Long-term effect of non-surgical periodontal treatment on glycaemic control in patients with diabetes with periodontitis: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Non-surgical periodontal therapy consisting of scaling and root planning has been shown to be effective in the improvement of glycaemic control in patients with diabetes with periodontitis for up to 3 months. However, questions remain about this beneficial effect over a longer period of time. This systematic review and meta-analysis aims to determine the long-term effect (at least 6 months from the therapy) of non-surgical periodontal therapy with or without adjuvant on glycaemic control of patients with diabetes with periodontitis.

Methods and analysis This systematic review will include randomised control trials with a follow-up period of at least 6 months after initial therapy, with measurement of glycated haemoglobin as the primary endpoint. A literature search will be conducted in MEDLINE, CENTRAL, EMBASE, CINAHL, The Cochrane Oral Health Group Trials Register, and the US National Institutes of Health Trials Registry: ClinicalTrials.gov, from inception to 30 June 2020. Selection of studies, data extraction and bias assessment will be conducted independently by two reviewers. A DerSimonian-Laird random-effect meta-analysis will be conducted to pool studies deemed to be homogeneous. A subgroup analysis will be conducted in case of substantial heterogeneity. Egger’s test and observation of the funnel plot will be used to assess publication bias. The statistical analysis will be done using R V.4.0.0 software.

Strengths and limitations of this study

- This review will be one of the first assessing the long-term effect (over 6 months) of non-surgical periodontal therapy with or without adjuvant on glycaemic control in diabetics.
- Rigorous methods and robust statistical analyses will be used to minimise bias and provide accurate estimates.
- No language restrictions will be applied, allowing the maximum number of studies to be included in this review.
- The large and varied number of adjuvants to periodontal therapy is a source of heterogeneity that can limit the analysis of the data.
- The limited number of studies on the topic in low-income and middle-income countries may represent an important setback.

INTRODUCTION

Periodontitis is a chronic polymicrobial and inflammatory infection, initiated by an accumulation of pathogenic plaque called biofilm above and below the marginal gum, within which bacterial products cause a chronic, permanent and destructive inflammatory response. Severe periodontitis is a major cause of tooth loss, nutritional compromise, language impairment, low self-esteem and poor quality of life. About 45%–50% of adults suffer from periodontitis. This rate increases to 60% of subjects over 65 years old with a periodontitis. Severe periodontitis is the sixth most prevalent condition globally, affecting 10.8% of the world’s population or 743 million individuals, and is frequently found in patients suffering from chronic diseases such as diabetes mellitus.

Diabetes mellitus is a metabolic disorder characterised and identified by the presence of hyperglycaemia in the absence of treatment, due to defects in insulin secretion and/or action, disturbances of carbohydrate, fat and protein metabolism. According to WHO, 422 million people suffered from diabetes in 2014, that is, 8.5% of the adult population. This prevalence is constantly increasing, having doubled since the 1980s when it was estimated at 3.1%. There are six main types of diabetes: type 1 diabetes, type...
2 diabetes mellitus (T2DM), hybrid forms of diabetes, other specific types, unclassified diabetes and hyperglycaemia first detected during pregnancy. T2DM accounts for 90% of diabetes cases. Age is an important factor justifying the cohabitation of diabetes with periodontitis. Thus, the risk of developing diabetes like periodontitis increases with age.

Diabetes is a major risk factor for periodontal disease. The relationship between periodontal disease and diabetes is established in the literature and the mechanisms of a proposed two-way interrelationship. Glycated haemoglobin A (HbA1c) is recognised as a biomarker of glycaemic control in patients with diabetes and reflects equilibrium over the three last months. An HbA1c value greater than 7% indicates poor glycaemic control. Severe periodontitis is associated with an increase in glycated haemoglobin levels in patients with non-diabetes and diabetes. Similarly, there is an association between severe periodontitis and dyslipidaemia and an increase in serum markers of oxidative stress in T2DM. Furthermore, an improvement in serum HbA1c levels after non-surgical periodontal therapy (NSPT) in patients with T2DM with chronic periodontitis has been reported, with a reduction of about −0.36% (95% CI −0.54% lower to −0.19% higher). However, there is controversy in the literature regarding the improvement of glycemic control after the management of periodontitis in unbalanced patients with T2DM. Better periodontal health is associated with a decrease in glycated haemoglobin levels. While diabetic complications (retinopathy, nephropathy, neuropathic foot ulceration, various cardiovascular diseases and mortality) are associated with the presence of periodontitis. Then the long-term beneficial effect of periodontal treatment on glycemic control could improve the follow-up of patients with diabetes and the occurrence of those complications. Systematic reviews of randomised clinical trials by Engbreston and Kocher and Simpson et al, and the umbrella systematic review by Botero et al, provide evidence of an effect on improving glycaemic control in patients with diabetes with a reduction of HbA1c varying from −0.54% to −0.10% at three or 4 months after NSPT with or without adjuvant treatment. Nevertheless, the beneficial effect of the said treatment over a longer period (more than 6 months) remains unknown and has not yet been addressed by a synthesis of studies on the topic at a global scale. Thus, we propose this systematic review and meta-analysis protocol to critically synthesise data reporting the information on this effect over the long term. This study will provide evidence-based data to draw the attention of researchers, clinicians and health policy-makers to the importance of periodontal disease control in the overall management of people with diabetes mellitus.

