Does Non-Surgical Periodontal Treatment Improve Glycemic Control? A Comprehensive Review of Meta-Analyses

Fadi Ata-Ali,[1] Maria Melo,[2,3] Teresa Cobo,[1] Magda Aline Nagasawa,[4] Jamil Awad Shibli[4] and Javier Ata-Ali[1,2,5]

[1]Department of Surgery and Medical-Surgical Specialities, Area of Orthodontics, University Medical and Dental School, University of Oviedo (Spain), Instituto Asturiano de Odontologia, Oviedo, Spain; [2]Universidad Europea de Valencia, Faculty of Health Sciences. Department of Dentistry, Valencia, Spain; [3]Facultad de Medicina y Odontologia, Universidad de Valencia, Valencia, Spain; [4]Department of Periodontology and Oral Implantology, Dental Research Division, Guarulhos University, Guarulhos, São Paulo, Brazil; [5]Public Dental Health Service, Conselleria de Sanitat Universal i Salut Pública, Generalitat Valenciana, Valencia, Spain

ABSTRACT

Aims: Periodontal treatment is reported to be associated with an improved periodontal condition in diabetic patients. Therefore, a comprehensive review of meta-analyses was conducted to evaluate whether periodontal treatment can improve glycemic control in patients with type 2 diabetes.

Materials and methods: The search on electronic databases included PubMed-Medline, Cochrane Library, Scopus, and LILACS databases. The methodological quality of the systematic reviews was evaluated using AMSTAR, and primary studies were performed in accordance with PRISMA guidelines. The weighted mean difference (WMD) was calculated, nested in a random-effects model with corresponding Z scores, p-values, and 95% confidence intervals.

Results: A total of 11 meta-analyses were included, and a meta-analysis of 11 primary studies comprising a total of 1341 participants was carried out. All the studies evaluated glycosylated hemoglobin (Hb1Ac), and 6 of the 11 publications evaluated fasting plasma glucose (FPG). The AMSTAR scores ranged between 9 and 11, with a median of 10.3. Statistically significant reductions were observed in HbA1c values [-0.32% (3.5 mmol/mol); 95%CI: -0.50 to -0.15] and FPG values (-11.59 mg/dl; 95%CI: -15.16 to -8.01).

Conclusions: The review of currently available clinical studies concludes that periodontal treatment is associated with improved glycemic control in patients with type 2 diabetes. New guidelines, including periodontal treatment as a routine public health measure to improve glycemic control in diabetic patients, would be of great value.

Keywords: Blood glucose control; Periodontal diseases; HbA1c; Diabetes Mellitus; Periodontal therapy; Overviews.

INTRODUCTION

The prevalence of periodontal disease in adults over 65 years examined in the 2009-2010 United States National Health and Nutrition Examination Survey (NHANES) was 70.1% (Eke *et al*., 2012). Chronic periodontitis may lead to the development of severe systemic disease burden (Shangase *et al*., 2013), and can affect general health (Hung *et al*., 2013). It has been reported that chronic periodontitis is associated with several systemic diseases such as rheumatoid arthritis (Chen *et al*., 2013) and cardiovascular disease (Holtfreter *et al*., 20130). Over the last 20 years, a series of studies have reported on the bidirectional association between periodontal disease and diabetes, and indicated that patients with diabetes have an increased risk of developing periodontal disease

Correspondence to: Dr. Javier Ata-Ali, Public Dental Health Service. Department of the Hospital Universitario y Politécnico la Fe., Avenida Fernando Abril Martorell, 46026-Valencia, Spain
E-mail: javiataali@hotmail.com

and that periodontal disease is more severe in patients with diabetes (Mealey and Oates, 2006; Atieh *et al.*, 2014).

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia and disturbed carbohydrate, fat, and protein metabolism caused by defective insulin secretion, action, or both. The disease is now considered a global epidemic. In 2014, it is estimated that 346 million people are affected worldwide, and the World Health Organization (WHO) predicts that this figure will increase to 439 million - almost 10% of all adults - by the year 2030 (World Health Organization, 2015).

Diabetes-associated medical complications have significant adverse effects on a patients' quality of life, in addition to healthcare costs. Many factors contribute to the onset of diabetes and its associated medical complications, including genetics, diet, lifestyle, age, and obesity (Morgan *et al.*, 2000; Bergman *et al.*, 2013). It is therefore biologically plausible that non-resolving chronic inflammation secondary to periodontal disease may have an impact on beta-cell function, insulin resistance, and consequently, glycemic control and diabetes-related medical complications (Chapple and Genco, 2013). Previous studies also indicated that diabetic patients with severe periodontal disease are 6 times more likely to have poor glycemic control (Taylor *et al.*, 1996; Taylor *et al.*, 2004).

Although periodontal treatment may improve periodontal and inflammatory status in diabetic patients, consensus evidence of improved glycemic control is lacking (Chen *et al.*, 2012). The existing evidence is conflicting and appears to be insufficient to establish a firm clinical recommendation. Therefore, a comprehensive review of meta-analyses should address some significant drawbacks between periodontal treatment and diabetes. The present study sought to conduct a systematic overview of meta-analysis to determine whether periodontal therapy can improve blood glucose levels in patients with type 2 diabetes.

MATERIALS AND METHODS

Overview of Strategy

In the first part of this study, we conducted an overview of meta-analyses that investigated the effect of periodontal treatment on blood glucose levels in patients with type 2 diabetes. In the second part of the study, we performed a meta-analysis of primary studies investigating the same issue. A written study protocol was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Moher *et al.*, 2009) and the Cochrane Collaboration methodology and the available methodological guidelines were applied throughout the study (Higgins and Green, 2011).

Data sources and searches

We searched the PubMed-MEDLINE, Cochrane Library, Scopus, and LILACS databases from their inception dates up to September 30th, 2019. The specific search strategies are shown in Table 1. The search was completed with a review of the references cited in the selected articles to identify additional studies not found in the initial search. This, in turn, was supplemented by a manual search in relevant journals. Any obscure or missing data were obtained by contacting the authors. The electronic search included all articles, with no restrictions in terms of year of publication or language.

Table 1. Electronic databases searched and search strategies used in the systematic review.

Database	Search strategy used	Hits
MEDLINE searched via Pubmed (www.ncbi.nlm.nih.gov/pubmed)	((periodontitis [mesh] OR periodontal disease OR periodontal therapy OR periodontal treatment OR periodontal intervention) AND ("diabetes" OR "diabetes mellitus" OR "glycemic control" OR "glycaemic control"))	7015
Cochrane Database of Systematic Reviews searched via The Cochrane Library (www.thecochranelibrary.com)	(periodontitis* OR periodontal disease* OR periodontal therapy* OR periodontal treatment* OR periodontal intervention*) and ((diabetes*) OR (diabetes mellitus*) OR (glycemic control*) OR (glycaemic control*))	15
LILACS (http://lilacs.bvsalud.org/es)	(periodontitis OR periodontal disease OR periodontal therapy OR periodontal treatment OR periodontal intervention) AND (diabetes OR diabetes mellitus OR glycemic control OR glycaemic control)	493
SCOPUS (www.scopus.com)	(ALL("periodontitis* OR periodontal disease* OR periodontal therapy* periodontal treatment* OR periodontal intervention*") AND ALL(diabetes* OR diabetes mellitus* OR "glycemic control*" OR "glycaemic control*"))	6837
Total		14360

Study selection of systematic reviews

Two criteria were considered for further evaluation of abstracts: 1) the study is defined as an overview of meta-analysis, and: 2) the study investigates the association between non-surgical periodontal therapy and glycemic control in patients with type 2 diabetes. Guidelines and systematic reviews without meta-analyses were excluded. Subsequently, full texts of all relevant abstracts were obtained and screened to identify systematic reviews of interest-based on: 1) the use of at least one medical database (e.g., MEDLINE; 2) the inclusion of at least one primary study; 3) the inclusion of patients with type 2 diabetes subjected to periodontal treatment; and 4) an outcome variable defined as blood glucose level measured as glycated hemoglobin (HbA1c) and/or fasting plasma glucose (FPG), analyzed before and after periodontal treatment. All the articles selected in the electronic and manual searches were evaluated independently by two authors (F.A.A. and J.A.A.), in accordance with the established inclusion criteria. Any disagreement between the two review authors was resolved by a third one (JAS).

Inclusion and exclusion criteria for primary studies

The studies from the included meta-analyses were considered for inclusion according to the following criteria: 1) the include studies are randomized controlled trials (RCTs); 2) a follow-up period of at least three months; and 3) studies in which the control group consisted of patients not subjected to any periodontal treatment. Observational, retrospective, nonrandomized primary studies, unpublished dissertations and conference papers were excluded. In relation to studies involving both type 1 and type 2 diabetic patients, we only included the publications in which the data exclusively referred to type 2 diabetics could be extracted to be integrated within the quantitative analysis. Studies pooling or combining the results of both type 1 and type 2 diabetic patients were excluded.

