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VICTOR BENTO OLIVEIRA

EFEITO DA TERAPIA PERIODONTAL SUBGENGIVAL NO CONTROLE GLICÊMICO DE PACIENTES COM DIABETES TIPO 2: REVISÃO SISTEMÁTICA E META-ANÁLISE DE ENSAIOS CLÍNICOS RANDOMIZADOS COM 6 MESES DE ACOMPANHAMENTO

FORTALEZA
2022

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Defesa de dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Federal do Ceará, como requisito parcial à obtenção do título de Mestre. Área de concentração: Clínica Odontológica.

Orientador: Prof. Dr. Rodrigo Otávio Citó César Rêgo

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RESUMO

O tratamento da diabetes mellitus tipo 2 (DM2) requer a compreensão de múltiplas vias metabólicas para manter os alvos glicêmicos adequados. A terapia periodontal é capaz de controlar a infecção oral e reduzir a carga inflamatória sistêmica. Assim, muitos ensaios clínicos investigaram o efeito potencial do tratamento da periodontite no controle glicêmico. Previamente, estudos secundários compilaram dados sobre esse tema, mas ainda há necessidade de esclarecimento sobre o efeito a longo prazo da terapia periodontal, sem uso de adjuvantes, no controle glicêmico de pacientes com DM2. Esta revisão sistemática visa responder a seguinte questão: a terapia periodontal subgengival é capaz de melhorar o controle glicêmico, reduzindo os níveis de hemoglobina glicosilada (HbA1c) em pacientes com DM2 e periodontite em comparação a pacientes não tratados após 6 meses de acompanhamento? Nove bases de dados eletrônicas foram acessadas para coletar informações primárias na literatura científica sem restrição ao tempo de publicação. Os critérios de inclusão foram: Ensaios Clínicos Controlados Randomizados (ECRs) com pelo menos 6 meses de acompanhamento após terapia subgengival (raspagem e alisamento radicular com ou sem acesso cirúrgico), com status periodontal avaliado por exame periodontal completo, uso de uma definição clara de periodontite com base em medidas clínicas e/ou radiográficas e controle glicêmico avaliado por HbA1c. Foram excluídos os estudos escritos em alfabeto não latino (romano) e aqueles que utilizaram terapia antimicrobiana sistêmica ou local (aplicação subgengival). Para a meta-análise, a diferença média ponderada (WMD) e o intervalo de confiança de 95% (ICs) foram calculados para HbA1c. O total de 11 estudos foi incluído na revisão sistemática e 10 na meta-análises (1.324 pacientes). A terapia subgengival resultou em uma redução de 0,24% (WMD=0,24, IC 95% 0,06 – 0,4; p=0,01) no nível de HbA1c em comparação com o tratamento periodontal não ativo. A certeza no corpo de evidências foi avaliada como moderada. Os resultados desse estudo mostram que a terapia periodontal subgengival está associada a uma melhora significativa do controle glicêmico ao longo de seis meses em pacientes com DM2 e periodontite.

Palavras-chave: Periodontite; Diabetes Mellitus tipo 2; HbA1c

ABSTRACT

The treatment of diabetes mellitus type 2 (T2DM) requires understanding of multiple metabolic pathways in order to maintain appropriate glycemic targets. Periodontal therapy is able to control the oral infection and reduce the systemic inflammatory burden, thus, many clinical trials investigated the potential effect of treating periodontitis on glycemic control. Previously, secondary studies summarized data about that topic, but there is still a need for clarification on the long-term effect of periodontal therapy (without the use of adjuvants) on glycemic control of patients with T2DM. This systematic review aims to answer the following question: Is subgingival periodontal therapy able to improve glycemic control by reducing glycated hemoglobin (HbA1c) levels in patients with T2DM compared to untreated diabetic patients after 6-months of follow-up? Nine electronic databases were accessed to collect primary information in the scientific literature without time restriction. The inclusion criteria were Randomized Controlled Clinical Trials (RCTs) with at least 6-months follow-up after subgingival therapy (scalling and root planing with or without open flap procedure), with periodontal status assessed by full mouth examination and a clear definition of periodontitis based on clinical and/or radiographic measures. The glycemic control should have been assessed by HbA1c. Studies written in non-Latin (Roman) alphabet and those that used systemic or local-delivery antimicrobial therapy were excluded. For meta-analysis, weighted mean differences (MDs) and 95% confidence intervals (CIs) were calculated for HbA1c. A total of 11 studies were included in the systematic review and 10 in meta-analyses (1324 patients). Subgingival therapy resulted in 0.24% lower HbA1c (WMD=0.24, 95%CI 0.06 – 0.41; p=0.01) compared to non-active periodontal treatment. The certainty in the body of evidence was assessed as moderate. The results of this study showed that subgingival periodontal therapy is associated with a significant improvement of glycemic control over six months in patients with T2DM and periodontitis.

Key-Words: Periodontitis; Type 2 Diabetes Mellitus; HbA1C

LISTA DE ABREVIATURAS E SIGLAS

DM2	Diabetes Mellitus Tipo 2
NIC	Nível de Inserção Clínica
CONSORT	*Consolidated Standards of Reporting Trials*
DP	Desvio Padrão
ECR	Ensaio Clínico Randomizado
EUA	Estados Unidos da América
FGP	Glicemia Plasmática em Jejum
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	Hemoglobina Glicosilada
IC	Intervalo de Confiança
IHO	Instrução de Higiene Oral
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PROSPERO	International Prospective Register of Systematic Reviews
PS	Profundidade de Sondagem
RAR	Raspagem e Alisamento Radicular
RevMan	Software Review Manager
RoB	Ferramenta *Risk of Bias 2*
WMD	Diferença de Média Ponderada

SUMÁRIO

1 INTRODUÇÃO GERAL

A associação entre periodontite e diabetes mellitus tipo 2 (DM2) é amplamente estudada e possui plausibilidade biológica bem estabelecida e coerente. Os resultados de diversos estudos observacionais e ensaios clínicos evidenciam a significante relação bidirecional entre ambas as doenças, assim como a simultaneidade de ocorrência e progressão entre elas em pacientes mais velhos.

Estudos representativos da população americana foram realizados a partir do National Health and Nutritive Examination Survey (NHANES).(GARCIA; TARIMA; OKUNSERI, 2015; TSAI; HAYES; TAYLOR, 2002) Uma análise dos dados do NHANES 1988-1994 mostrou que o grau de controle glicêmico, mensurada através da hemoglobina glicosilada (HbA1c), foi a variável mais importante na determinação do risco para a presença de periodontite severa em indivíduos com DM2 e que adultos com DM2 com pobre controle glicêmico (HbA1c > 9%) apresentavam três vezes maior risco de ter periodontite severa em comparação aos sem diabetes.(TSAI; HAYES; TAYLOR, 2002) Posteriormente, uma análise do NHANES 2009-2012 observou da mesma forma que o risco para periodontite aumenta à medida que crescem os níveis de glicemia.(GARCIA; TARIMA; OKUNSERI, 2015)

Indivíduos sem diabetes e com periodontite apresentam pior controle glicêmico e maior risco de desenvolver diabetes.(GRAZIANI; GENNAI; SOLINI; PETRINI, 2018) Estudos longitudinais observaram que a severidade da doença periodontal está associada a incidência de intolerância à glicose e diabetes em pacientes não diabéticos ao longo de 10 anos(SAITO; SHIMAZAKI; KIYOHARA; KATO *et al.*, 2004) e que a presença de bolsas periodontais (profundidade de sondagem >3mm) aumentam o risco de hiperglicemia incidente em 33%.(CHIU; LAI; YEN; FANN *et al.*, 2015)

Uma vez que a eficácia da terapia periodontal é bem estabelecida na literatura, e o manejo de paciente com doença periodontal é amplamente disseminado entre cirurgiões-dentistas e passível de condução em ambiente clínico, é importante saber para prevenção e controle futuro da diabetes se a periodontite realmente desempenha um papel no desenvolvimento e controle

da DM2 e das suas complicações potencialmente fatais.(LALLA; PAPAPANOU, 2011; TAYLOR; PRESHAW; LALLA, 2013)

Diversos ensaios clínicos randomizados já foram conduzidos partindo da hipótese de que a infecção e inflamação associada à periodontite contribuem significativamente para a carga inflamatória sistêmica e afeta negativamente a eficiência do controle farmacológico da DM2.(GENCO; GRAZIANI; HASTURK, 2020) Dentre os estudos de maior amostra e robustez metodológica, os resultados sobre o efeito da terapia periodontal no controle glicêmico são divergentes, pois mostram uma redução clinicamente relevante nos níveis de HbA1c ao longo do tempo(D'AIUTO; GKRANIAS; BHOWRUTH; KHAN *et al.*, 2018) ou um efeito não é significativo.(ENGEBRETSON; HYMAN; MICHALOWICZ; SCHOENFELD *et al.*, 2013)

2 PROPOSIÇÃO

Objetivo Geral

Avaliar o efeito da terapia periodontal no controle glicêmico de pacientes com DM2 e periodontite.

Objetivos Específicos

1. Sumarizar a evidência científica sobre o efeito da instrumentação subgengival na redução dos níveis de HbA1c após 6 meses de intervenção em pacientes com DM2 e periodontite.
2. Calcular a mudança nos níveis de HbA1c após 6 meses de intervenção através de uma meta-análise e avaliar a relevância clínica dessa mudança
3. Apontar considerações metodológicas, analisar o risco de viés e a qualidade do corpo da evidência sobre a temática.

3 CAPÍTULOS

A presente dissertação segue o regimento interno do Programa de Pós-Graduação em Odontologia (PPGO-UFC), que regulamenta o formato alternativo de teses e dissertações e permite a inserção de artigos científicos de autoria ou co-autoria do candidato (Anexo 1). Esse trabalho passou por revisão de língua portuguesa. Por se tratar de uma pesquisa secundária e não envolver diretamente seres humanos ou animais, não houve necessidade de submissão a um comitê de ética em pesquisa. O protocolo da revisão sistemática foi registrado na plataforma PROSPERO, número CRD42021234864 (Anexo 2). A dissertação é composta por um capítulo, conforme descrito a seguir:

Capítulo 1: *Effect of Subgengival Periodontal Therapy on Glycemic Control in Type 2 Diabetes Patients: Meta-Analysis and Meta-regression of 6-months Follow-up Randomized Clinical Trials*.

O presente artigo será submetido à publicação no periódico "*Journal of Clinical Periodontology"* (ISSN: 1600-051X; Fator de Impacto: 7.478), seguindo às normas de submissão da revista (Anexo 4).

CAPÍTULO 1

TITLE PAGE

Título: Effect of Subgengival Periodontal Therapy on Glycemic Control in Type 2 Diabetes Patients: Meta-Analysis and Meta-regression of 6-months Follow-up Randomized Clinical Trials.

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Author's contribution:

VBO and ROR contributed to the conception and design of the study. VBO, ROR and FWGC contributed to the identification, screening and study selection and extraction of data. ROR and ANH were involved in the quantitative/statistical analysis of the data. VBO and ROR were responsible for data interpretation, writing and editing of the article. FWGC and ANH were involved in reviewing the manuscript.