**RESEARCH QUESTION**

For patients with diabetes with periodontitis, is nonsurgical periodontal treatment (NSPT) with or without adjuvant, effective in significantly reducing glycated haemoglobin for at least six consecutive months compared with no active treatment?

**OBJECTIVE**

This systematic review and meta-analysis aims to investigate the long-term effect of NSPT on glycaemic control of patients with diabetes.

**METHOD AND DESIGN**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocol standards were used to design this protocol (see online supplemental appendix 1).

**Criteria for inclusion of studies in the review**

Only randomised clinical trials with at least 6 months post procedure follow-up will be considered for the current review.

**Participants**

Studies including participants aged 15 years and above will be included. The diagnosis of diabetes mellitus must have been made in accordance with the WHO definition of type 1 and T2DM.

The diagnosis of periodontitis (adult or chronic, juvenile or aggressive periodontitis) will be included, as will the diagnosis of periodontitis by stage and grade, in accordance with the 2017 classification of periodontal disease.

Studies with inpatients or outpatients will be considered regardless of their history.

**Type of intervention**

NSPT encompassing scaling+root planning or subgingival debridement as well as provision of antimicrobial adjuvants; antiseptic or antibiotic (locally applied, by systemic administration) and complementary oral hygiene education will be considered as intervention.

Comparison will be made with no treatment, or routine care practice (supragingival scaling or oral hygiene instruction alone), or the use of placebo.

**Primary outcome**

The percentage of HbA1c at 6 months and above will be our primary endpoint.

**Secondary outcomes**

1. The change in the measure of clinical attachment.
2. The change in depth of periodontal pockets on probing.
3. The 1972 O’Leary Plaque Index (PI).
4. Gingival indices of inflammation and bleeding (bleeding on probing (BoP) Ainamo and Bay 1975).
5. Systemic biomarkers of oxidative stress such as: Total Antioxidant Capacity (TAOS), Malondialdehyde...
(MDA), superoxide dismutase (SOD), nitric oxide (NO).
6. Inflammatory biomarkers: C reactive protein and tumour necrosis factor (TNF-α) circulating level.
7. The occurrence of side effects of the therapy.
8. The occurrence of diabetes complications.

**Strategy for research and identification of relevant studies**

**Electronic search**
The identification of relevant studies will be made through individualised searches MEDLINE, CENTRAL, EMBASE, CINAHL, The Cochrane Oral Health Group Trials Register and the US National Institutes of Health Trials Registry: ClinicalTrials.gov, until 30 June 2020. The syntax used for searching in MEDLINE will be combined with the Cochrane Highly Sensitive Search Strategy (CHSSS) tool for the identification of randomised clinical trials, 2008 optimised version. The terms used in the search will be: “periodont*”, “periodontal diseases”, “chronic periodontitis”, “aggressive periodontitis”, “Diabetes Mellitus type 1”, “Diabetes mellitus type 2”, “glycated hemoglobin A”, “oral hygiene”, “dental scaling”, “root planning”, “periodontal therapy”, “randomised control trials” as topic, “time factors” associated with the Boolean operators AND, OR. Online supplemental tables 1 and 2 present the search strategy for PubMed and Cochrane Library which will be adapted to fit with other databases. No language restrictions will be applied. For articles published in languages other than English and French, an experienced translator in the language concerned will be contacted for translation. Only studies conducted in humans will be considered.

**Searching for other sources**
The following journals will be scanned as potential additional source of articles: Journal of Clinical periodontology, Journal of periodontology, Periodontology 2000, Journal of periodontal research. Concerning grey literature, the review authors will hand search the ‘Journal de parodontologie et implantologie orale’ and the ‘Revue internationale du college d’odontostomatologie africain et de chirurgie maxillofaciale’. Furthermore, references of all included articles will also be scrutinised.

**Exclusion criteria**
- Trials with a split-mouth or cross-over design.
- Studies that do not report HbA1c at 6 months.
- Studies with patients with gestational diabetes or metabolic syndrome.
- Any surgical procedure such as a sanitation flap or gingivectomy.