Data extraction and quality assessment

For each meta-analysis included in the study, two reviewers independently extracted the data, including the number of patients, interventions, follow-up period, inclusion criteria, databases (search period), number of included studies, method of assessment of quality and quality of the evidence. The same authors independently assessed the included reviews for methodological quality using the Assessment of Multiple Systematic Reviews (AMSTAR) Instrument. The AMSTAR was chosen because of its reported inter-rater reliability, construct validity and feasibility. An eleven-item questionnaire is designed to elicit responses of "Yes", "No", "Cannot answer", or "Not applicable". The response "Cannot answer" is chosen when an item is relevant but not described. The response "Not applicable" is chosen when an item is not relevant. Based on the results of the critical appraisal, reviews were divided into three categories: "lower" (score 0-3), "middle" (score 4-7), and "upper" (score 8-11). These categories reflect the existence of "major", "moderate", and "minor or no methodological limitations" in the included reviews, respectively.

The decisions made for each review were independently reassessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system criteria (Guyatt *et al*., 2008). The GRADE identifies five key elements (risk of bias, inconsistency, indirectness, imprecision and publication bias) that may influence the quality of evidence. These components were assessed and combined to define the quality of evidence for each outcome of interest as high, moderate, low, or very low. The level of agreement between the two reviewers was assessed based on the Cohen kappa statistic (Cohen, 1968).

Data synthesis and analysis of primary studies

A meta-analysis of RCTs was conducted in which the intervention group received periodontal treatment and the control group received no treatment. The primary outcome was the difference between the mean of the parameter at the end of follow-up (T2) (%HbA1c T2) and its baseline value (T1) (%HbA1c T1):

$$\Delta\%\ \text{HbA1c} = \%\text{HbA1c T2} - \%\text{HbA1c T1}$$

If the standard deviation (S) of the differences was not reported in the publication, we estimated it from the following equation:

$$S = \sqrt{ST1^2 + ST2^2 - 2rST1ST2}$$

where r is the correlation between the baseline and end of follow-up values, and S T1 and S T2 are the standard deviations of the baseline and end of follow-up values, respectively. We assumed that $r = 0.5$, as previously described (Ioannidou *et al*., 2006). For each meta-analysis, the weighted mean difference (WMD) was calculated and nested in a random-effects model with corresponding Z scores, p-values, and 95% confidence intervals (95%CI). Also, a test for heterogeneity was performed. For this test, the I^2 statistic describing the percentage of the total variation across studies that is attributable to heterogeneity rather than chance was used to assess between-studies heterogeneity. The I^2 statistic was calculated as follows: 100% × (Q-df)/Q, where "Q" is Cochrane heterogeneity statistic and df represents the degrees of freedom. Conventionally, I^2 values of 25%, 50%, and 75% indicate low, moderate and great heterogeneity, respectively (Higgins and Thompson, 2002). Forest plots afford a weighted compilation of all the effect sizes reported by each study, and also provide an indication of the heterogeneity between studies.

Furthermore, the heterogeneity was complemented by the Galbraith plot. Potential publication bias was evaluated by visual inspection of the funnel plots. It was quantitatively assessed using the rank correlation of Begg's test (Begg and Mazumdar, 1994) and Egger's test (Egger *et al.*, 1997).

The statistical analysis was performed using the SPSS version 17.0 statistical package for Microsoft Windows (SPSS, Chicago, IL, USA) and R version 3.0.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Risk of bias assessment of primary studies

The risk of bias of the included RCTs was independently assessed by the two reviewers using the Cochrane Collaboration tool for assessing the risk of bias of RCTs (Higgins and Green, 2011). The criteria included: sequence generation; allocation sequence concealment; blinding; incomplete outcome data; selective outcome reporting and other sources of bias. Those RCTs with inadequate random sequence generation, allocation concealment or reporting bias were considered as studies with a high risk of bias. When sufficient information was not provided on these different domains of bias to allow definite judgment, the risk of bias was considered unclear. In contrast, when a study was free of such bias, the risk of bias was considered as low. According to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0, studies with a high risk of bias are not considered for quantitative analysis (Higgins and Green, 2011). The level of agreement between the two reviewers was assessed based on the Cohen kappa statistic (Cohen, 1968).

RESULTS

Search results

The electronic search procedure and excluded articles are outlined in Figure 1. The combinations of search terms resulted in a list of 14,360 titles. After eliminating duplicate articles, a total of 9861 articles were reviewed. In turn, 7875 articles were excluded based on the evaluation of the title and abstract, leaving 1986 articles to be assessed for eligibility. Of these 42 publications, 31 were excluded (the reasons for exclusion are specified in Table 2).

A total of 11 meta-analyses (Janket *et al.*, 2005; Teeuw *et al.*, 2010; Simpson *et al.*, 2010; Engebretson and Kocher, 2013; Sgolastra *et al.*, 2013; Liew *et al.*, 2013; Wang *et al.*, 2014; Sun *et al.*, 2014; Simpson *et al.*, 2015; Li *et al.*, 2015; Jain *et al.* 2019) were included in the review. These 11 meta-analyses comprised a total of 27 primary studies (Figure 1).

Sixteen studies were finally included (Grossi *et al.*, 1997; Kiran *et al.*, 2005; Hong, 2005; Jones *et al.*, 2007; Yun *et al.*, 2007; Singh *et al.*, 2008; Katagiri *et al.*, 2009; Sun *et al.*, 2011; Koromantzos *et al.*, 2011; Li *et al.*, 2011; Moeintaghavi *et al.*, 2012; Chen *et al.*, 2012; Zhang *et al.*, 2013; Engebretson *et al.*, 2013; Raman *et al.*, 2014; Gay *et al.*, 2014), and a meta-analysis was conducted including 11 of them (Chen *et al.*, 2012; Kiran *et al.*, 2005; Jones *et al.*, 2007; Singh *et al.*, 2008; Sun *et al.*, 2011; Koromantzos *et al.*, 2011; Moeintaghavi *et al.*, 2012; Zhang *et al.*, 2013; Engebretson *et al.*, 2013; Raman *et al.*, 2014; Gay *et al.*, 2014), since 5 publications (Grossi *et al.*, 1997; Hong *et al.*, 2009; Yun *et al.*, 2007; Katagiri *et al.*, 2009; Li *et al.*, 2011) presented a high risk of bias and were therefore excluded.

Study characteristics

The characteristics of the 11 included meta-analyses (number of patients, interventions, follow-up period, inclusion criteria, databases [search period], number of included studies, assessment quality and quality of the evidence [GRADE]) are summarized in Table 3. All the included studies analyzed glycemic control after periodontal treatment by evaluating the difference in HbA1c levels before and after the treatment. Three of these studies also (Teeuw *et al.*, 2010; Sgolastra *et al.*, 2013; Sun *et al.*, 2014) used FPG to assess metabolic control.

In the second part of the study, we conducted a meta-analysis of 11 RCTs (Chen *et al.*, 2012; Kiran *et al.*, 2005; Jones *et al.*, 2007; Singh *et al.*, 2008; Sun *et al.*, 2011; Koromantzos *et al.*, 2011; Moeintaghavi *et al.*, 2012; Zhang *et al.*, 2013; Engebretson *et al.*, 2013; Raman *et al.*, 2014; Gay *et al.*, 2014). The characteristics of the included studies (number of patients, interventions, follow-up period, outcome variable, mean age, results of HbA1c as a percentage and mmol/mol and results of FPG in mg/dl) are summarized in Table 4. All the included RCTs have analyzed glycemic control after periodontal treatment, based on the difference in HbA1c levels. Six of these studies (Chen *et al.*, 2012; Kiran *et al.*, 2005; Singh *et al.*, 2008; Sun *et al.*, 2011; Moeintaghavi *et al.*, 2012; Zhang *et al.*, 2013) evaluated FPG in addition to HbA1c.

The methodological quality of the included meta-analyses

The methods used in the meta-analyses review were assessed using the AMSTAR tool (Shea *et al.*, 2007). None of the ten included meta-analyses presented methodological limitations (score ≥ 8). The AMSTAR scores ranged between 9 and 11, with a median of 10.3 (Table 5). All the included meta-analyses have satisfied 5 of the 11 criteria: "*A priori* design", "Study characteristics", "Quality assessed", "Quality used" and "Methods appropriate". The agreement between the reviewers referred to quality assessment was 0.92 based on the kappa statistic.