Abstract

Aim: Previous studies demonstrated that various forms of periodontal treatment may improve glycemic control in type 2 diabetes mellitus (T2DM) patients. However, the effect of the gold-standard treatment, comprised exclusively by mechanical debridement, still needs to be summarized and evaluated. Therefore, the following question was addressed: is standard periodontal therapy, comprised by mechanical debridement without adjuvants, able to improve glycemic control in patients with T2DM compared to untreated patients after 6 months of follow-up? **Methods:** Nine electronic databases were searched. Randomized trials of at least 6 months of follow-up after therapy (mechanical debridement with or without open flap) were included. Studies using systemic or local-delivery antimicrobial therapies were excluded. **Results:** A total of 10 studies were included in the quantitative analyses (1324 patients). Mechanical periodontal therapy resulted in 0.24% lower glycosylated hemoglobin (95%CI 0.06–0.41; p=0.01) compared to no periodontal treatment. The certainty in the body of evidence was assessed as moderate. Meta-regression demonstrated that the percentage of females and time of diabetes diagnosis significantly explained the observed heterogeneity. **Conclusion:** Subgengival periodontal therapy results in a significant and clinically relevant improvement of glycemic control over six months in patients with T2DM and periodontitis.

Keywords: Periodontitis, Type 2 Diabetes Mellitus, HbA1c

Clinical Relevance:

Scientific Rationale: Periodontitis is a focus of infection that potentiates the systemic burden of inflammation. Subgengival periodontal therapy controls the infection from periodontitis and reduces inflammation at a local and systemic level, being able to improve metabolic parameters.

Main Findings: Subgengival instrumentation is able to reduce glycosylated hemoglobin levels by 0.24% after 6 months of follow-up.

Practical Implications: Subgingival periodontal therapy works as a non-pharmacological complementary treatment of reducing hyperglycemia in patients with T2DM and periodontitis.

INTRODUCTION

The International Federation of Diabetes estimated that in 2021 there were 537 million people (age 18–99 years) living with diabetes worldwide, representing a large social, financial and health system burden across the world.[1-3] According to a Global Burden of Disease study, the prevalence of severe periodontitis is near 7.5% worldwide, peaking at the age group from 55 to 60 years old, being the sixth most prevalent disease in the world.[4,5] Diabetes increases the risk of periodontitis incidence by 86%,[6] consisting in a risk factor for the progression of periodontitis[7] and hindering the response to periodontal therapy[8] by causing a hyperinflammatory response to the bacterial challenge in periodontitis and impairing tissue repair.[9,10]

Due to the destruction of the tooth support apparatus (periodontal ligament, cementum and alveolar bone), severe periodontitis may lead to tooth loss and cause changes in food ingestion, as low ingestion of nutritional and healthy foods,[11] affecting patients' quality of life and increasing the risk of chronic diseases.[12] Periodontitis works as a focus of local infection and a source of low-grade chronic inflammation,[13] which allows the translocation of bacteria and their products to distant sites in the body, as well as the constant production and dissemination of inflammatory mediators through the bloodstream,[13,14] contributing to the systemic inflammatory burden, increasing the risk of insulin resistance,[15] development of diabetes[16] and its complications.[17]

Periodontal therapy requires a combination of therapeutic modalities with safety and efficacy already well-established in the literature,[18] primarily targeting the microbial component of the disease by mechanical debridement of tooth surfaces with or without flap surgery. Furthermore, mechanical therapy can be combined with the use of adjunctive pharmacotherapies, as antimicrobials (local or systemic).[10]

Diabetes is not a single disorder, and the heterogeneity of the disease is becoming more evident with better understanding of the multiple pathophysiological defects underlying it. Thus, addressing multiple metabolic pathways simultaneously leads to an increased hypoglycemic effect.[19] In addition to advances in complementary medicine research, in recent years there has also been an interest in adopting safe and effective non-drug strategies for the complementary treatment of diabetes.

It is important to know for future prevention and control of diabetes whether periodontitis indeed plays a role in the disease control and its potentially fatal complications.[10,20] Changes in HbA1c% levels of type 2 diabetes patients undergoing basic periodontal therapy (scaling and root planing) suggest that periodontitis significantly contributes to the inflammatory burden and negatively affects the efficiency of T2DM pharmacological control and that treating an oral infection may result in better glycemic control.[29] Thus, considering that periodontal therapy is able to control the infection and reduce inflammation at local and systemic levels,[30,31] the effect of this intervention could provide another basis for complementary glucose reduction in addition to the pharmacological therapy already used by diabetic patients.

Many systematic reviews with meta-analysis have described the effect of non-surgical periodontal therapy in reducing HbA1c% levels in patients with periodontitis and T2DM.[32-34] Most of these reviews could summarize data on the short-term (3 months) effect of therapy, mixing various periodontal therapeutical approaches, including or not antimicrobial adjuvants, such as antibiotics and laser therapy. Therefore, there is still a need for clarification on the medium- to long-term (at least 6 months) effect of periodontal therapy without the use of adjuvants. Thus, this systematic review aimed to answer the following question: is subgingival periodontal therapy, comprised by mechanical debridement without adjuvants, able to improve glycemic control in patients with T2DM compared to untreated patients after 6 months of follow-up?

METHODS

Standards of Reporting

This study was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020

recommendation[35]. The methodology available in the Cochrane Handbook for Systematic Reviews of Interventions[36] was taken as basis for this review. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42021234864.

Review Question

The investigation question was designed using the PICOTS acronym: Population (P) – Patients with Type 2 Diabetes Mellitus (T2DM) and Periodontitis; Intervention (I) – Mechanical debridement with or without surgical access; Comparison (C) – Patients with diabetes and periodontitis that did not receive subgingival intervention; Outcome (O) – Glycemic control assessed by glycosylated hemoglobin (HbA1c%) levels; Time (T) – At least 6 months of follow-up; Setting (S) – Randomized Clinical Trials (RCTs).

Selection Criteria

Studies must meet the following inclusion criteria: (1) RCTs with at least 6-month follow up; (2) Studies with periodontal status assessment applying full mouth examination; (3) Studies with a clear definition of periodontitis based on clinical and/or radiographic measurements of periodontal conditions, e.g. Periodontal Probing Depth (PPD), Clinical Attachment Level (CAL) or Alveolar Bone Height; (4) Studies with diabetic test group undergoing mechanical periodontal therapy (subgingival scaling and root planing or scaling with open flap surgery) compared to diabetic positive control group ongoing non-active periodontal therapy (oral hygiene instructions, prophylaxis or supragingival scaling) or without periodontal intervention (no treatment); (5) Studies in which the glycemic control was assessed by glycosylated hemoglobin (HbA1c%) levels.

The following studies were excluded: (1) RCTs written in non-Latin (Roman) alphabet; (2) Studies that used systemic or local (subgingival) antimicrobial therapy; (3) Studies that used laser as the only form of subgingival therapy; (4) Multiple studies that evaluated the same sample were excluded, with only the longest follow-up study being included.

Source of Information and Search strategy

Nine online databases were accessed to collect primary information in the scientific literature from the initial indexing moment of the bases up to 3 February 2021: MEDLINE (through PubMed), Scopus, Embase, Web of Science, Latin American and Caribbean Health Science Information – LILACS (through Virtual Health Library), Livivo, DOSS (through EBSCO host), CINAHL (through EBSCO host) and Cochrane Library. The gray literature available on ProQuest, Open Grey and Google Scholar (up to 6 March 2021) was also searched. In addition, the reference list of selected RCTs, which consisted in previously published reviews, either systematic or non-systematic, were hand searched for additional articles. All database research was updated after data extraction (28 April 28 2021) to check if there was any new study.

A search algorithm built by combining indexed terms, non-indexed terms and their synonyms was individualized to accommodate the individual requirements of each database (Supplementary). The sensitivity of the search algorithm was assessed in PubMed, whereupon at least seven of eight sentinel articles selected by the authors should be retrieved by the final search algorithm.

Selection Process

References retrieved from the literature searches were imported into Endnote X7 for exclusion of duplicates. This process was complemented in an Excel spreadsheet. The search and selection of articles were performed in two stages by a single researcher (V.B.O.). Firstly, a screening against the eligibility criteria of all electronic citations found regarding their titles and abstracts was carried out. Secondly, the full text of potential articles was read based on the inclusion criteria. Both stages were independently checked by two other researchers (R.O.R. and F.W.G.C.) and a study was considered eligible and selected if it received a positive evaluation by the three researchers. Any discrepancies were discussed and resolved by consensus.

Data Collection Process and Data Items

A pilot spreadsheet was filled out by V.B.O. with data from three of those included articles and independently checked by R.O.R. and F.W.G.C. All the discrepancies that emerged were solved by consensus discussion and the

necessary modifications were made in the spreadsheet before the final extraction process was undertaken.

The relevant methodological data and results with statistical measures were extracted from the articles (Supplementary). The online tool WebPlotDigitizer 4.4 (Pacifica, California, USA – Ankit Rohatgi, November 2020) was used to extract data from graphic images when the results were not reported in numbers. All corresponding authors of included studies were contacted via email until February 2022, in cases where data were not informed or not clearly described on the paper.

Risk of Bias Assessment

The risk of bias assessment in individual studies and among them was independently performed by two researchers (V.B.O. and R.O.R.). The Cochrane Collaboration critical risk of bias assessment tool for RCTs (RoB 2)[37] was used and a previous training was done with three articles selected in the review. Discrepancies raised during the process were discussed with a third researcher (F.W.G.C.) until an agreement was reached. The following domains of RoB 2 were used to assess the risk of bias. The risk of bias was judged as high, low, or unclear (when there is a lack of sufficient information for judgment) and a summary graphic illustration done with Review Manager (RevMan) [Computer program] version 5.4.1, The Cochrane Collaboration, 2020.

Effect Measures and Synthesis Methods

The primary outcome of this systematic review was the HbA1c concentration in percentage. Meta-analytical commands were performed to compare baseline and final HbA1c concentrations between. Means and standard deviations (SD) were used to estimate the weighted mean difference (WMD) and its 95% confidence interval (95%CI). Quantitative analyses were conducted applying linear meta-analyses. Heterogeneity was assessed by the Q test and quantified with the I^2 statistic. Random effects models were applied using the DerSimonian and Laird method due to high heterogeneity across studies. Publication bias was assessed using funnel plots and the Egger test.

The sources of heterogeneity were assessed applying linear meta-regression. The following study characteristics were included in meta-

regression models as continuous variables: year of publication, percentage of females in the test group, mean age of participants in the test group, percentage of smokers in the test group, mean HbA1c baseline, and final mean pocket depth in the test group. The time of diabetes diagnosis was dichotomized using the median among the included studies (8.5 years of diabetes). Stratified analysis was conducted according to the two categories of time for diagnosis to provide descriptive estimates of the effect of this variable on the final concentration of HbA1c.

All analyses were conducted using Stata software version 15 (Stata Corp., College Station, Texas, USA).

Certainty Assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE)[38] guidance was followed to obtain the level of certainty in the body of evidence for direct estimates. A summary of evidence profiles was provided using GRADEpro Guideline Development Tool software (available on http://gdt.guidelinedevelopment.org).

RESULTS

Study Selection

The literature search through main databases identified 1662 records and a total of 667 were retained for further analysis after the exclusion of 995 duplicates. In the gray literature and manual search, 725 records were identified, and 33 duplicates were excluded. A total of 1359 potentially eligible studies were screened and, out of these, 1291 were considered unsuitable according to titles and abstracts. Afterwards, 68 studies were fully accessed and 57 were excluded for different reasons. After full-text evaluation, 11 RCTs fulfilled the criteria and were selected for data extraction as shown in the study flowchart (Figure 1). Finally, a total of ten studies provided data for quantitative analysis.

