-term studies should focus on lifestyle related factors and other social factors that could be affecting those having diabetes.

CONCLUSIONS

Within the limitations of this review, short-term studies with smaller sample size and high levels of heterogeneity suggest that periodontal treatment could help improve glycaemic control at 3 months in patients having type 2 diabetes and periodontitis. However, longer-term studies having sufficient sample size do not provide evidence that periodontal therapy improves glycaemic control in these patients. The evidence is inconclusive that periodontal therapy improves glycaemic control for patients with type 1 diabetes and current evidence does not support the use of adjunctive antimicrobial agents in periodontal therapy for the purpose of improving glycaemic control.

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