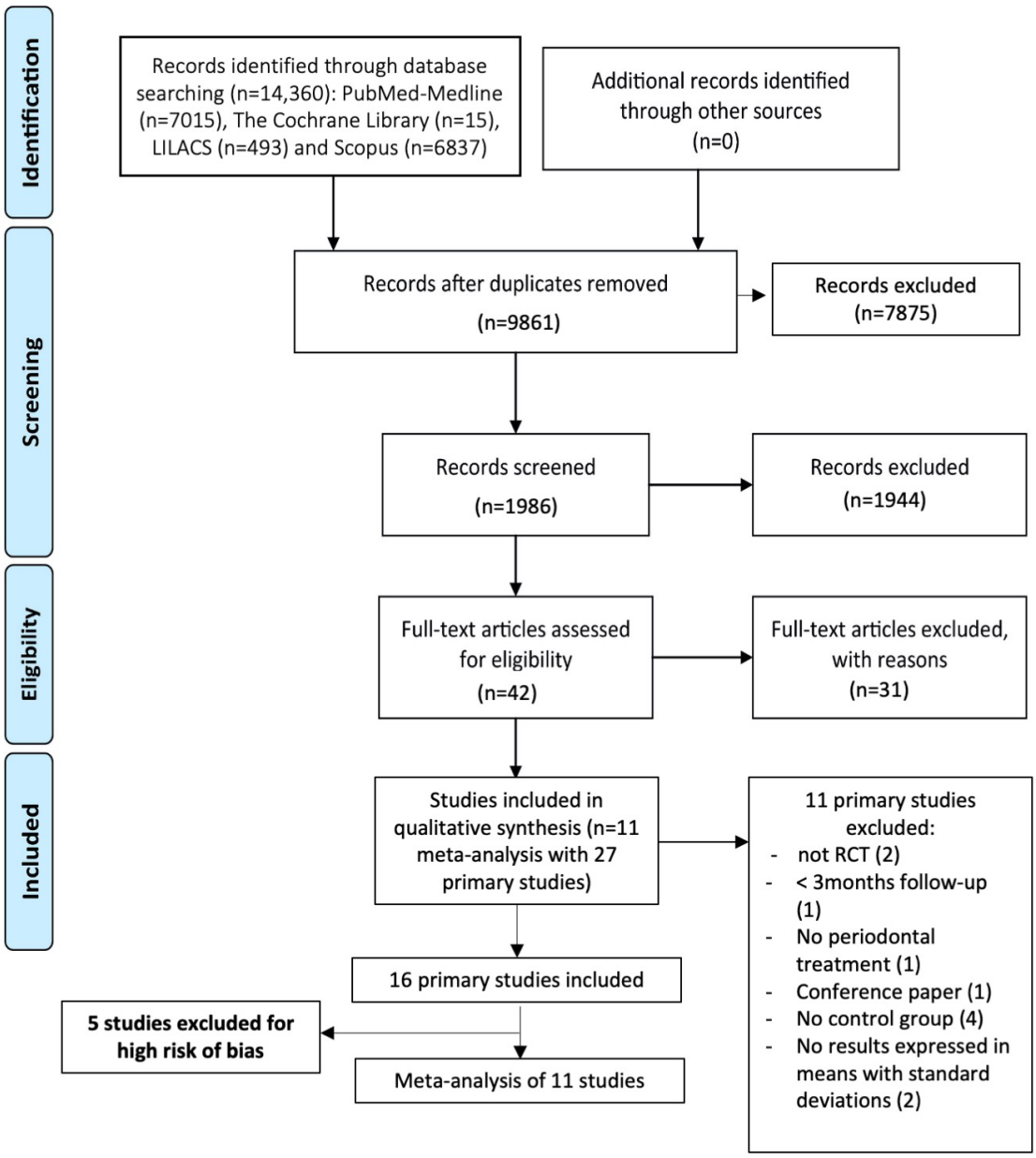

Figure 1. Flow diagram of the search processes and results.

Risk of bias assessment of the primary studies

The risk of bias of the included primary studies is summarized in Table 6. Following the application of the inclusion criteria, a total of 16 primary studies were included. Five of these studies (Jones *et al*., 2007; Koromantzos *et al*., 2011; Zhang *et al*., 2013; Engebretson *et al*., 2013; Gay *et al*., 2014) presented a low risk of bias; 6 studies (Chen *et al*., 2012; Kiran *et al*., 2005; Singh *et al*., 2008; Sun *et al*., 2011; Moeintaghavi *et al*., 2012; Raman *et al*., 2014) presented a moderate risk of bias; and 5 studies (Grossi *et al*., 1997; Hong, 2005; Yun *et al*., 2007; Katagiri *et al*., 2009; Li *et al*., 2011) presented a high risk of bias. The five studies with a high risk of bias were excluded from the quantitative analysis, leaving a final total of 11 studies for the analysis. The agreement between the reviewers referred the risk of bias assessment, based on the kappa statistic, was 0.90.

Periodontal treatment intervention and HbA1c level

All the included meta-analyses reported absolute variations (Δ) in HbA1c as the glycemic control parameter. Eight meta-analyses (Janket *et al*., 2005; Teeuw *et al*., 2010; Simpson *et al*., 2010; Engebretson *et al*., 2013; Sgolastra *et al*., 2013; Liew *et al*., 2013; Wang *et al*., 2014; Sun *et al*., 2014) showed significant improvement in glycemic control after periodontal treatment, as measured by a significant decrease in HbA1c levels compared with the untreated control group (Intervention-Control [I-C] Δ 1.03% (11.3 mmol/mol) (Sun *et al*., 2014); I-C Δ -0.27% (3.0 mmol/mol) (Li *et al*., 2015); I-C Δ -0.41% (4.5 mmol/mol) (Liew *et al*., 2013); I-C Δ 0.65% (7.1 mmol/mol) (Sgolastra *et al*., 2013); I-C Δ -0.40% (4.4 mmol/mol) (Teeuw *et al*., 2010); I-C Δ -0.41% (4.5 mmol/mol) (Simpson *et al*., 2015); I-C Δ -0.36% (3.9

Table 2. List of excluded papers with reasons for exclusion.

First author	Year	Journal	Reason for exclusion
Wilson TG Jr.	1989	Diabetes Educ.	Reason 1
Oliver RC.	1994	J Periodontol.	Reason 1
Kinane DF.	1997	Curr Opin Periodontol.	Reason 1
Gustke CJ.	1999	J Clin Periodontol.	Reason 1
Rees TD.	2000	Periodontol 2000	Reason 1
Matthews DC.	2002	J Can Dent Assoc.	Reason 1
Taylor GW.	2003	J Am Dent Assoc.	Reason 1
Mealey BL.	2006	J Periodontol.	Reason 1
Khader YS.	2006	J Diabetes Complications	Reason 2
Alves C.	2007	Arq Bras Endocrinol Metab.	Reason 1
Darré L.	2008	Diabetes Metab.	Reason 3
Javed F.	2009	J Periodontol.	Reason 2
Chávarry NG	2009	Oral Health Prev Dent	Reason 2
Lima-Costa KL.	2009	R. Periodontia	Reason 5
Phillips NM.	2012	Am J Nurs.	Reason 4
Corbella S.	2013	J Diabetes Investig.	Reason 3
Borgnakke WS.	2013	J Clin Periodontol.	Reason 3
Wang X.	2014	PLoS ONE	Reason 3
Pushparani DS.	2014	Curr Diabetes Rev.	Reason 1
Atieh MA.	2014	Diabetes Res Clin Pract.	Reason 2
Llambés F.	2015	World J Diabetes	Reason 1
Mauri-Obradors E.	2015	Odontology	Reason 3
Artese HP.	2015	PLoS ONE	Reason 2
Esteves-Lima RP.	2016	J Periodontol.	Reason 3
Al-Hamoudi N.	2017	Photodiagnosis Photod	Reason 2
Hasuike A.	2017	Med Oral Pathol Oral	Reason 3
Sanz M	2018	J Clin Periodontol	Reason 1
De Morais EF	2018	Arch Oral Biol	Reason 2
Li S	2018	J Periodontal Res	Reason 5
Garde S.	2019	Int J Mol Sci	Reason 2
Hsu YT.	2019	J Clin Peridontol	Reason 2

Reason 1: Not a systematic review; **Reason 2:** Unrelated to glycaemic control and periodontal disease; **Reason 3:** Not type 2 diabetes Mellitus; **Reason 4:** Results published in another study; **Reason 5:** Systematic review but without meta-analysis.

mmol/mol) (Engebretson *et al*., 2013) and I-C Δ -0.40% (4.4 mmol/mol) (Simpson *et al*, 2010). Only two meta-analyses showed a nonsignificant decrease in HbA1c after periodontal treatment compared with the control group (I-C Δ -0.23% (2.5 mmol/mol) (Wang *et al*., 2014) and I-C Δ -0.70% (7.7 mmol/mol) (Janket *et al*., 2005).

Non-Surgical Periodontal treatment intervention and FPG

Three studies (Teeuw *et al*., 2010; Sgolastra *et al*., 2013; Sun *et al*., 2014) reported the variation in FPG as glycemic control parameter, and two of them showed a nonsignificant decrease in FPG after non-surgical periodontal treatment compared with the control group (I-C Δ 0.69 mg/dl (Sun *et al*., 2014) and I-C Δ 2.30 mg/dl (Teeuw *et al*., 2010). Only one study (Sgolastra *et al*., 2013) showed a significant decrease in FPG after periodontal treatment compared with the control group (I-C Δ 9.04 mg/dl).

A Meta-analysis of the primary studies

The results of the meta-analysis are shown in Figure 2. The 11 RCTs included in the meta-analysis comprised a total of 1341 participants (724 in the intervention group and 617 in the control group). The 11 studies analyzed glycemic control after non-surgical periodontal treatment, based on the difference in HbA1c, and recorded statistically significant results [-0.32% (3.5 mmol/mol); 95%CI: -0.501 to -0.146; $p<0.001$]. Of these studies, 6 analyzed glycemic control after scaling and root planning based on the differences in FPG, and likewise recorded statistically significant results (-11.59 mg/dl; 95%CI: -15.16 to -8.01; $p<0.001$). The results of the meta-analysis for HbA1c and FPG are summarized in Table 7.

Regarding the heterogeneity of the included studies, we found high heterogeneity for HbA1c ($I^2 = 83.2\%$) and low heterogeneity for FPG ($I^2 = 10.3\%$). Despite these observations, the Galbraith plot showed that the studies are distributed around the adjusted regression line – all within the corresponding 95% confidence limits (Figure 3).