Study Characteristics

Methodology characteristics

Table S1 summarizes the methodology characteristics of the included studies. The 11 trials were performed in different populations from distinct countries: Brazil,[21] China,[22,27,28,39] Greece,[40] India,[41] Japan,[26] Spain,[42] UK[23] and USA[24]. The study period took place in different years, between 2008 and 2018, and ranged from 11 to 40 months. One study[41] had four arms of comparison, two studies[22,28] had three arms, while the other eight studies had two arms. Ten studies provided details of sample size calculation, considering type I error (α=0.05) and power of 80% or higher.

Periodontitis and T2DM Diagnosis

Details about the criteria used to define periodontitis by each study are shown in Table 1. Different T2DM diagnostic criteria were reported in eight studies, as previous diagnosis by a clinician[24,26] or standards established by the World Health Organization[21,22,39] and the American Diabetes Association.[23,28,41] T2DM treatments were mainly based in different combinations of oral hypoglycemic drugs, insulin supplementation and diet.

HbA1c Measurements

Different laboratory methods for HbA1c measurement were used, such as High Performance Liquid Chromatography (HPLC),[21,23,24,26,40,42] Boronate-Affinity Chromatography,[22] Latex Agglutination Inhibition Assay,[41] Immunoturbidimetry[27] and Cation Exchange Chromatography.[28] Engebretson et al. [24] quoted a reference range for the HbA1c test on trial protocol and the method was calibrated against the National Glycohemoglobin Standardization Program (NGSP) from the USA. The method's coefficient of variation (CV) for HbA1c was described by Engebretson et al.[24] (1.4-1.9%) and by Chen et al.[22] (1.2-2.8%). The baseline HbA1c levels ranged from 7.31±1.23[22] to 8.4±1.1[39] for test groups and from 7.25±1.49[22] to 8.3±1.2[39] for control groups, with no significant difference between study groups. A significant decrease on the HbA1c level was demonstrated in five studies over 6months for the periodontal therapy group.[27,28,40-42]A neutral effect of periodontal therapy was showed as a non-significant decrease in four studies[21-23,26] and as a non-significant increase in two.[4,39]

Participant Characteristics

Mean age of participants varied from 51.82 ± 5.85[41] to 64.7 ± 8.3[39] (Table 2). The eleven studies included provided a total sample of 1413 adults (>18 years old) with T2DM and periodontitis; among these, 1390 were statistically analyzed (Intention to Treat analyses=1147; Per protocol analyses[22,27,28]=243). The sample was composed of 641 (46.1%) females and 749 (53.9%) males. Nine studies informed a mean time of T2DM diagnosis ranging from 4±1.76[27] to 17±9.21[39] years, with no significant difference between study groups. Body Mass Index (BMI) was reported in ten studies, ranging between 22.14±0.72[27] and 34.2±6.7.[24] Smoker participants were included in eight studies, [22-24,26,39,40,42] representing more than 40% of the sample in five studies.

Risk of Bias

Based on methodological details available on published articles, protocol registry, supplementary material and information provided by contacted authors, more than 70% (9/11) of the evidence summarized in this review comes from studies with high risk of bias. Nine studies had at least one domain assessed as high risk of bias. None of the eleven studies were assessed as low risk of bias. The main source of high risk of bias was the lack of blinding in participants and personnel who delivered the clinical intervention, followed by attrition bias. Figures 2a-b show the graphic and the summary for risk of bias, respectively.

Meta-analysis

The HbA1c values from Artese et al. could not be extracted, so this study was excluded from the quantitative analyses. The ten studies included in the meta-analysis accounted for a total of 1324 patients. Figure S1 shows the forest plot of baseline HbA1c concentration and demonstrated that there was no statistically nor clinically significant differences between test and control groups (WMD=-0.02, p=0.34). Contrarily, there was a statistically significant difference between groups in the final HbA1c concentration (Figure 3). Mechanical periodontal therapy resulted in 0.24% lower HbA1c (WMD=0.24, 95%CI 0.06 – 0.41; p=0.01) compared to control group. There was no evidence of publication

bias as observed in the funnel plot (Figure S2) and determined by the Egger test (p=0.29).

Meta-regression

One study[26] had missing data for the variables of interest analyzed in the meta-regression and was excluded. This study had the smallest sample size, and the meta-analytical estimates did not change after its exclusion (Figure S3), also resulting in a WMD for the final HbA1c concentration equal to 0.24% (95%CI 0.06 – 0.42; p=0.01) in favor of mechanical periodontal therapy. Therefore, nine studies with 1287 patients were included in the meta-regression.

A stratified analysis according to time for diabetes diagnosis in the test group (Figure 4) demonstrated that subgingival therapy resulted in 0.33% lower HbA1c levels than the control group (p<0.001) in studies with an average time lower or equal to 8.5 years. Nevertheless, in studies with greater average time for diabetes diagnosis, there were no significant differences between test and control groups in final HbA1c concentration (WMD=0.16, p=0.44).

Table S2 shows the findings of the meta-regression analysis. In the univariable models, none of the variables explained the heterogeneity at the 0.05 significance level. Nevertheless, in the final multivariable model, the percentage of females in the test group and time for diabetes diagnosis were significantly associated with the differences between test and control groups in the final HbA1c concentration. A higher percentage of females in a study was associated with 0.04% greater difference in HbA1c levels in favor of the test group, whereas a diabetes diagnosis of more than 8.5 years was associated with 0.30% lower difference in HbA1c levels in test groups than in control groups.

Certainty in the Body of Evidence

There is moderate certainty in the body of evidence on the HbA1c-lowering effect of subgingival periodontal therapy alone in patients with T2DM and periodontitis. Thus, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different and future research may change the estimate and the recommendation. Table S3 shows

the certainty of evidence appraisal according to GRADE. One level was downgraded for high risk of bias.

DISCUSSION

The present systematic review summarized the available evidence on HbA1c-lowering effect of mechanical periodontal therapy in patients with T2DM and periodontitis. The meta-analysis of ten studies including 1324 participants from distinct global regions showed 0.24% lower HbA1c 6 months after therapy compared to the control group. It has been well-established that HbA1c is an important clinical outcome to consider in individuals with T2DM, and glycemic management is a key component of clinical guidelines for T2DM.[43] A progressively increasing risk for cardiovascular diseases and total mortality was associated for each higher percentage point in HbA1c levels, and no risk increase at low HbA1c levels even for patients with longer diabetes duration.[44] These estimates put into perspective the clinical relevance of the effect of periodontal therapy on glycemic control.

There is limited evidence on the assumption of the true long-term effect of periodontal therapy on glycemic control. Many of the previous pooled analyses available on literature come from studies with 3 months of follow-up and they usually compile studies that used adjunctive therapies, as antibiotics, with data from the studies that did not use them. Previous systematic reviews with meta-analysis, despite having demonstrated some reduction in HbA1c levels after periodontal intervention, failed to find benefits for periodontal therapy due to the lack of significant difference at a 6-month follow-up.[45,46]

A Cochrane review[32] published in 2015 found evidence to demonstrate that the treatment of periodontitis does improve glycemic control in people with diabetes, with a mean percentage reduction of 0.29% in HbA1c levels at 3-4 months. However, the authors did not detect any evidence that periodontal treatment results in a significant effect after 6 months, representing a non-significant mean percentage of 0.02%. This data was extracted from a pooled analysis of five studies, combining 826 patients. Four of these studies had less than 150 patients and one used a topical antibiotic.

The finding of the present systematic review is consistent with previous reviews where a significant benefit of periodontal therapy has been shown with

a reduction of 0.5% to 1.18% in HbA1c levels after 6 months.[34,47,48] To better understand the clinical significance and applicability of a 0.24% reduction in HbA1c levels, a comparison can be made with the efficacy of some oral antidiabetic agents. For instance, the drug rosiglitazone, a thiazolidinedione derivative, can achieve a reduction of 0.22% in HbA1c levels when used as add-on drug in patients receiving metformin-based background therapy.[49] Another comparative result is from the systematic data about sulfonylurea gliclazide efficacy. This drug belongs to the sulfonylurea class and can low HbA1c levels significantly more than other oral insulinotropic agents with a difference of 0.11%.[50] This result gives scientific support to international guidelines to keep this drug in the core of pharmacological approach to T2DM management.[51]

Considering that it is necessary to manage lifestyle and many systemic components to reduce the risk of critical complications in patients with diabetes, the effect of the modest reduction in HbA1c levels was questioned about its major population-level effect, mainly when the estimated time of periodontal therapy effectiveness is taken into account.[32] Many population-based studies already observed a reduction in the risk of diabetic complications after an improvement in glycemic control. The United Kingdom Prospective Diabetes Study observed, after 10 years of follow-up, that the risk of diabetic complications is strongly associated with hyperglycemia and any improvement in glycemic control across the diabetic range is likely to reduce the risk of diabetic complications.[52]

Data from the Swedish National Diabetes Register (NDR) observed the improvement of risk factor control by treatment goal achievement, which includes glycemic control measured by HbA1C levels; in the first years of T2DM, being is associated with a low remaining modifiable risk of 20% for coronary heart disease in 10 years.[53] After 6 years of follow-up, a relative risk reduction for fatal/nonfatal cardiovascular disease in 35% was associated with a decrease of 0.5% in HbA1c levels only.[54]

Despite the statistical significance of the result of the present meta-analysis, a cautious interpretation is necessary to make a suggestion due to some methodological aspects of the studies included and to the certainty of the evidence provided by them. The meta-regression demonstrated that the clinical

benefits of periodontal therapy on glycemic control shown in the present study are associated with some baseline characteristics of the sample. A higher percentage of females in a study and a diagnosis of diabetes of more than 8.5 years explained approximately 99% of the variability between studies.

The baseline HbA1c level variable did not explain the heterogeneity between the studies included in this review, different from other analysis of covariates which showed that a high HbA1c level at baseline (>8%) significantly and independently predicted the variance in HbA1c decline over 6 months, and, consequently, the clinical benefit of the periodontal intervention.[40,47] A recent meta-regression analysis[48] demonstrated that much of the benefits seen from periodontal therapy on changes in HbA1c levels are due to limitations in study design and the contradictory results seen in RCTs may be mostly explained by sample size and risk of bias.[48] It is important to highlight that the high risk of bias assessed in the studies included in the present review can be explained by the mechanical nature of the intervention, which can explain the lack of blinding of operators and participants.

Certain limitations can be pointed out in this review. An extensive search in the main databases and gray literature was made to redeem as many papers as possible, but it is not possible to guarantee that all studies on this topic were included, even because of the language restriction. The eligibility criteria adopted in this review accepted the non-uniformity of periodontitis classification and the diagnosis criteria defined by each study, which is considered a common source of variability in meta-analyses[6] that can influence the prevalence estimates of periodontitis between populations.[55] The severity of periodontitis defined by case criteria and the success of periodontal therapy to eliminate the periodontal infection and its contribution to systemic inflammation burden should also be highlighted due to the variability of intervention protocols adopted by each study.

The present study emphasizes that periodontal therapy has a clinical significance beyond improving periodontal status and maintaining natural dentition; therefore, its applicability should be beyond dental setting. It is also supported that patients with T2DM may be followed by a multidisciplinary team with a dentist (periodontist). They should be screened for periodontitis, have access to dental treatments and be orientated to keep a good oral health.

Further RCTs are required to strengthen the evidence on this topic. Future studies should be based on the larger trials[23,24] included in this review to ensure sufficient sample size and power, provide longer follow-up periods (>6 months), adopt robust diagnosis criteria for periodontitis[4,56] and diabetes.[57] It is also recommended to provide complete data of full mouth periodontal examination (including microbiological evaluation), perform a broad metabolic evaluation (including immune-inflammatory evaluation) and, finally, evaluate outcomes related to the patient, as quality of life outcomes, and those important to health promoters, as cost-effectiveness data.