**Selection of studies for inclusion in the review**
After the implementation of the search strategy, all identified references will be imported into the Endnote software and duplicates will be removed. Two independent reviewers (WNB and CD) will evaluate the studies obtained (titles and abstracts) for inclusion. Only clearly irrelevant articles will be excluded. The full text of articles selected at this stage will be searched and retrieved by one reviewer (WNB). Subsequently, retrieved full texts will independently be assessed for their final inclusion by two reviewers, who will resolve any discrepancies by consensus. For studies published in more than one report, the one with the largest sample size will be considered. Studies for which the full text is not available either online or from the corresponding author will be excluded.

**Evaluation of the methodological quality and reporting of data**
The methodological quality and the risk of bias in the selected studies will be assessed using the tool for assessing the risk of bias in randomised clinical trials presented in the Cochrane Handbook of systematic reviews of interventions. Studies will be categorised according to a low, high and undetermined risk of bias (when residual uncertainty exists after evaluation by the criteria used). The criteria considered will be the following: randomisation sequence generation, concealment of allocation, blinded participants, blinded clinical operator, results with incomplete data, selective reporting of results, other biases. The quality of the diagnosis of diabetes will be judged: adequate (reported clinical confirmation), inadequate (patient presenting as diabetic), indeterminate (no mention of the author in the report). Studies with a high risk of bias and those with an undetermined risk of bias will be analysed separately.

**Data extraction and management**
The following data will be extracted from each study and reported in a preconceived data extraction form:
- General characteristics: the name of the first author, the year and country in which the study was conducted, the design of the clinical trial, the sample size, the allocation method, the binding and the characteristics of the groups being compared.
- The study population: source, type of diabetes, duration of diabetes, glycaemia control at inclusion, presence of other conditions. The nature and severity of periodontitis will also be recorded (chronic/adult, aggressive/juvenile, stage and grade, mild, moderate or severe periodontitis), alcohol, tobacco and medication use.
- The intervention: type of periodontal treatment (scaling+surfacing/debridement), motivation for oral hygiene, use of antimicrobials or other treatments, supragingival scaling, periodontal follow-up.
- The primary endpoint will be the initial HbA1c level after 3 months, 6 months and beyond.
- The secondary outcomes: baseline and follow-up clinical attachment loss levels, probing depth, PI and BoP, systemic biomarkers of oxidative stress such as: TAOS, MDA, SOD, NO. Inflammatory biomarkers: C reactive protein and TNF-α circulating level. The occurrence of diabetes complications and side effects of the procedure will be noted.
Data synthesis and analysis
To determine the long-term effect of NSPT, a DerSimonian-Laird random-effect meta-analysis of randomised clinical trials (if at least four similar studies are found) will be conducted. The mean difference of intervention and control group will be pooled together to obtain the overall effect size (standardised mean difference) and its 95% CI.

The statistical evaluation of heterogeneity will be done by the Cochran’s Q test $\chi^2$ and will be quantified by the I$^2$ test. The publication bias will be evaluated by the inspection of the funnel plot and the Egger’s test (if at least three studies). If substantial heterogeneity is found in our results, a subgroup analysis will be conducted to assess its source. The subgroup analysis will be conducted according to: the methodological quality of the studies, the severity of periodontitis, glycaemic control (HbA1c<7, 7–8.5 and >8.5), age, gender, smoking and other chronic diseases (high blood pressure, chronic kidney disease, joint disease, respiratory diseases, etc). The inter-rater variability for inclusion of studies between researchers will be assessed using Cohen’s $\kappa$ coefficient. Data analysis will be done using R software V.4.0.0.

Presentation and dissemination of results
The study selection process will be summarised using a flow chart. Quantitative data will be presented in tables of individual studies, as well as in summary tables and forest plots where appropriate. The quality scores and risk of bias for each eligible study will be indicated accordingly. Data for which it will not be possible to synthesise quantitatively (with a meta-analysis), a qualitative synthesis using tables and figures will be made, especially if the predictors reported are not the same in all the studies.

Patient and public involvement
Patients and the public will not be involved in the design or planning of the study.

Potential modifications
We do not plan to change the protocol to avoid reporting bias. However, if necessary, any changes in the review process will be reported for the sake of transparency.

ETHICS AND DISSEMINATION
Since primary data are not collected, ethical approval is not required. The final report will be published in a peer-reviewed journal.

Contributors WNB came up with the idea, WNB and AMD and CD designed the protocol. WNB wrote the manuscript. RNTN, AMD and HMB reviewed the manuscript critically for both methodology and content. WNB, AMD and CD are the guarantors of the review. The authors have approved the final version of this manuscript.

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REFERENCES