The results of Begg's test with continuity correction and Egger's test confirmed that there was no evidence of publication bias for both HbA1 and FPG. The p value for HbA1c was 0.542 for the Begg's test, versus 0.089 for the Egger's test. In turn, the result of FPG was 0.719 for the Begg's test and 0.937 for the Egger's test. Figure 4 shows the funnel plot of the studies that analyzed Hb1Ac and FPG.

The statistical power was calculated to identify a mean effect size (Cohen d) of 0.2 for the Hb1Ac, and (Cohen d) of 0.35 for FPG) as being statistically significant, with a 95% confidence level. The statistical power of the study was 95%.

Table 3. Characteristics of the included meta-analysis.

Study	Nº pat. I/C	Intervention	Follow-up Period (weeks)	Inclusion criteria	Data bases, (search period), number of included studies	Assessment quality	Quality of the evidence (GRADE)
Janket *et al*. 2005	Total: 228	SRP ± CHX irrigation or gel ± local ATB	2-48	Original investigation of intervention where causal inferences may be made; duration of the study of at least 2 months; Primary or secondary outcome was a measure of glycemic control (Hb1Ac level) and the predictor was a periodontal treatment. 2005. Limits: Humans and English language	MEDLINE, Evidence based Medicine (EBM) Reviews and Cochrane Central Register of Controlled Trials (1980-01/2005), 5 studies included	Modification of quality used by Janket	⊕⊕◦◦
Teeuw *et al*. 2010	199/183	SRP + oral hygiene + topical ATB	12–36	RCT´s and CCT´s diabetic patients with periodontitis receiving periodontal treatment and diabetic patients with periodontitis receiving no periodontal treatment and follow-up was for ≥ 3 months. Limits: Humans and English language	MEDLINE and the Cochrane Library (01/1960-31/03/2009), 5 studies included	Dutch Cochrane Centre and the Dutch Institute for Healthcare Improvement CBO	⊕⊕⊕◦
Simpson *et al*. 2010	119/125	Oral hygiene + SRP ±adjunctive ATB	12-24	RCT´s with people with type 1 and type 2 diabetes with a diagnosis of periodontitis with at least 3 months of follow up. No limits.	Cochrane Oral Health Group's Trials Register, CENTRAL,MEDLINE, EMBASE, CINAHL, ZETOC, ISI Web of Knowledge and LILACS (from their inception to 24/03/2010), 3 studies included	Cochrane Handbook for Systematic Reviews of Interventions	⊕⊕⊕⊕
Engebretson and Kocher 2013	Total: 689	Oral hygiene + SRP + adjunctive ATB + CHX	40-165	RCT´s 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 were included.	MEDLINE (10/2009-07/2012), 9 studies included	Cochrane Handbook for Systematic Reviews of Interventions	⊕⊕⊕⊕
Sgolastra *et al*. 2013	159/111	SRP, mechanical tooth cleaning	12–24	RCT´s that comparing nonsurgical SRP alone with non-treatment, coronal SRP, or mechanical tooth cleaning; patients diagnosed with type 2 diabetes and CP and studies conducted on adult patients (aged ≥18 years).	MEDLINE, Cochrane Controlled Clinical Trial Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CINAHL, Science Direct, ISI Web of Knowledge and SCOPUS (from their inception to 16/05/2012), 5 studies included	Consolidated Standards of Reporting Trials (CONSORT) statement	⊕⊕⊕⊕

Table 3 continued overleaf.....

Table 3 continued.....

Study	Nº pat. I/C	Intervention	Follow-up Period (weeks)	Inclusion criteria	Data bases, (search period), number of included studies	Assessment quality	Quality of the evidence (GRADE)
Liew *et al*. 2013	206/267	Oral hygiene + SRP + curettage + debridement + adjunctive ATB + CHX	12-24	RCT´s. Population: Patients with type 2 diabetes, at least 16 years old, diagnosed with periodontitis; non-surgical periodontal treatment with or without adjunctive use of local drug delivery and systemic antibiotics; a minimal follow-up period of 3 months. Limits: English language	MEDLINE, EMBASE and Cochrane CENTRAL (from their inception to 31/03/2012), 6 studies included	Cochrane Handbook for Systematic Reviews of Interventions	⊕⊕⊕◦
Wang *et al*. 2014	71/72	SRP + adjunctive ATB	12–16	RCT´s with subjects with type 2 diabetes and PD; comparison of different periodontal therapies and studies providing comparable numerical results for HbA1c measurement. Reference lists of the relevant studies were searched manually. Titles and abstracts were screened for all studies and full-text was then obtained for those that met the inclusion criteria.	MEDLINE, EMBASE and the Cochrane CENTRAL (from their inception to 01/2014), 4 studies included	Cochrane Handbook for Systematic Reviews of Interventions	⊕⊕⊕⊕
Sun *et al*. 2014	265/250	SRP	12–36	RCT´s with diabetic patients with periodontitis, receiving periodontal treatment with or without adjunctive antimicrobial therapy, and control groups receiving no periodontal treatment and follow-up was for at least 3 months. Limits: Humans and English language	MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews (01/1980-31/07/2012), 8 studies included	Cochrane Handbook for Systematic Reviews of Interventions	⊕⊕⊕◦
Simpson *et al*. 2015	1101/961	Oral hygiene + SRP ±adjunctive ATB	12-24	RCT´s with people with type 1 and type 2 diabetes with a diagnosis of periodontitis. No limits	MEDLINE, EMBASE, the Cochrane Oral Health Group Trials Register, the Cochrane CENTRAL, LILACS, CINAHL, ZETOC and Web of Knowledge (from their inception to 31/12/2014), 14 studies included	Cochrane Handbook for Systematic Reviews of Interventions	⊕⊕⊕⊕
Li *et al*. 2015	575/491	Oral hygiene + SRP + supragingival profilaxis	12-24	RCT´s with people with type 2 diabetes mellitus diagnosed with periodontitis; non-surgical periodontal treatment without adjunctive use of local drug delivery and systemic antibiotics at least 3 months of follow-up. Limits: English language	MEDLINE, EMBASE, ISI Web of Science and Cochrane CENTRAL (from their inception to 01/04/2015), 9 studies included	Cochrane Handbook for Systematic Reviews of Interventions	⊕⊕⊕⊕

Table 3 continued overleaf.....

Table 3 continued.....

Study	Nº pat. I/C	Intervention	Follow-up Period (weeks)	Inclusion criteria	Data bases, (search period), number of included studies	Assessment quality	Quality of the evidence (GRADE)
Jain *et al.* 2019	410/402	SRP	12-24	RCT´s. Population: type 2 diabetes mellitus diagnosed with periodontitis; non-surgical periodontal treatment without adjunctive use of local drug delivery and systemic antibiotics at least 3 months of follow-up. Limits: English language	MEDLINE and EMBASE (between June 2006 to June 2016), 6 studies included	Cochrane Handbook for Systematic Reviews of Interventions	⊕⊕⊕◦

CCT = Controlled clinical trial; RCT= Randomized controlled clinical trial; HbA1c = Glycated hemoglobin; CHX: chlorhexidine; ATB: Antibiotics; CINAHL = Cumulative Index to Nursing & Allied Health Literature; PD = Periodontitis; CP = chronic periodontitis; Nº pat = Number of patients; I= Intervention group; C= Control group; SRP= scaling and root planning; ⊕⊕⊕⊕ = High quality: Further research is very unlikely to change our confidence in the estimate of effect; ⊕⊕⊕◦ = Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; ⊕⊕◦◦ = Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; ⊕◦◦◦ = Very low quality: We are very uncertain about the estimate.

Table 4. Characteristics of included primary studies.

Primary study	Nº pac I/C	Intervention	Follow-up time (months)	Outcome	Mean Age (I/C)	Results HbA1c (%) [mmol/mol]	Results FPG (mg/dl)
Kiran *et al.*[38] 2005	22/22	I: SRP C: No treatment	3	HbA1c FPG	55.95/ 52.82	I: Δ -0.86 ± 0.77 [9.4 ± 8.4] (P-be= 0.0000) C: Δ 0.31 ± 1.83 [3.4 ± 20] (p=0.033)	I: Δ -3.96 ± 30.58 C: Δ 1.22 ± 37.49 (p=0.481)
Jones *et al.*[40] 2007	74/80	I: SRP + CHX 0.12% rinses C: Regular dental care	4	HbA1c	57.79/ 58.96	I: Δ -0.65 ± 1.21 [7.1 ± 13.2] C: Δ -0.49 ± 1.22 [5.4 ± 13.3] (p>0.05)	NA
Singh *et al.*[42] 2008	30/15	I: SRP C: No treatment	3	HbA1c FPG	NA	I: Δ -0.65 ± 0.65 [7.1 ± 7.1] C: Δ 0.06 ± 0.72 [0.7 ± 7.9] (p>0.05)	I: Δ -4.10 ± 13.11 C: Δ 1.80 ± 12.35

Table 4 continued overleaf.....

Table 4 continued.....