CONCLUSION

The results of this systematic review and meta-analysis show that mechanical periodontal therapy, without the use of systemic or local-delivery drugs, is able to improve glycemic control by reducing glycosylated hemoglobin levels at 0.24% in patients with T2DM after 6 months of follow-up. The quality of the body of evidence for this finding was assessed as moderate and future research can change this result.

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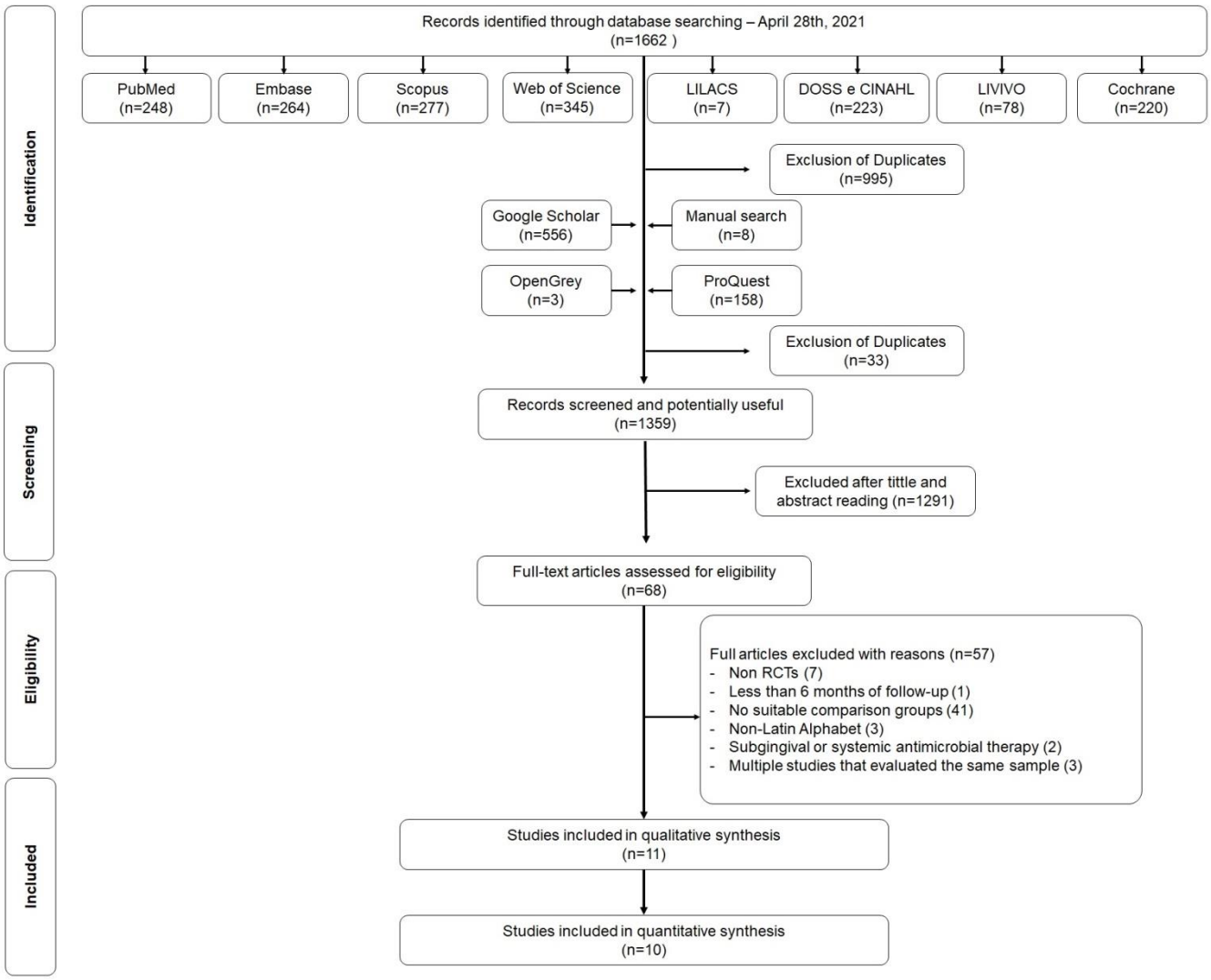

FIGURE 1 – PRISMA flowchart.

TABLE 1 - General characteristics of the included studies regarding the diagnosis of T2DM and periodontitis. (cont.)

Study	T2DM Diagnostic Critieria	T2DM Treatment changes	Hba1c Laboratory Method	Minimum T2DM Duration (months)	Periodontitis Classification	Periodontitis Diagnostic Criteria	Periodontal Examination	Periodontal Probe	Clinical Periodontal Parameters	Radiographic Periodontal Parameters (Method)	Minimum Number of Teeth
Artese et al. 2015	WHO 2006(ORGANIZATION, 2006)	No	HPLC	> 36	Generalized severe chronic Periodontitis	Number of PPD sites ≥ 30%, CAL > 4 mm and BOP	Six sites/tooth, excluding third molars	UNC-15	PI, GI, BOP, PPD e CAL	NA	≥15
Chen et al. 2012	WHO 1998(ALBERTI; ZIMMET, 1998)	NI	Boronate-Affinity Chromatography	>12	Chronic Periodontitis. including slight, moderate and severe periodontitis	AAP,1999(ARMITAGE, 1999)	Six sites/tooth, excluding third molars	Williams	PI, BOP, PPD, CAL, GL	NA	≥16
D'Aiuto et al. 2018	ADA 2016(ASSOCIATION, 2016)	Yes (similiar between groups)	HPLC	≥ 6	Moderate to Severe Periodontitis	≥20 periodontal pockets, PPD > 4 mm and BOP and ABL >30%	Six sites/tooth	NI	PI, BOP, PPD, GL	Marginal Alveolar Bone Loss (NI)	≥15
Engebretson et al. 2013	Previous diagnosis by a physician	Yes (similiar between groups)	HPLC	≥ 3	Moderate to Advanced Chronic Periodontitis	CAL and PPD ≥ 5 mm in 2 or more quadrants of the mouth	Six sites/tooth	UNC-15	PI and GI (6 index teeth); BOP, PPD e CAL (6 sites/tooth)	Alveolar Bone Height (OPG)	≥16
Kaur et al. 2015	ADA 2011(ASSOCIATION, 2011)	NI	Latex Agglutination Inhibition Assay	≥ 12	Moderate or Severe generalized chronic periodontitis	CDC/AAP, 2012(EKE; PAGE; WEI; THORNTON-EVANS *et al.*, 2012)	Six sites/tooth, excluding third molars	Williams	PI, IG,SS, PPD, CAL, GL, PISA, PESA, ALSA, RSA	NA	≥ 12
Koromantzos et al. 2011	N.I	No	HPLC	NI	Moderate to Severe	At least 8 sites with PPD ≥ 6mm and 4 sites with CAL ≥ 5 mm, distributed in at least two different quadrants	Six sites/tooth, including third molars	Manual Probe	IG, PPD, CAL, BOP, Tooth Loss	NI (OPG)	≥16

NI= Not Informed; T2DM= Type 2 Diabetes Mellitus; HbA1c= Glycated Hemoglobin; FPG= Fasting Plasma Glucose; PPG= Post-Pandrial Glucose; HPLC= High Performance Liquid Chromatography; UNC-15= University of North Carolina probe of 15mm; CP-11= Clinical Periodontal Probe of 11mm; PI= Plaque Index; GI= Gingival Index; BOP= Bleeding on Probe; PPD= Periodontal Pocket Depth; CAL= Clinical Atachment Level; GL= Gingival Level; PISA= Periodontal Inflamed Surface Area; PESA= Periodontal Epithelial Surface Area; ALSA=Attachment Loss Surface Area; RSA= Recession Surface Area; OPG= Orthopantomographic Radiograph; * It is understood that 6 sites/tooth were examined, as the AAP 1999 classification were used in this study; ; WHO= World Health Organization; ADA= American Diabetes Association; AAP= American Academy of Periodontology

TABLE 1 - General characteristics of the included studies regarding the diagnosis of T2DM and periodontitis. (final)

Study	T2DM Diagnostic Critieria	T2DM Treatment changes	Hba1c Laboratory Method	Minimum T2DM Duration (months)	Periodontitis Classification	Periodontitis Diagnostic Criteria	Periodontal Examination	Periodontal Probe	Clinical Periodontal Parameters	Radiographic Periodontal Parameters (Method)	Minimum Number of Teeth
Mauri-Obradors et al. 2018	N.I	No	HPLC	≥ 18	Generalized chronic periodontitis (AAP 1999 criteria)[13]	PPD sites ≥ 30% with CAL > 4 mm	Six sites/tooth	UNC-15	PI, IG, PPD, CAL, GL	NA	≥ 9
Mizuno et al. 2017	Previous diagnosis by a physician	Yes	HPLC	≥ 2	Mild to advanced chronic periodontitis (CDC/AAP, 2012)	CDC/AAP, 2012	Six sites/tooth in all teeth	CP-11	PI, BOP, PPD, CAL	Alveolar Bone Height (OPG)	NI
Wang et al. 2020	HbA1c> 6,5%	No	NI	> 60	Chronic Periodontitis	PPD sites ≥ 4 mm; >25% of interproximal sites with CAL ≥ 5 mm	Six sites/tooth, excluding third molars	UNC-15	PI, BOP, PPD, CAL, GL	NA	≥ 8
Wu et al. 2015	N.I	NI	Immunoturbidimetry	> 12	Chronic Periodontitis	AAP,1999[13]	All teeth*	NI	IG, BOP, PPD, CAL	NA	≥16
Zhang et al. 2013	(1) postprandial plasma glucose ≥200 mg/dL (11.1 mmol/L); (2) Fast plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L); (3) 2-hour oral glucose tolerance test ≥200 mg/dL (11.1 mmol/L)	No	Cation Exchange Chromatography	≥ 12	Chronic Periodontitis	4 teeth with PPD ≥5 mm, CAL ≥4 mm and BOP, distributed in two or more oral quadrants	Six sites/tooth, excluding third molars	Williams	PI, BOP, PPD, CAL, GL	NA	≥16

NI= Not Informed; T2DM= Type 2 Diabetes Mellitus; HbA1c= Glycated Hemoglobin; FPG= Fasting Plasma Glucose; PPG= Post-Pandrial Glucose; HPLC= High Performance Liquid Chromatography; UNC-15= University of North Carolina probe of 15mm; CP-11= Clinical Periodontal Probe of 11mm; PI= Plaque Index; GI= Gingival Index; BOP= Bleeding on Probe; PPD= Periodontal Pocket Depth; CAL= Clinical Atachment Level; GL= Gingival Level; PISA= Periodontal Inflamed Surface Area; PESA= Periodontal Epithelial Surface Area; ALSA=Attachment Loss Surface Area; RSA= Recession Surface Area; OPG= Orthopantomographic Radiograph; * It is understood that 6 sites/tooth were examined, as the AAP 1999 classification were used in this study; ; WHO= World Health Organization; ADA= American Diabetes Association; AAP= American Academy of Periodontology

TABLE 2 - General characteristics of the included studies regarding the characteristics of the sample.

Study (Country)	Test Sample							Control Sample						
	Sample	Female (%)	Age	BMI (kg/m²)	Smokers (%)	Present Teeth	Time of Diabetes (years)	Sample	Female (%)	Age	BMI (kg/m²)	Smokers (%)	Present Teeth	Time of Diabetes (years)
Artese et al. 2015 (Brazil)[17]	12 (M=48%,F=52%)	52.0	52.0 ± 3.3	26.9 ± 3.8	0	NI	NI	12 (M=43.7%,F=56.3%)	56.3	54.4 ± 5.8	25.6 ± 4.4	0	NI	NI
Chen et al. 2012 (China)[18]	43 (M=26, F=17)	47.6	57.91 ± 11.35	23.88±3.56	10/43	NI	6.93±4.31	41 (M=17,F=24)	58.5	63.2 ± 8.51	23.51±3.10	7/41	NI	9.56±6.02
D'Aiuto et al. 2018 (UK)[9]	133 (M=82, F=51)	38	58.2 ± 9.7	30±5	14	26±4	8.3±7.4	131 (M=48, F=83)	37	55.5 ± 10.0	31±6	15	26±4	8.7±8.4
Engebretson et al. 2013 (USA)[10]	240 (M=126 , F=114)	44.4	56.7 ± 10.5	34.7±7.5	15.2	25.4±3.7	12.3±8.2	236 (M=113,F=123)	47,9	57.9 ± 9.6	34.2±6.7	10.5	24.7±3.6	11.3±8.4
Kaur et al. 2015 (India)[19]	50 (M=22, F=28)	56	51.82 ± 5.85	26.41±3.47	0	22.98±4.59	8.57±6.39	50 (M=26, F=24)	48	52.94 ± 6.03	26.43±3.41	0	24.30±2.88	7.05±4.43
Koromantzos et al. 2011 (Greek) [20]	30 (M=17, F=13)	43.3	59.62 ± 7.95	27.76±3.68	13.3	23.52 ±3.99	7.76±4.33	30 (M=16, F=14)	46,7	59.42 ± 9.8	27.51±3.83	23.3	24.23±3.78	7.84±6.8
Mauri-Obradors et al. 2018 (Spain)[21]	42 (M=17, F=25)	59.5	61 ± 11	29.04±3.91	35.7	NI	10±10	48 (M=20, F=28)	58,3	62 ± 10	29.39±4.38	6.3	NI	11±12
Mizuno et al. 2017 (Japan)[22]	20 (M=13; F= 7)	35	61.2 ± 9.2	25.4±3.6	10	24.3±6.2	NI	17 (M=15; F=2)	21,8	62.8 ± 12.1	27.0±4.4	29.4	24.8±4.8	NI
Wang et al. 2020 (China)[23]	29 (M=17, F=12)	41.4	64.4 ± 9.3	26.4±3	10.3	NI	17.3±9.1	29 (M=16, F=13)	44,8	64.7 ± 8.3	25.9±3.5	13.8	NI	16.2± 7.8
Wu et al. 2015 (China)[24]	23 (M=12, F=11)	47.8	54.09 ± 6.57	22.22±0.64	0	22.09±1.88	4.00±1.76	23 (M=10, F=13)	56,5	55.52 ± 5.22	22.14±0.72	0	21.87±1.87	4.22± 1.57
Zhang et al. 2013 (China)[25]	49 (M=21; F=28)	57.1	60.4 ± 9.77	NI	12/49	NI	8.63±4.20	22 (M=10, F=12)	54,5	62.7 ± 10.7	NI	6/22	NI	7.29± 5.61

NI=Not Informed; M= Male; F= Female; BMI= Body Mass Index;

TABLE 3 - General characteristics of the included studies regarding the intervention. (cont.)

Study (Country)	Test Intervention (Subgingival Therapy)				Control Intervention (Non-Active Treatment)		Instruments used for Periodontal Therapy
	Teeth Extractions performed	At Baseline	At Follow-up	Endpoint	At Baseline	At Follow-up	
Artese et al. 2015 (Brazil)[17]	NI	OHI + Supra and Subgingival SRP (in sites with PPD ≥ 4 mm) under local anesthesia (3% prilocaine with felypressin), in two appointment lasting ~120min	**At 6mo:** Supportive therapy for biofilm control by professional instructions	Not established	OHI + Supragingival scaling, in one appointment lasting ~60min	Supportive therapy for biofilm control by professional instructions	Ultrassonic instrument and manual curets
Chen et al. 2012 (China)[18]	NI	Group 2: OHI + SRP under local anesthesia completed within 24 hours	**At 3mo:** OHI + Supragingival prophylaxis	Not established	No treatment		Ultrassonic instrument and manual curets
D'Aiuto et al. 2018 (UK)[9]	Yes	OHI + Full-mouth SRP under local analgesia, with no time limit set for the duration of the session	**At 2mo:** Periodontal surgery for patients with good oral hygiene (dental plaque scores of ≤20%) and at least one 6 mm or deeper residual periodontal pocket; Additional SRP under local anesthesia for patients who still had suboptimum oral hygiene or did not have residual 6 mm or deeper periodontal pockets; **At 6, 9 and 12mo:** Additional SRP under local anesthesia	Not established	OHI + Supragingival scaling and polishing of all dentition	**At 2, 6, 9 and 12mo:** OHI + Supragingival scaling and polishing of all dentition	NI
Engebretson et al. 2013 (USA)[10]	NI	OHI + Full-mouth supra- and subgingival SRP completed in two or more sessions, each lasting ~90 min, and within 42 days of randomization, under local anesthesia if necessary + Antimicrobial mouth rinse for 2 weeks (Chlorhexidine Gluconate 0.12%, 0.5 oz rinse for 30 s twice daily)	**At 3 and 6mo:** OHI + SRP for ~1 hour during a single session.	Not established	OHI	**At 3 and 6mo**: OHI	Sonic or Ultrasonic instruments and manual curets
Kaur et al. 2015 (India)[19]	NI	OHI + SRP in four sessions over a maximum of 2 weeks	**At 3 and 6mo:** OHI + Additional supportive SRP when necessary	Not established	No treament		Ultrassonic instrument and manual curets
Koromantzos et al. 2011 (Greek)	Yes	OHI + Full-mouth SRP under local anesthesia, in two sessions, 1 week apart	**At 1, 3 and 6mo:** OHI + Additional supportive SRP, if necessary (presence of sites with BOP and/or increased PPD)	Not established	OHI + Supragingival scaling	**At 1, 3 and 6mo:** OHI	Ultrassonic and hand instruments

NI= Not Informet; WHO= World Health Organizattion; ADA= American Diabetes Association; T2DM= Type 2 Diabetes Mellitus; HbA1c= Glycated Hemoglobin; AAP= American Academy of Periodontology; PPD= Periodontal Pocket Depth; CAL= Clinical

Attcahment Level; ABL= Alveolar Bone Loss; BOP= Bleeding on Probe; OHI= Oral Hygiene Instruction; SRP= Scaling and Root Planning

TABLE 3 - General characteristics of the included studies regarding the intervention. (continuation)

Study (Country)	Test Intervention (Subgingival Therapy)				Control Intervention (Non-Active Treatment)		Instruments used for Periodontal Therapy
	Teeth Extractions performed	At Baseline	At Follow-up	Endpoint	At Baseline	At Follow-up	
Mauri-Obradors et al. 2018 (Spain)[21]	NI	OHI + Full-mouth SRP	**At 3 and 6 mo:** Additional SRP when need (presence of points of bleeding and/or increased PPD)	Not established	OHI + Supragingival scaling	**At 3 and 6 mo:** OHI	Ultrassonic instrument
Mizuno et al. 2017 (Japan)[22]	NI	OHI + Supra-gingival plaque removal + SRP lasting at least 60min, during 2 or more sessions completed within 42 days after the baseline visit	**At 3 and 6mo:** oral hygiene instructions and oral prophylaxis for approximately 1 hour during a single session	Not established	OHI	**At 3 and 6 mo:** OHI	Ultrassonic instrument and manual curets
Wang et al. 2020 (China)[23]	Yes	OHI + SRP through 2–3 sessions within 1–2 weeks according to the individual severity of periodontitis.	**At 3mo:** OHI + Plaque removal	Not established	OHI	**At 3mo:** OHI	Piezoelectric ultrasonic instrument and hand instruments
Wu et al. 2015 (China)[24]	NI	OHI + SRP completed within 1 month of the first visit	None	Not established	OHI	None	NI
Zhang et al. 2013 (China)[25]	No	OHI + Supra and Subgingival scaling and manual curettage, which were completed within 2 weeks after the baseline evaluation	**At 3mo:** (sub-ERP group) full-month ultrasonic scaling and manual root planing of the teeth with PPD≥4 mm; (subprophylaxis group) full-month ultrasonic scaling to remove calculus and plaque	Not established	No treament		Ultrassonic instrument and manual curets

NI= Not Informet; WHO= World Health Organizattion; ADA= American Diabetes Association; T2DM= Type 2 Diabetes Mellitus; HbA1c= Glycated Hemoglobin; AAP= American Academy of Periodontology; PPD= Periodontal Pocket Depth; CAL= Clinical Attcahment Level; ABL= Alveolar Bone Loss; BOP= Bleeding on Probe; OHI= Oral Hygiene Instruction; SRP= Scaling and Root Planning

TABLE 4 - General characteristics of the included studies regarding periodontal parameters and HbA1c level changes.