Primary study	Nº pac I/C	Intervention	Follow-up time (months)	Outcome	Mean Age (I/C)	Results HbA1c (%) [mmol/mol]	Results FPG (mg/dl)
Sun *et al.*[44] 2011	82 / 75	I: SRP C: No treatment	3	HbA1c FPG	55.1 / 54.2	I: Δ -0.50 ± 0.18 [5.5 ± 2] C: Δ -0.14 ±0.12 [1.5 ± 1.3]	I: Δ -21,08 ± 8,83 C: Δ -7,92 ± 4,32
Koromantzos *et al.*[45] 2011	30 / 30	I: SRP C: oral hygiene Instructions	3 and 6	HbA1c	59.6 / 59.4	I: Δ -0.73 ± 0.66 [8 ± 7.2] C: Δ -0.18 ±0.59 [2 ± 6.4]	NA
Chen *et al.*[16] 2012	83 / 41	I: SRP C: No treatment	3 and 6	HbA1c FPG	58.9 / 63.2	I: Δ 0.07 ± 1.40 [0.8 ± 15.3] C: Δ 0.34 ± 1.52 [3.7 ± 16.6]	I: Δ 0.00 ± 34,05 C: Δ 6.13 ± 46,31
Moeintaghavi *et al.*[47] 2012	22 / 18	I: SRP C: No treatment	3	HbA1c FPG	50.9 (overall)	I: Δ -0.74 ± 1.18 [8.1 ± 12.9] C: Δ 0.25 ± 2.05 [2.7 ± 22.4]	I: Δ -17.5 ± 48.9 C: Δ 9.78 ± 38.0
Zhang *et al.*[48] 2013	49 / 23	I: SRP C: No treatment	3	HbA1c FPG	60.4 / 62.7	I: Δ -0.13 ± 0.34 [1.4 ± 3.7] C: Δ 0.03 ± 0.22 [0.3 ± 2.4]	I: Δ -54,06 ± 329,8 C: Δ 0 ± 380,22
Engebretson *et al.*[49] 2013	241 / 236	I: SRP C: oral hygiene Instructions	3 and 6	HbA1c	56.7 / 57.9	I: Δ 0.15 ± 0.63 [1.6 ± 6.9] C: Δ 0.10 ± 0.63 [1.1 ± 6.9]	NA
Raman *et al.*[50] 2014	25 / 17	I: SRP + CHX 0.12% rinses C: oral hygiene Instructions	3	HbA1c	57.7 / 54.6	I: Δ -0.7 ± 1.37 [7 ± 15] C: Δ -0.5 ± 1.37 [5.5 ± 15]	NA
Gay *et al.*[51] 2014	66 / 60	I: SRP C: oral hygiene Instructions	4	HbA1c	51.5 / 54.0	I: Δ -0.6 ± 2.1 [6.6 ± 23] C: Δ -0.3± 1.7 [3.3 ± 18.6]	NA

CHX= Chlorhexidine; SRP= scaling and root planning; I= Intervention; C= Control; FPG= fasting plasma glucose; HbA1c = Glycated hemoglobin; NA= Not available; Δ= difference between baseline and end of trial

Table 5. AMSTAR Criteria for each included meta-analysis.

Study	A priori design	Duplicate selection/DA	Literature search	Publication status	List of studies	Study characteristics	Quality assessed	Quality used	Methods appropriate	Publication bias assessed	Conflicts stated	AMSTAR rating
Janket *et al*. 2005	+	+	+	-	+	+	+	+	+	+	+	10
Teeuw *et al*. 2010	+	+	+	+	o	+	+	+	+	+	o	9
Simpson *et al*. 2010	+	+	+	+	+	+	+	+	+	+	+	11
Sgolastra *et al*. 2013	+	+	+	+	+	+	+	+	+	+	+	11
Engebretson and Kocher 2013	+	-	-	+	+	+	+	+	+	+	+	9
Liew *et al*. 2013	+	+	+	+	+	+	+	+	+	+	o	10
Wang *et al*. 2014	+	+	+	+	+	+	+	+	+	+	+	11
Sun *et al*. 2014	+	+	+	+	+	+	+	+	+	o	+	10
Simpson *et al*. 2015	+	+	+	+	+	+	+	+	+	+	+	11
Li *et al*. 2015	+	+	+	+	+	+	+	+	+	+	+	11
Jain *et al*. 2019	+	+	-	+	-	+	+	+	+	+	+	11

"+" = Yes (clearly done); "-"= No (clearly not done); "o" = can´t answer, "NA" = Not Applicable

Table 6. Risks of Bias for the primary studies.

Primary study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias	Risk of bias
Grossi *et al.*[37] 1997*	Unclear	Unclear	High	High	Unclear	High	High
Kiran *et al.*[38] 2005	Low	Low	High	Low	Unclear	Low	Moderate
Hong *et al.*[39] 2005*	High	High	Unclear	Unclear	Unclear	High	High
Jones *et al.*[40] 2007	Low	Low	Low	Low	Low	Low	Low
Yun *et al.*[41] 2007*	Unclear	Unclear	High	High	Unclear	Unclear	High
Singh *et al.*[42] 2008	Unclear	High	Low	Low	Low	Low	Moderate
Katagari *et al.*[43] 2009*	Unclear	High	High	Low	Unclear	High	High
Sun *et al.*[44] 2011	Unclear	Unclear	High	Low	Low	Low	Moderate
Koromantzos *et al.*[45] 2011	Low	Unclear	Low	Low	Low	Low	Low
Li *et al.*[46] 2011*	Unclear	Unclear	Unclear	High	Unclear	High	High
Chen *et al.*[16] 2012	Low	Unclear	Unclear	High	Low	Low	Moderate
Moeintaghavi *et al.*[47] 2012	Low	Unclear	High	Low	Unclear	Low	Moderate
Zhang *et al.*[48] 2013	Low	Low	Low	Low	Low	Low	Low
Engebretson *et al.*[49] 2013	Low	Low	Low	Low	Low	Low	Low
Raman *et al.*[50] 2014	Low	Unclear	Unclear	Low	Low	Unclear	Moderate
Gay *et al.*[51] 2014	Low	Low	Low	Low	Low	Low	Low

* Studies with high risk of bias are excluded from the meta-analysis

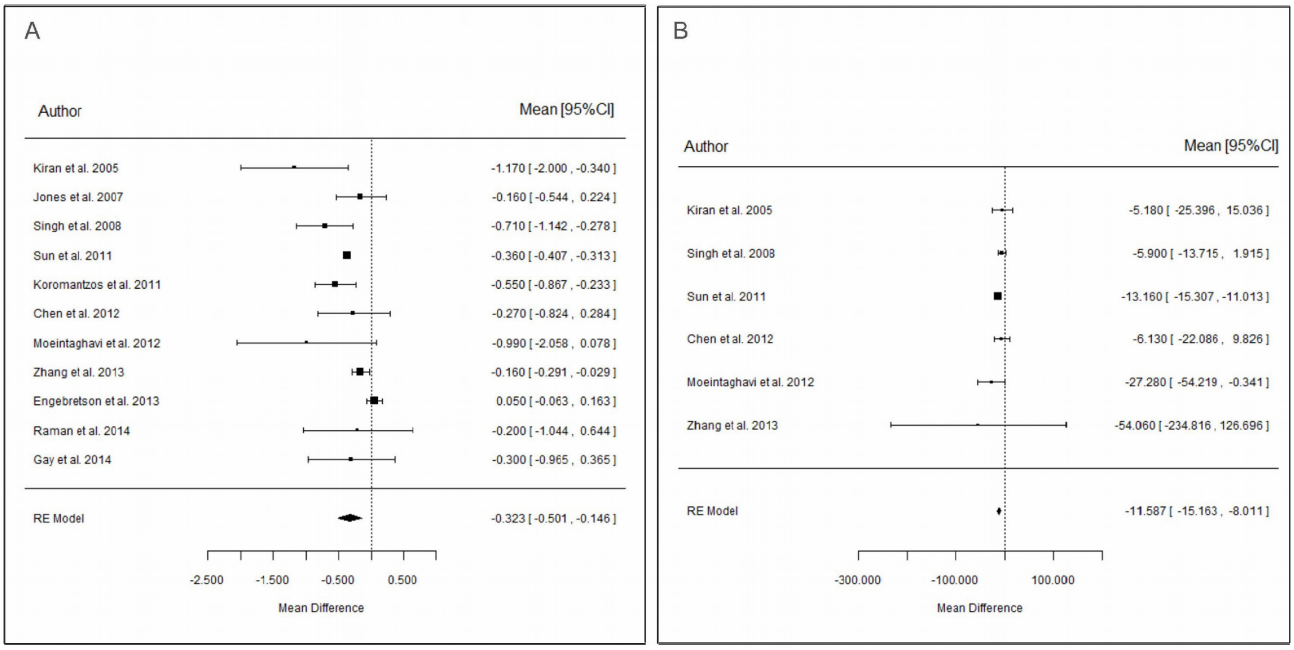

Figure 2. Forest plot of changes in A) HbA1c and B) FPG.

Table 7. Results of the meta-analyses for HbA1c and FPG.