Study (Country)	Test Intervention (Subgingival Therapy)			Control Intervention (Non-Active Therapy)			Test *vs* Control	Adverse Events
	PPD mm (mean±SD)	CAL mm (mean±SD)	HbA1c % (mean±SD)	PPD mm (mean±SD)	CAL mm (mean±SD)	HbA1c % (mean±SD)	ΔHbA1c%	
Artese et al. 2015 (Brazil)[17]	Baseline= 4.75±NI 6months=2.32±NI Δ=NI	Baseline=4.29±NI 6months=3.31±NI Δ=NI	NI	Baseline=4.47±NI 6months=3.30±NI Δ=NI	Baseline=4.77±NI 6months=4.26±NI Δ=NI	NI	NI	NI
Chen et al. 2012 (China)[18]	Baseline= 2.57±0.66 6months=2.10± 0.39 Δ=NI	Baseline=2.95±1.21 6months=2.55±1.16 Δ=NI	Baseline=7.29±1.55 6months=6.87±1.12 Δ=NI	Baseline=2.47±0.57 6months=2.42±0.50 Δ=NI	Baseline=3.37±1.24 6months=3.41±1.23 Δ=NI	Baseline=7.25±1.49 6months=7.38±1.57 Δ=	NI	No adverse effects reported by any patient
D'Aiuto et al. 2018 (UK)[9]	Baseline= 3.9±0.7 6months=2.9±0.2[a] Δ= NI	NI	Baseline=8.1±1.7 6months=8.0±0.2 Δ=NI	Baseline=3.09±0.8 6months=3.7±NI Δ=NI	NI	Baseline=8.1±1.7 6months=8.1±0.2[a] Δ=	-0.3±NI	Some adverse study-related effects were reported
Engebretson et al. 2013 (USA)[10]	Baseline=3.25±0.08[a] 6months=2.78±N [a] Δ=NI	Baseline=3.48±0.12[a] 6months=3.12±NI[a] Δ=NI	Baseline=7.84±0.65 6months=8.02±NI Δ=0.15±NI	Baseline=3.28±0.9[a] 6months=3.13±NI[a] Δ=NI	Baseline=3.48±0.11[a] 6months=3.34±0.12[a] Δ=NI	Baseline=7.78±0.60 6months=7.9±NI[a] Δ=0.09±NI	NI	Some adverse study-related effects were reported, but none serious event
Kaur et al. 2015 (India)[19]	Baseline= 2.96±0.46 6months=2.15±0.42 Δ=0.81±0.28	Baseline=3.46±0.53 6months=2.75±0.62 Δ=0.71±0.36	Baseline=8.17±2.49 6months=7.29±1.61 Δ=-0.88±1	Baseline=3.08 ± 0.55 6months=3.13 ± 0.57 Δ=-0.06 ± 0.08	Baseline=3.37±0.61 6months=3.44±0.64 Δ=-0.07 ± 0.08	Baseline=7.87±2.56 6months=8.06±2.72 Δ=0.18±0.38	NI	NI
Koromantzos et al. 2011 (Greek) [20]	N.I	NI	Baseline=7.87±0.74 6months=7.16±0.69 Δ=-0.72±0.93	NI	NI	Baseline=7.59±0.66 6months=7.46±0.72 Δ=0.13±0.46	NI	NI
Mauri-Obradors et al. 2018 (Spain)[21]	Baseline=3.56±0.12[a] 6months=2.55±0.17[a] Δ= -0.99 ±0.61	NI	Baseline=7.7±0.1[a] 6months=7.1±0.2[a] Δ= -0.47 ±0.90	Baseline=2.99±0.2[a] 6months=2.99±0.1[a] Δ= -0.11 ±0.54	NI	Baseline=7.7±0.2[a] 6months=7.6±0.3[a] Δ= -0.00 ±0.83	NI	N
Mizuno et al. 2017 (Japan)[22]	Baseline= 2.4±0.5 6months=2.2±0.5 Δ=NI	Baseline=2.6±0.6 6months=2.4±0.6 Δ=NI	Baseline=7.5±1.7 6months=7.4±1.3 Δ=NI	Baseline=2.4±0.7 6months=2.6±0.9 Δ=NI	Baseline=2.7±0.9 6months=2.8±1.0 Δ=NI	Baseline=7.7±1.2 6months=7.6±1.1 Δ=	-0.07±NI	No study-related serious adverse events occurred in any patients
Wang et al. 2020 (China)[23]	Baseline= 3.10±1.21 6months=2.37±0.57 Δ=-0.63±0.55	Baseline=4.29±1.77 6months=3.89±1.11 Δ=-0.42±0.50	Baseline=8.4±1.1 6months=8.5±0.9 Δ=-0.1±0.8	Baseline=2.92±0.99 6months=3.01±0.74 Δ=NI	Baseline=3.97±1.32 6months=4.28±1.35 Δ=0.32 ± 0.86	Baseline=8.3±1.2 6months=8.4±1.2 Δ=0.1±0.13	NI	NI
Wu et al. 2015 (China)[24]	Baseline= 3.73±0.58 6months=3.10±0.62 Δ=NI	Baseline=3.66±1.29 6months=3.24±1.16 Δ=NI	Baseline=7.41±0.20 6months=7.09±0.12 Δ=NI	Baseline=3.71±0.61 6months=3.51±0.71 Δ=NI	Baseline=3.90±1.18 6months=4.0±1.17 Δ=NI	Baseline=7.39±0.16 6months=7.42± 0.18 Δ=NI	NI	NI
Zhang et al. 2013 (China)[25]	Baseline= 2.50±0.45 6months=1.87±0.30[a] Δ= 0.639± 0.253	Baseline=3.41±0.97 6months=2.9±0.9[a] Δ= 0.523± 0.311	Baseline=7.68±1.22 6months=7.51±1.31 Δ= 0.161± 0.525	Baseline=2.43±0.47 6months=2.54±0.46 Δ= -0.0995± 0.186	Baseline=3.33±0.97 6months=3.5±0.9 Δ= -0.212± 0.421	Baseline=7.38±1.30 6months=7.4±1 Δ= -0.0182± 0.316	NI	NI

NI= Not Informed; M= Male; F= Female; BMI= Body Mass Index; PPD= Periodontal Probing Depth; CAL= Clinical Attachment Level; HbA1c= Glycated Hemoglobin; Δ= Mean difference between 6months and baseline results [6months-Baseline]; Δ= Mean difference between test and control at 6months follow-up; a= Data extracted from graphic imagens using WebPlotDigitizer online tool

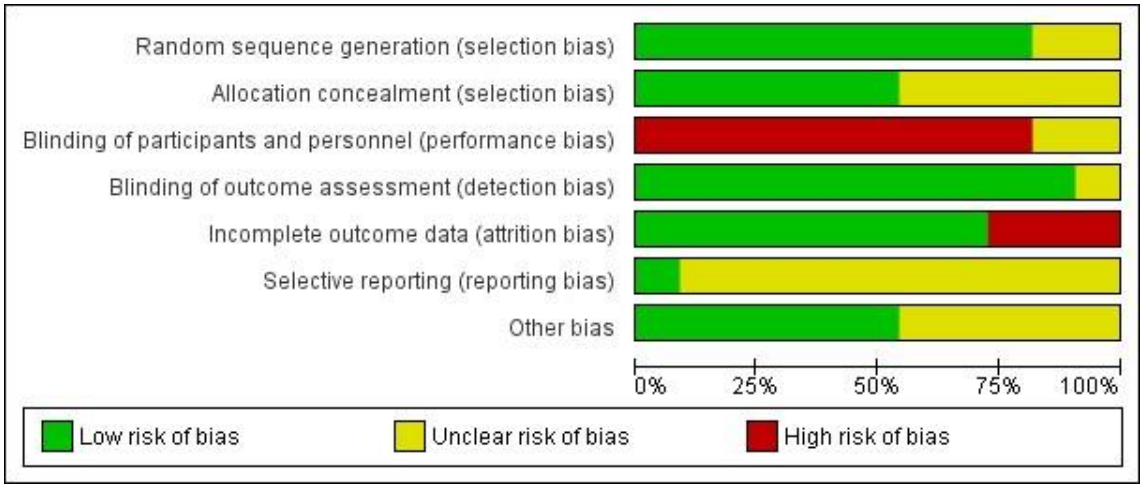

FIGURE 2a – GRAPHIC OF RISK OF BIAS.

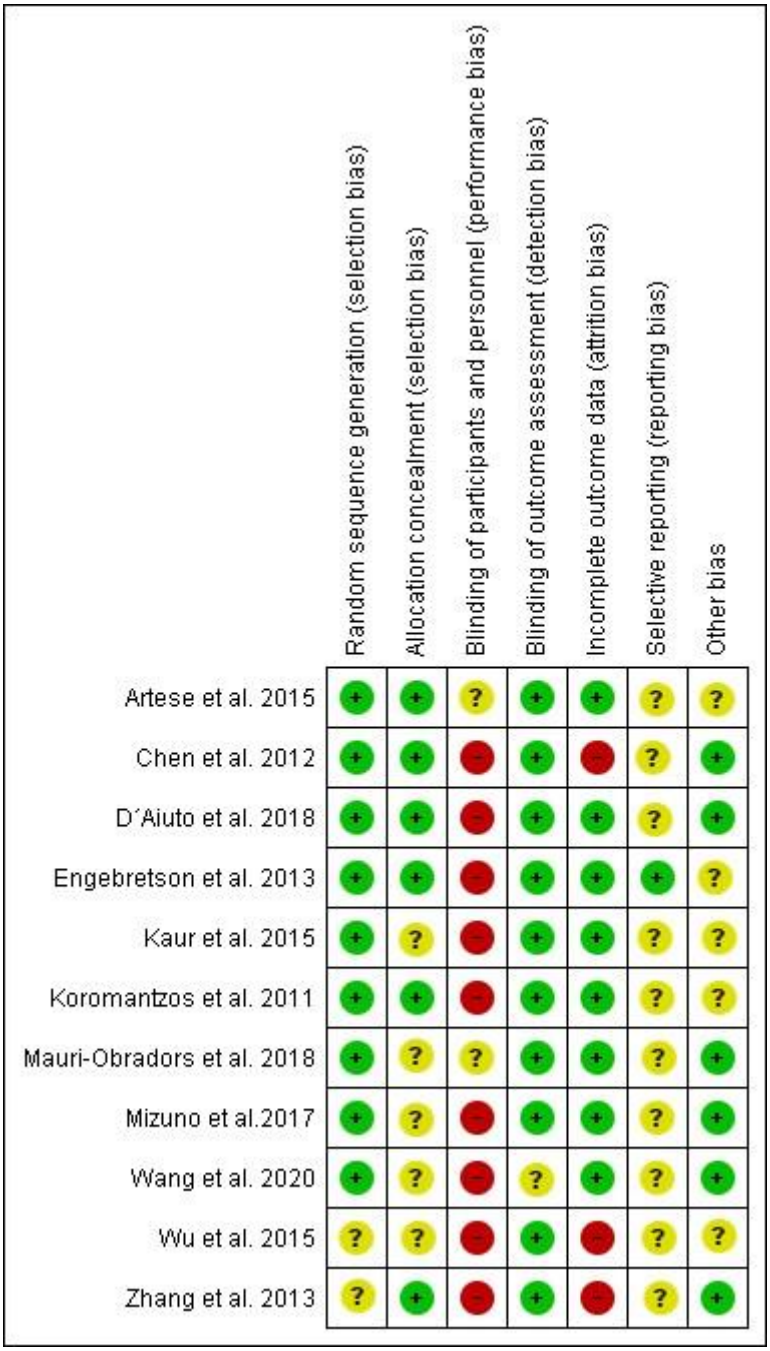

FIGURE 2b – SUMMARY OF RISK OF BIAS

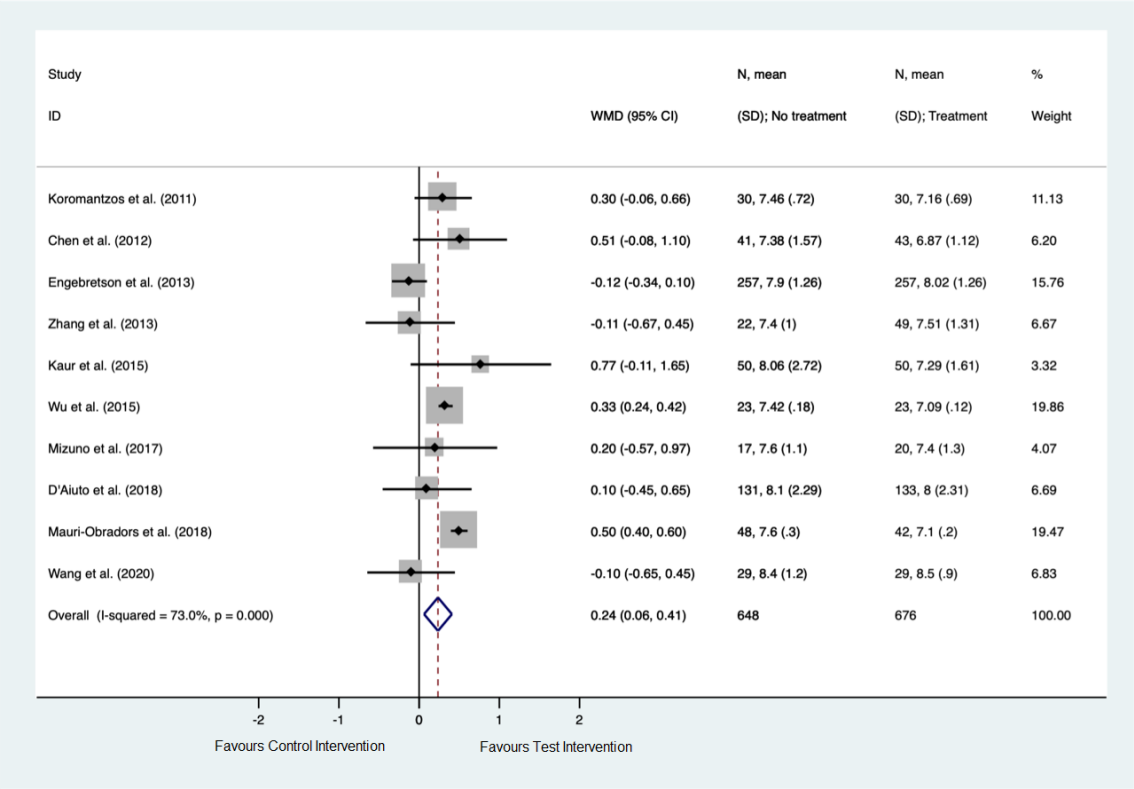

FIGURE 3 – FOREST PLOT OF THE FINAL CONCENTRATION OF HBA1C (%) IN THE TEST AND CONTROL GROUPS.