HbA1c

Number of studies	Patients I/C	WMD	Standard error	CI 95% lower	CI 95% upper	Z	p-value	I2	p-value (heterog.)
11	724/617	-0.32	0.09	-0.50	-0.15	-3.57	<0.001*	83.2%	<0.001

FPG

Number of studies	Patients I/C	WMD	Standard error	CI 95% lower	CI 95% upper	Z	p-value	I2	p-value (heterog.)
6	288/194	-11.59	1.82	-15.16	-8.01	-6.35	<0.001*	10.3%	0.350

WMD= Weighted mean difference;
I2= percentage of between-studies variability to total
I/C= Intervention/Control
* Statistically significant

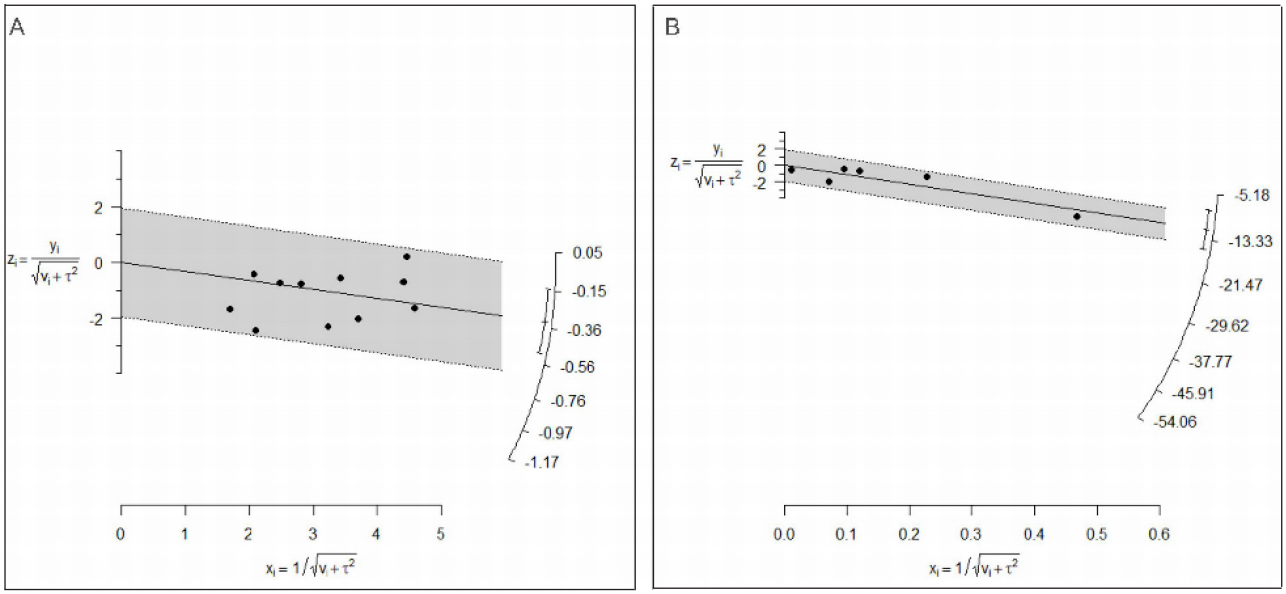

Figure 3. Galbraith plot of A) HbA1c and B) FPG.

DISCUSSION

The present review offers solid and interesting methodological evidence to date on the positive influence of periodontal treatment on the general health of type 2 diabetic patients by improving glycemic control after a follow-up period of at least three months. The moderate effect size of -0.32% (3.5 mmol/mol) for HbA1c (95%CI: -0.50 to -0.15) observed among all 11 studies remains statistically significant, which is consistent with the two recent systematic reviews [-0.27% (3.0 mmol/mol) HbA1c, 95%CI: -0.46 to -0.07) (Li *et al*., 2015) and [-0.36% (3.9 mmol/mol) HbA1c, 95%CI: -0.54 to -0.19] (Engebretson *et al*., 2013). The moderate effect size of -11.59 mg/dl for FPG (95%CI: -15.16 to -8.01) observed among all the six studies remains statistically significant, which is consistent with the other clinical study (-13.16 mg/dl FPG, CI: -15.30 to -11.01) (Sun *et al*., 2015). Therefore, the present meta-analysis indicates that periodontal treatment may reduce the levels of both HbA1c and FPG. We believe that the inclusion criteria applied to the available studies led to better understanding of the effect of periodontal treatment on diabetic patients, due to the following reasons: 1) the inclusion of studies that analyzed differences in HbA1c after a minimum follow-up of three months, since analyses of HbA1c corresponding to shorter periods of time is clinically irrelevant (Mealey and Ocampo, 2007); 2) the inclusion of only RCTs with no periodontal treatment in the control group; 3) calculation of the weighted mean difference instead of the standardized mean difference, in order to avoid overestimation of the total effect of periodontal treatment; and 4) the inclusion of patients with only type 2 diabetes, since some studies (Darré *et al*., 2008; Wang *et al*., 2014) analyzed the effect of periodontal treatment on glycemic control in patients with both type 1 and type 2 diabetes (Wang *et al*., 2014). Taking into account the different etiopathogenic mechanisms involved in the two types of diabetes (Standards

of Medical Care in Diabetes, 2016), it is preferable to examine the effect of periodontal treatment on each type independently.

To determine the degree of heterogeneity of HbA1c at which the reliability of the results obtained could be affected, a sensitivity analysis was conducted. The analysis revealed a significant decrease in heterogeneity (I^2= 20.9%) after excluding two studies (Zhang *et al.*, 2013; Engebretson *et al.*, 2013), nevertheless, the same effect of treatment was observed ($p<0.001$). The inclusion of these two studies in the meta-analysis was necessary due to their precision and strength (considering the sample size in one case - Engebretson *et al.*, 2013 - and the low deviation in the other - Zhang *et al.*, 2013). However, it has been shown that these two studies induce heterogeneity, and that their exclusion does not modify the results obtained – thus indicating excellent reliability of the meta-analysis. A funnel plot served as a visual means for assessing any disproportionate representation of the results according to strength and precision. Regarding the HbA1c results, supplementary Figure 4 shows slight asymmetry which could be attributed to studies with a high standard error (scantly precise due to small sample size or high variability). The zone in which the asymmetry is noted (at lower right area of the figure) corresponds to studies in which periodontal treatment exerted no influence on glycemic control. Moreover, one study in which FPG was considered as an outcome was noted in the lower zone of the figure. This could be explained by the signicant standard deviation for FPG in the study.

In this overview, we found that patients with type 2 diabetes subjected to periodontal treatment experienced a mean decrease in HbA1c levels of 0.32% (3.5 mmol/mol), and a mean decrease in FPG of 11.59 mg/dl. Taking into consideration that the development of diabetes-related medical complications is a multifactorial phenomenon, it is important from a clinical perspective to maintain good periodontal health, as it may positively contribute to the maintenance of blood glucose level within the normal range. Interestingly, improvement in glucose metabolism following periodontal therapy was more frequently observed for HbA1c than for FPG. This observation could be explained by the fact that FPG reflects the current blood glucose level at the time when the test was performed, while the HbA1c, reflects glucose metabolism over the preceding 1-3 months (Teeuw *et al.*, 2010). The HbA1c test has several advantages over the FPG test, such as being more convenient (fasting is not required), has more pre-test stability, and less day-to-day perturbations during stress and illness. However, these advantages may be offset by the lower sensitivity of HbA1c at the designated cutoff point, greater cost, limited availability and imperfect correlation with the average blood glucose in specific individuals (Cowie *et al.*, 2010). Despite the numerous reports in the scientific literature about the course of periodontal disease in diabetic patients (Liew *et al.*, 2013; Wang *et al.*, 2014; Sun *et al.*, 2014), evaluation of the accumulated research should be done with caution, since considerable diversity of populations, varying definitions of the parameters under investigation, or small numbers of study subjects may have an impact upon the results (Mealey *et al.*, 2006).

Periodontal disease can be an early complication of diabetes mellitus and diabetes is an important health care problem (Lamster *et al.*, 2014; Löe, 1993). Although periodontal disease is considered as the sixth

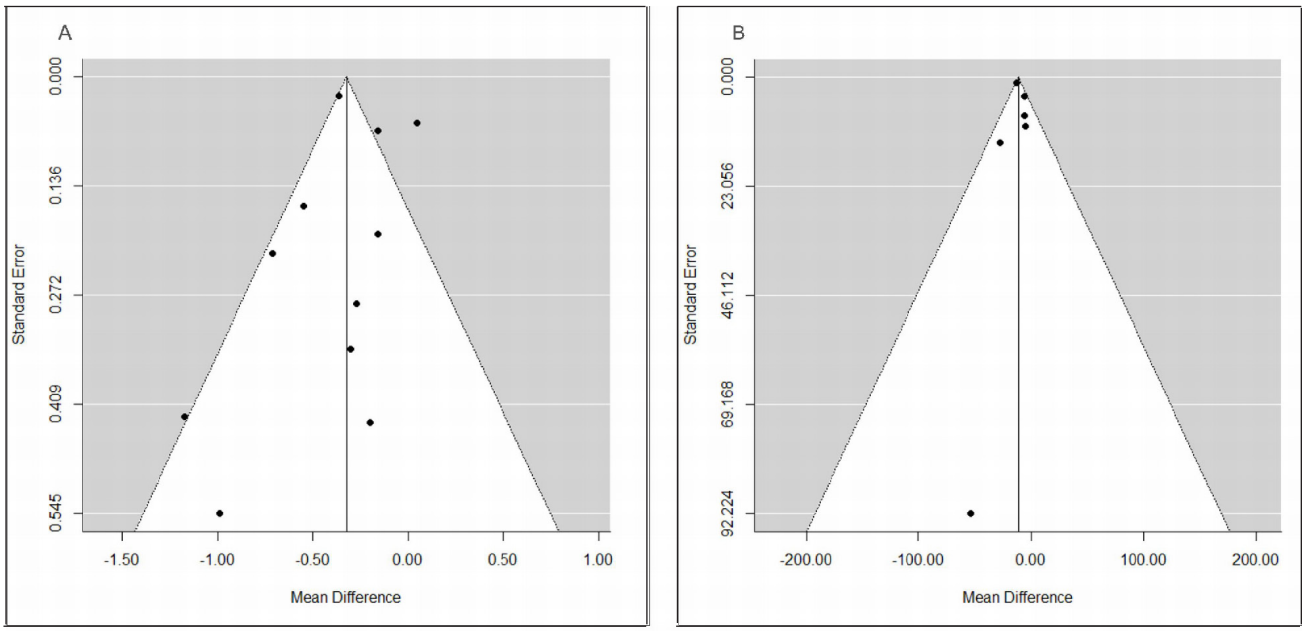

Figure 4. Funnel plot of A) HbA1c and B) FPG.

complication of diabetes in addition to retinopathy, neuropathy, nephropathy, altered wound healing and macrovascular diseases (Löe, 1993) some of the current guidelines (American Diabetes Association, 2013; Chamberlain *et al*., 2016) do not contemplate periodontal treatment in their diabetes management protocol. This review has shown that periodontal treatment improves glycemic control in patients with type 2 diabetes through significant reductions in both HbA1c and FPG levels. On the contrary, Faggion, *et al.* (2016) in a recent review of systematic reviews stated that their study did not support the notion that periodontal treatment may improve glycemic control. This finding was based on the assumption that the impact of periodontal treatment was not effective on HbA1c reduction when the follow-up was longer than 6 months. Finally, this contrast could also be attributed to the different approaches used in our study design, which evaluated the effects of periodontal treatment in patients with type 2 diabetes. In the last consensus reached in this subject (Sanz *et al*., 2018) The European Federation of Periodontology (EFP) and the International Diabetes Federation (IDF) concluded that periodontal therapy is safe and effective in people with diabetes, and it is associated with reductions in HbA1C of 0.27–0.48% after 3 months. Myllymäki *et al.* (2018) in a large longitudinal study with 395 patients suggest that periodontal condition appears to predict the development of type 2 diabetes in an exposure–response manner. This result is in agreement with the results of this meta-analysis.

As in any meta-analysis, the strength of the current study is largely determined by the study design and quality and number of the included studies. In this regard, the inclusion of studies with a randomized controlled design provides a comprehensive overview of the evidence on the topic addressed by our study. Moreover, to strengthen the results and minimize bias, we excluded all studies with a high risk of bias from the quantitative analysis. Nevertheless, randomization and the inclusion of a non-periodontal treatment group were the most important quality factors for our review. Further strengths of the study were the fact that we carried out a meta-analysis of RCTs rated as having a high level of evidence and conducted a systematic search of different international medical databases with the aim of minimizing publication bias. Moreover, no restrictions referred to language or publication date were set to ensure inclusion of as many data as possible from appropriate studies. Two reviewers independently chose, extracted and evaluated data quality to reduce bias and transcription errors.

This overview also has certain limitations. Firstly there was heterogeneity in the HbA1c parameter (I^2 = 83.2%). Despite this heterogeneity, the Galbraith plot indicated that the studies are distributed within the confidence limits. To determine the extent to which the heterogeneity affects the global results obtained, we performed a stratified analysis, extracting each of the studies individually and examining how they influenced the global result. Another limitation is the fact that we accepted the reference to "periodontal disease" of each of the included studies. The prevalence of periodontal disease varies in different populations around the globe. Furthermore, prevalence estimates are influenced by the methodology used, including measurement techniques, case definitions, and periodontal examination protocols, as well as by differences in oral health status. Consequently, comparisons between populations are severely hampered, and inferences regarding global variations in prevalence are difficult to establish. To overcome these limitations, standardized principles have recently been proposed for reporting the prevalence and severity of periodontal diseases in future epidemiological studies (Holtfreter *et al*., 2015).

CONCLUSIONS

The current overview ratifies previous meta-analyses presenting that non-surgical periodontal therapy was favorable and can improve HbA1c and FPG levels of periodontally diseased patients with type 2 diabetes to a greater extent than in non-intervention control subjects. Therefore, it could be suggested to include periodontal evaluation in the prevention and management protocol of diabetic patients, which contributes to the reduction of the medical complications associated with hyperglycemia, at least, in type 2 diabetes.

CONFLICT OF INTEREST

The authors report no conflict of interest related to the present paper.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the help of María Jesús Baeza, librarian of Arnau de Vilanova Hospital (Valencia, Spain). No funding was received for this review.

REFERENCES

Alves C, Andion J, Brandão M and Menezes R. Mecanismos patogênicos da doença periodontal associada ao diabetes melito. *Arquivos Brasileiros de Endocrinologia & Metabologia* 2007; **51**:1050-1057

American Academy of Periodontology Task Force Report on the Update to the 1999 Classification of periodontal diseases and conditions. *Journal of Periodontol*ogy 2015; **86**:835-838.

American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2013; **36**:11-66.

Artese HP, Foz AM, Rabelo Mde S, Gomes GH, Orlandi M, Suvan J, *et al.* Periodontal therapy and systemic inflammation in type 2 diabetes mellitus: a meta-analysis. *Public Library of Science One* 2015; **10**:e0128344.

Atieh MA, Faggion CM Jr and Seymour GJ. Cytokines in patients with type 2 diabetes and chronic periodontitis: A systematic review and meta-analysis. *Diabetes Research Clinical Practice* 2014; **104**:38-45.

Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**:1088-1101.

Bergman M. Pathophysiology of prediabetes and treatment implications for the prevention of type 2 diabetes mellitus. *Endocrine* 2013; **43**:504-513.

Borgnakke WS, Ylöstalo PV, Taylor GW and Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. *Journal of Clinical Periodontology* 2013; **40**:135-152.

Chamberlain JJ, Rhinehart AS, Shaefer CF Jr and Neuman A. Diagnosis and management of diabetes: Synopsis of the 2016 American Diabetes Association standards of medical care in diabetes. *Annals of Internal Medicine* 2016; **164**:542-552.

Chapple IL and Genco R. Working group 2 of joint EFP/AAP workshop. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *Journal of Clinical Periodontology* 2013; **40**:106-112.

Chávarry NG, Vettore MV, Sansone C and Sheiham A. The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. *Oral Health and Preventive Dentistry* 2009; **7**:107-127.

Chen HH, Chen DY, Lai KL, Chen YM, Chou YJ, Chou P, *et al.* Periodontitis and etanercept discontinuation risk in anti-tumor necrosis factor-naive rheumatoid arthritis patients: a nationwide population-based cohort study. *Journal of Clinical Rheumatology* 2013; **19**:432-438.

Chen L, Luo G, Xuan D, Wei B, Liu F, Li J*, 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. *Journal of Periodontol*ogy 2012; **83**:435-443.

Cohen J. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. *Psychological Bulletin Journal* 1968; **70**: 213-220.

Consensus Report: Chronic Periodontitis. 1999 International Workshop for a Classification of Periodontal Diseases and Conditions. *Annals of Periodontology* 1999; **4**:38.

Corbella S, Francetti L, Taschieri S, De Siena F and Fabbro MD. Effect of periodontal treatment on glycemic control of patients with diabetes: A systematic review and meta-analysis. *Journal of Diabetes Investigation* 2013; **4**:502-509.

Costa KLL, Montenegro Jr. RM and Rêgo RO. Influência do tratamento periodontal sobre o controle glicêmico de diabéticos do tipo 2 – revisão sistemática. *Periodontia* 2009; **19**:11-19.

Cowie CC, Rust KF, Byrd-Holt DD, Gregg EW, Ford ES, Geiss LS, *et al.* Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988-2006. *Diabetes Care* 2010; **33**:562-568.

Darré L, Vergnes JN, Gourdy P and Sixou M. Efficacy of periodontal treatment on glycaemic control in diabetic patients: A meta-analysis of interventional studies. *Diabetes & Metabolism* 2008; **34**:497-506.

Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal* 1997; **315**:629-634.

Eke PI, Dye BA, Wei L, Thornton-Evans GO and Genco RJ. CDC Periodontal Disease Surveillance workgroup. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *Journal of Dental Research* 2012; **91**:914-920.

Engebretson S and Kocher T. Evidence that periodontal treatment improves diabetes outcomes: a systematic review and meta-analysis. *Journal of Clinical Periodontology* 2013; **40**:153-163.

Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, *et al.* The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. *Journal of the American Medical Association* 2013; **310**:2523-2532.

Esteves Lima RP, Cyrino RM, de Carvalho Dutra B, Oliveira da Silveira J, Martins CC, Miranda Cota LO, *et al.* Association between periodontitis and gestational diabetes mellitus: Systematic review and meta-analysis. *Journal of Periodontol*ogy 2016; **87**:48-57.

Faggion CM Jr, Cullinan MP and Atieh M. An overview of systematic reviews on the effectiveness of periodontal treatment to improve glycaemic control. *Journal of Periodontal Research* 2016; **51**:716-725.

Gay IC, Tran DT, Cavender AC, Weltman R, Chang J, Luckenbach E, *et al.* The effect of periodontal therapy on glycaemic control in a Hispanic population with type 2 diabetes: a randomized controlled trial. *Journal of Clinical Periodontology* 2014; **41**:673-680.

Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, *et al.* Treatment of periodontal disease in diabetics reduces glycated hemoglobin. *Journal of Periodontol*ogy 1997; **68**:713-719.

Gustke CJ. Treatment of periodontitis in the diabetic patient. A critical review. *Journal of Clinical Periodontology* 1999; **26**:133-137.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal* 2008; **336**:924-926.

Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002; **21**:1539-1558.

Higgins JPT and Green S (Editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration*, 2011. Available from www.cochrane-handbook.org.

Holtfreter B, Albandar JM, Dietrich T, Dye BA, Eaton KA, Eke PI, *et al*. Standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies: Proposed standards from the Joint EU/USA Periodontal Epidemiology Working Group. *Journal of Clinical Periodontology* 2015; **42**:407-412.

Holtfreter B, Empen K, Gläser S, Lorbeer R, Völzke H, Ewert R, *et al*. Periodontitis is associated with endothelial dysfunction in a general population: a cross-sectional study. *Public Library of Science One* 2013; **8**:e84603.

Hong, Y. The effect of periodontal therapy on glycosylated hemoglobin in elderly patients with type 2 diabeties and periodontitis. *Chinese Journal of Geriatrics* 2005; **24**:438-440.

Hung HC, Willett W, Ascherio A, Rosner BA, Rimm E and Joshipura KJ. Tooth loss and dietary intake. *Journal of the American Dental Association* 2003; **134**:1185-1192.

Ioannidou E, Kao D, Chang N, Burleson J and Dongari-Bagtzoglou A. Elevated serum interleukin-6 (IL-6) in solid-organ transplant recipients is positively associated with tissue destruction and IL-6 gene expression in the periodontium. *Journal of Periodontol*ogy 2006; **77**:1871-1878.

Jain A, Gupta J, Bansal D, Sood S, Gupta S and Jain A. Effect of scaling and root planing as monotherapy on glycemic control in patients of Type 2 diabetes with chronic periodontitis: A systematic review and meta-analysis. *Journal of Indian Society of Periodontology* 2019;**23**:303-310.

Janket SJ, Wightman A, Baird AE, Van Dyke TE and Jones JA. Does periodontal treatment improve glycemic control in diabetic patients? A meta-analysis of intervention studies. *Journal of Dental Research* 2005; **84**:1154-1159.

Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A and Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. *Journal of Diabetes and Its Complications* 2006; **20**:59-68.

Kinane DF and Chestnutt IG. Relationship of diabetes to periodontitis. *Current Opinion in Periodontology* 1997; **4**:29-34.

Koromantzos PA, Makrilakis K, Dereka X, Katsilambros N, Vrotsos IA and Madianos PN. A randomized, controlled trial on the effect of non-surgical periodontal therapy in patients with type 2 diabetes. Part I: effect on periodontal status and glycaemic control. *Journal of Clinical Periodontology* 2011; **38**:142-147.

Lamster IB, Cheng B, Burkett S and Lalla E. Periodontal findings in individuals with newly identified pre-diabetes or diabetes mellitus. *Journal of Clinical Periodontology* 2014; **41**:1055-1060.

Lamster IB, Lalla E, Borgnakke WS and Taylor GW. The relationship between oral health and diabetes mellitus. *Journal of the American Dental Association* 2008; **139**:19-24.

Li Q, Hao S, Fang J, Xie J, Kong XH and Yang JX. Effect of non-surgical periodontal treatment on glycemic control of patients with diabetes: a meta-analysis of randomized controlled trials. *Trials* 2015; **16**:291.

Mauri-Obradors E, Jané-Salas E, Sabater-Recolons Mdel M, Vinas M and López-López J. Effect of nonsurgical periodontal treatment on glycosylated hemoglobin in diabetic patients: a systematic review. *Odontology* 2015; **103**:301-313.

Mealey BL, Oates TW and American Academy of Periodontology. Diabetes mellitus and periodontal diseases. *Journal of Periodontol*ogy 2006; **77**:1289-1303.

Mealey BL and Ocampo GL. Diabetes mellitus and periodontal disease. *Periodontology 2000* 2007; **44**:127-153.

Moeintaghavi A, Arab HR, Bozorgnia Y, Kianoush K and Alizadeh M. Non-surgical periodontal therapy affects metabolic control in diabetics: a randomized controlled clinical trial. *Australian Dental Journal* 2012; **57**:31-37.

Moher D, Liberati A, Tetzlaff J, Altman DG and PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine* 2009; **151**:264-269.

Morgan CL, Currie CJ and Peters JR. Relationship between diabetes and mortality: a population study using record linkage. *Diabetes Care* 2000; **23**:1103-1107.

Myllymäki V, Saxlin T, Knuuttila M, Rajala U, Keinänen-Kiukaanniemi S, Anttila S and Ylöstalo P. Association between periodontal condition and the development of type 2 diabetes mellitus-Results from a 15-year follow-up study. *Journal of Clinical Periodontology* 2018; **45**:1276-1286.

Oliver RC and Tervonen T. Diabetes--a risk factor for periodontitis in adults? *Journal of Periodontol*ogy 1994; **65**:530-538.

Phillips NM. Does treatment of periodontal disease improve glycemic control in diabetes? *American Journal of Nursing* 2012; **112**:22.

Pushparani DS. Zinc and type 2 diabetes mellitus with periodontitis – a systematic review. *Current Diabetes Reviews* 2014; **10**:397-401.

Raman RP, Taiyeb-Ali TB, Chan SP, Chinna K and Vaithilingam RD. Effect of nonsurgical periodontal therapy verses oral hygiene instructions on type 2 diabetes subjects with chronic periodontitis: a randomised clinical trial. *BioMed Central Oral Health* 2014; **14**:79.

Rees TD. Periodontal management of the patient with diabetes mellitus. *Periodontology 2000* 2000; **23**:63-72.

Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E, Shapira L, Tonetti M and Vegh D. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. *Journal of Clinical Periodontology* 2018; **45**:138-149.

Sgolastra F, Severino M, Pietropaoli D, Gatto R and Monaco A. Effectiveness of periodontal treatment to improve metabolic control in patients with chronic periodontitis and type 2 diabetes: a meta-analysis of randomized clinical trials. *Journal of Periodontology* 2013; **84**:958-973.

Shangase SL, Mohangi GU, Hassam-Essa S and Wood NH. The association between periodontitis and systemic health: an overview. *South African Dental Journal* 2013; **68**:10-12.

Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al.* Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BioMed Central Medical Research Methodology* 2007; **15**;7-10.

Simpson TC, Needleman I, Wild SH, Moles DR and Mills EJ. Treatment of periodontal disease for glycemic control in people with diabetes. *Cochrane Database of Systematic Reviews* 2010;CD004714.

Simpson TC, Weldon JC, Worthington HV, *et al.* Treatment of periodontal disease for glycemic control in people with diabetes mellitus. *Cochrane Database of Systematic Rev*iews 2015; **11**:CD004714.

Singh S, Kumar V, Kumar S and Subbappa A. The effect of periodontal therapy on the improvement of glycemic control in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. *International Journal of Diabetes in Developing Countries* 2008; **28**:38-44.

Standards of Medical Care in Diabetes-2016: Summary of Revisions. *Diabetes Care* 2016; **39**:4-5.

Sun QY, Feng M, Zhang MZ, Zhang YQ, Cao MF, Bian LX, *et al.* Effects of periodontal treatment on glycemic control in type 2 diabetic patients: a meta-analysis of randomized controlled trials. *Chinese Journal Physiology* 2014; **57**:305-314.

Sun WL, Chen LL, Zhang SZ, Wu YM, Ren YZ and Qin GM. Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis. *Internal Medicine* 2011; **50**:1569-1574.

Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, *et al.* Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *Journal of Periodontology* 1996; **67**:1085-1093.

Taylor GW, Manz MC and Borgnakke WS. Diabetes, periodontal diseases, dental caries, and tooth loss: a review of the literature. *Compendium of Continuing Education in Dentistry* 2004; **25**:79-84, 186-188, 190; quiz 192.

Taylor GW. The effects of periodontal treatment on diabetes. *Journal of the American Dental Association* 2003; **134**:41-48.

Teeuw WJ, Gerdes VE and Loos BG. Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. *Diabetes Care* 2010; **33**:421-427.

The R Project for Statistical Computing. (Home page on the Internet). Available from: http://www.r-project.org (Accessed March 11, 2016).

Wang TF, Jen IA, Chou C and Lei YP. Effects of periodontal therapy on metabolic control in patients with type 2 diabetes mellitus and periodontal disease: a meta-analysis. *Medicine (Baltimore)* 2014; **93**:e292.

Wang X, Han X, Guo X, Luo X and Wang D. The effect of periodontal treatment on hemoglobin a1c levels of diabetic patients: a systematic review and meta-analysis. *Public Library of Science One* 2014; **9**:e108412.

Wilson TG Jr. Periodontal diseases and diabetes. *Diabetes Educator* 1989; **15**:342-345.

Yun F, Firkova EI, Jun-Qi L and Xun H. Effect of non-surgical periodontal therapy on patients with type 2 diabetes mellitus. *Folia Medica (Plovdiv)* 2007; **49**:32-36.

Zhang H, Li C, Shang S and Luo Z. Scaling and root planing with enhanced root planing on healthcare for type 2 diabetes mellitus: A randomized controlled clinical trial. *Journal of Dental Sciences* 2013; **8**:272–280.