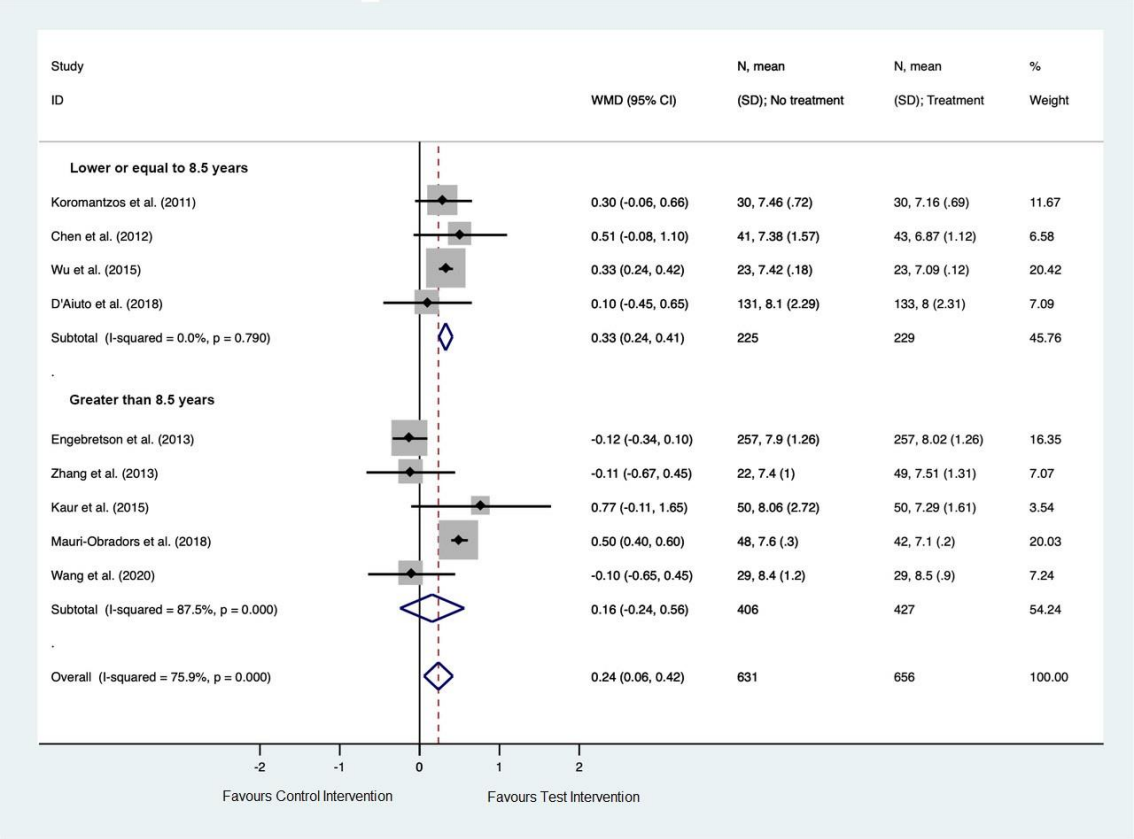

FIGURA E – STRATIFIED ANALYSIS.

SUPPLEMENTARY MATERIAL

TABLE S1 - General characteristics of the included studies regarding study design.

Study	Country (Number of Centers)	RCT Protocol Registry	Funding	Conflict of Interest	Study Duration (months)	Sample Calculation (α;β)	Follow-up Points (months)
Artese et al. 2015	Brazil (Unicenter)	NI	Yes	None	23	Yes (α=0.05; β=90)	Baseline and 6
Chen et al. 2012	China (Unicenter)	Yes	Yes	None	14	Yes (α=0.05; β=80)	Baseline, 1.5, 3 and 6
D'Aiuto et al. 2018	UK (Unicenter)	Yes	Yes	None.	13	Yes (α=0.05; β=95)	Baseline, 2, 6 and 12
Engebretson et al. 2013	USA (Multicenter)	Yes	Yes	Yes	29	Yes (α=0.05; β=90)	Baseline, 3 and 6
Kaur et al. 2015	India (Unicenter)	NI	NI	None	24	Yes (α=0.05; β=90)	Baseline, 3 and 6
Koromantzos et al. 2011	Greek (Unicenter)	NI	Yes	None	36	Yes (α=0.05; β=90)	Baseline. 1, 3 and 6
Mauri-Obradors et al. 2018	Spain (Unicenter)	Yes	Yes	None	18	Yes (α=0.05; β=80)	30days before baseline and 6
Mizuno et al. 2017	Japan (Unicenter)	Yes	Yes	None	24	Yes (α=0.05; β=80)	Baseline, 3 and 6
Wang et al. 2020	China (Unicenter)	Yes	Yes	None	40	Yes (α=0.05; β=80)	Baseline and 6
Wu et al. 2015	China (Unicenter)	NI	NI	NI	17	NI	Baseline, 3 and 6
Zhang et al. 2013	China (Unicenter)	Yes	Yes	None	11	Yes (α=0.05; β=80)	Baseline,1, 3 and 6

NI= Not Informed; α= Significance level (error type I); β= Statistical power (error type II)

TABELA S2 - Achados dos modelos de metarregressão para a concentração final de HbA1c.

	Univariable models			**Final multivariable model****		
Variable	**Coefficient**	**95%CI**	**p**	**Coefficient**	**95%CI**	**p**
Empty model*	0.24	0.01 – 0.46	0.04			
Year of publication	0.01	-0.08 – 0.09	0.87			
Percentage of females in the test group	0.02	-0.01 – 0.05	0.13	0.04	0.02 – 0.05	0.002
Mean age of the test group	-0.02	-0.10 – 0.06	0.52			
Percentage of smokers in test group	0.003	-0.02 – 0.02	0.75			
Time of diabetes diagnosis						
<=8.5 years	Ref.			Ref.		
>8.5 years	-0.15	-0.63 – 0.34	0.50	-0.30	-0.52 – 0.08	0.02
Baseline mean HBa1C in test and control groups	-0.36	-1.14 – 0.43	0.32			
Final PPD in the test group	-0.02	-0.76 – 0.74	0.97			

* R square = 75.9%; **Adjusted R square = 99.1%; tau2=0.0001.

TABLE S3 – Assesment of quality in the body of evidence following GRADE.

	Assesment of the Certainty of Evidence						Number of Participants		Efect		Certainty	Importance
Study	Study Desigd	Risk of Bias	Inconsistence	Indirectiness	Imprecision	Other considerations	Mechanical Periodontal Therapy	Non-active Periodontal Therapy	Relative (95% IC)	Absolute (95%)		
Reduction in HbA1c after 6 months of follow-up. (follow-up: average 6 months; assessed with: HbA1c)												
11	ECR	Grave	Non grave	Non grave	Non grave	None	676	648	-	**MD 0.24 %** (0.06-0.41)	⊕⊕⊕◯ Moderate	Important

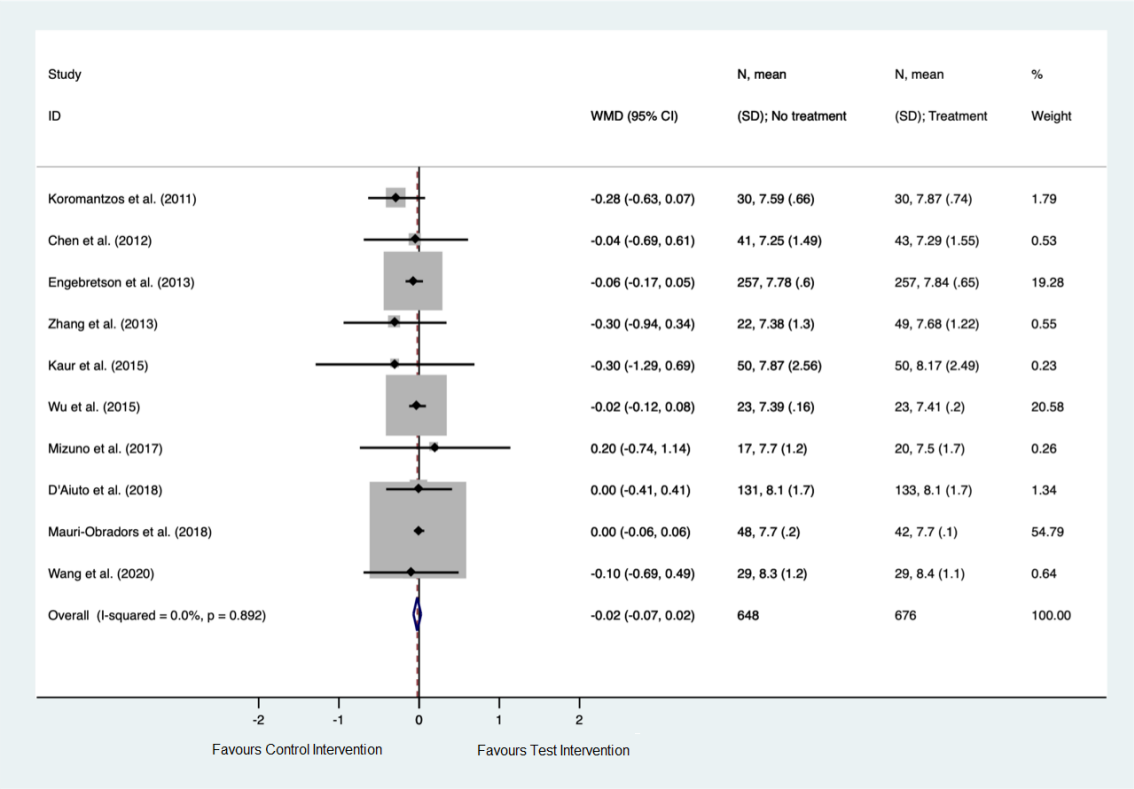

FIGURE S1 – FOREST PLOT OF HBA1C CONCENTRATION (%) IN BASELINE IN TEST AND CONTROL GROUPS.

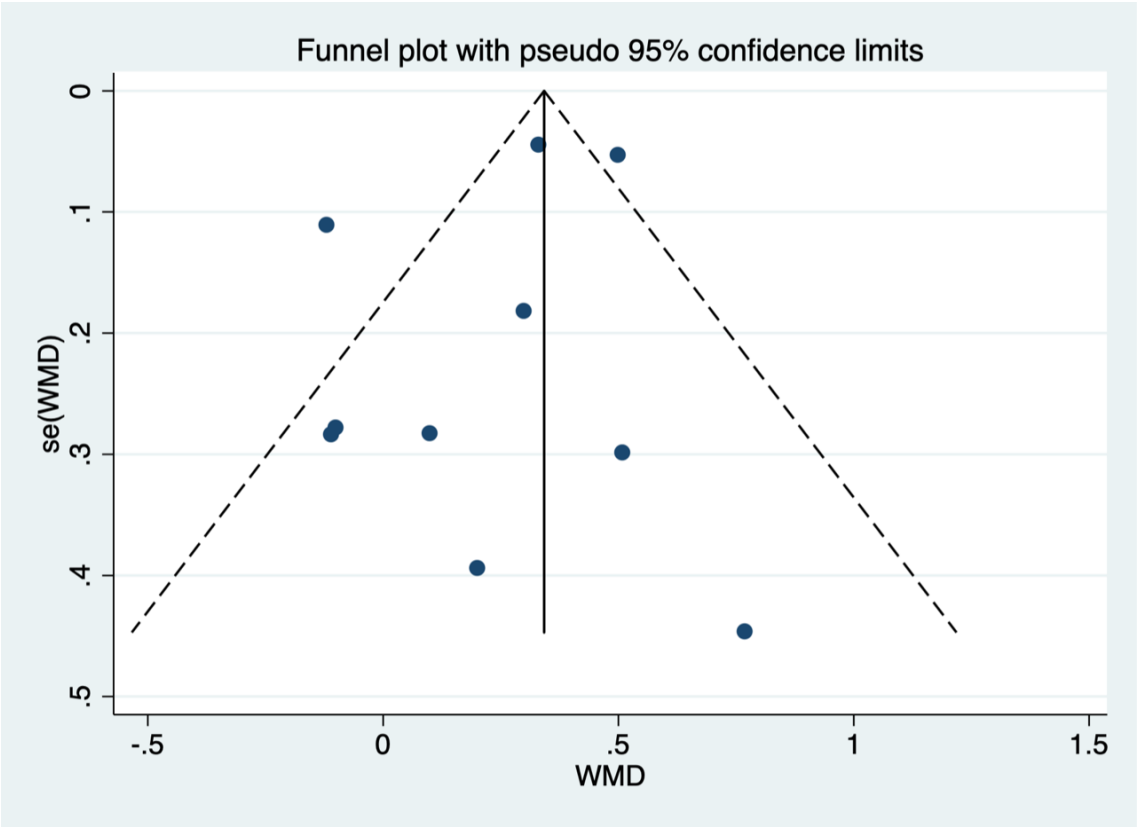

FIGURE S2 - FUNNEL PLOT OF STUDIES INCLUDED IN META-ANALYSIS.

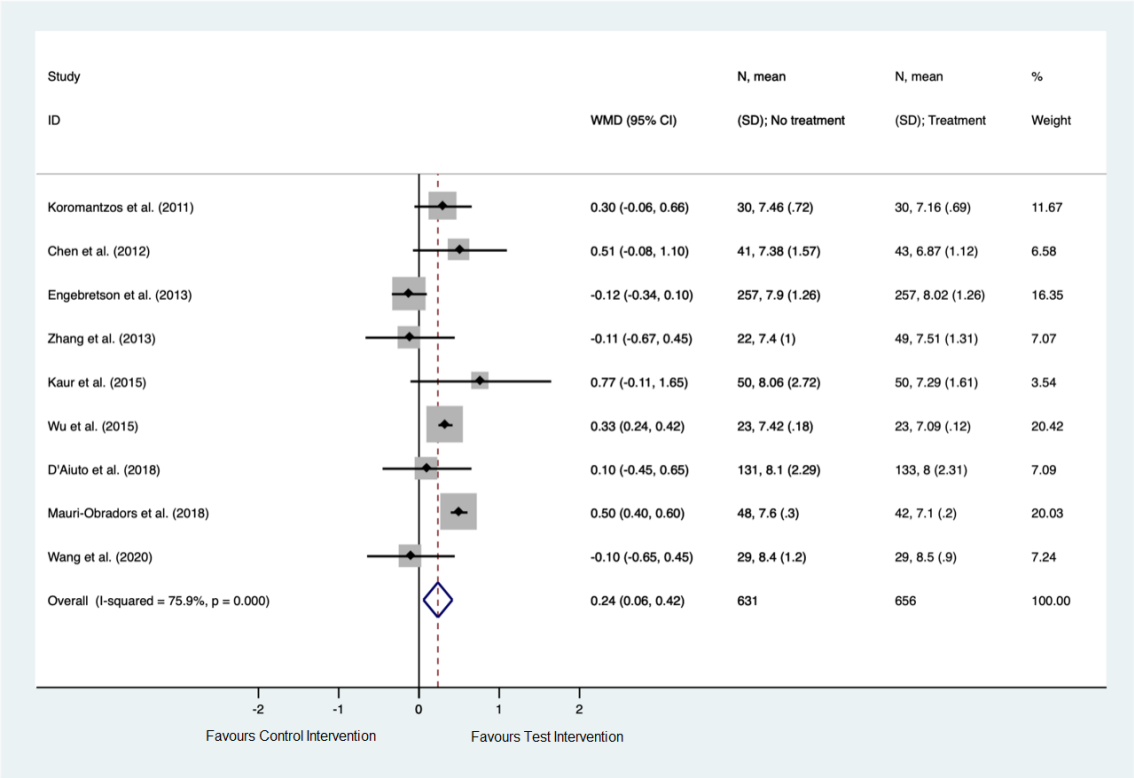

FIGURE S3 - FOREST PLOT OF THE 9 STUDIES INCLUDED IN THE METAREGRESSION.

SEARCH ALGORITHM INDIVIDUALIZED BY DATABASE

DATABASE	SEARCH ALGORITHM	04.28.21
Medline (through PubMed Central – PMC)	("Periodontal Diseases"[MeSH Terms] OR "Periodontal Diseases"[All Fields] OR "periodontitis"[MeSH Terms] OR ("periodontal"[All Fields] OR "periodontally"[All Fields] OR "periodontically"[All Fields] OR "periodontics"[MeSH Terms] OR "periodontics"[All Fields] OR "periodontic"[All Fields] OR "periodontitis"[MeSH Terms] OR "periodontitis"[All Fields] OR "periodontitides"[All Fields]) OR ("Periodontal Diseases"[MeSH Terms] OR ("periodontal"[All Fields] AND "diseases"[All Fields]) OR "Periodontal Diseases"[All Fields] OR "parodontosis"[All Fields]) OR "Periodontal Pathology"[All Fields]) AND ("diabetes mellitus, type 2"[MeSH Terms] OR "diabetes mellitus noninsulin dependent"[All Fields] OR "diabetes mellitus noninsulin dependent"[All Fields] OR "diabetes mellitus non insulin dependent"[All Fields] OR "diabetes mellitus non insulin dependent"[All Fields] OR "Non-Insulin-Dependent Diabetes Mellitus"[All Fields] OR "diabetes mellitus type ii"[All Fields] OR "NIDDM"[All Fields] OR "Type 2 Diabetes Mellitus"[All Fields] OR "Type 2 Diabetes"[All Fields]) AND ("Periodontal Debridement"[MeSH Terms] OR "Periodontal Debridement"[All Fields] OR "Surgical Periodontal Debridement"[All Fields] OR "Dental Scaling"[MeSH Terms] OR "Dental Scaling"[All Fields] OR "Subgingival Scaling"[All Fields] OR "Subgingival Curettage"[All Fields] OR "Periodontal Pocket Debridement"[All Fields] OR "Root Planing"[MeSH Terms] OR "Root Planing"[All Fields] OR "Scaling and Root Planing"[All Fields] OR "non-surgical periodontal therapy"[All Fields] OR "non-surgical therapy"[All Fields] OR "periodontal therapy"[All Fields] OR "periodontal therapeutics"[All Fields] OR "surgical periodontal therapy"[All Fields] OR "periodontal treatment"[All Fields] OR "periodontal intervention"[All Fields] OR "Periodontitis Treatment"[All Fields] OR "Intention-to-treat"[All Fields]) AND ("Glycemic control"[All Fields] OR "Glycated Hemoglobin A"[MeSH Terms] OR "glycated hemoglobin"[All Fields] OR ("Glycated Hemoglobin A"[MeSH Terms] OR "Glycated Hemoglobin A"[All Fields] OR "hba1c"[All Fields] OR "hba1c%"[All Fields]) OR "glucose levels"[All Fields] OR ("glycaemia"[All Fields] OR "glycaemias"[All Fields]) OR "hemoglobin A1c"[All Fields] OR "A1C"[All Fields] OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]) OR ("glucose"[MeSH Terms] OR "glucose"[All Fields] OR "glucoses"[All Fields] OR "glucose s"[All Fields]) OR "blood sugar level"[All Fields])	248
Embase (Elsevier)	('periodontal diseases' OR periodontitis OR parodontosis OR 'periodontal pathology') AND ('diabetes mellitus, type 2' OR 'diabetes mellitus, noninsulin-dependent' OR 'diabetes mellitus, noninsulin dependent' OR 'diabetes mellitus, non insulin dependent' OR 'diabetes mellitus, non-insulin-dependent' OR 'non-insulin-dependent diabetes mellitus' OR 'diabetes mellitus, type ii' OR 'niddm' OR 'type 2 diabetes mellitus' OR 'type 2 diabetes') AND ('periodontal debridement' OR 'surgical periodontal debridement' OR 'dental scaling' OR 'subgingival scaling' OR 'subgingival curettage' OR 'periodontal pocket debridement' OR 'root planing' OR 'scaling and root planing' OR 'non-surgical periodontal therapy' OR 'non-surgical therapy' OR 'periodontal therapy' OR 'periodontal therapeutics' OR 'surgical periodontal therapy' OR 'periodontal treatment' OR 'periodontal intervention' OR 'periodontitis treatment' OR 'intention-to-treat') AND ('glycemic control' OR 'glycated hemoglobin a' OR 'glycated hemoglobin' OR hba1c OR 'glucose levels' OR	264

	glycaemia OR 'hemoglobin a1c' OR a1c OR hemoglobin OR glucose OR 'blood sugar level')	
Scopus (Elsevier)	TITLE-ABS-KEY ("Periodontal Diseases" OR "Periodontal Diseases" OR periodontitis OR periodontitis OR parodontosis OR "Periodontal Pathology") AND TITLE-ABS-KEY ("Diabetes Mellitus, Type 2" OR "Diabetes Mellitus, Noninsulin-Dependent" OR "Diabetes Mellitus, Noninsulin Dependent" OR "Diabetes Mellitus, Non Insulin Dependent" OR "Diabetes Mellitus, Non-Insulin-Dependent" OR "Non-Insulin-Dependent Diabetes Mellitus" OR "Diabetes Mellitus, Type II" OR "NIDDM" OR "Type 2 Diabetes Mellitus" OR "Type 2 Diabetes") AND TITLE-ABS-KEY ("Periodontal Debridement" OR "Periodontal Debridement" OR "Surgical Periodontal Debridement" OR "Dental Scaling" OR "Dental Scaling" OR "Subgingival Scaling" OR "Subgingival Curettage" OR "Periodontal Pocket Debridement" OR "Root Planing" OR "Root Planing" OR "Scaling and Root Planing" OR "non-surgical periodontal therapy" OR "non-surgical therapy" OR "periodontal therapy" OR "periodontal therapeutics" OR "surgical periodontal therapy" OR "periodontal treatment" OR "periodontal intervention" OR "Periodontitis Treatment" OR "Intention-to-treat") AND TITLE-ABS-KEY ("Glycemic control" OR "Glycated Hemoglobin A" OR "glycated hemoglobin" OR hba1c OR "glucose levels" OR glycaemia OR "hemoglobin A1c" OR a1c OR hemoglobin OR glucose OR "blood sugar level")	277
Web of Science - (Clarivate Analytics)	TS=('Periodontal Diseases' OR 'Periodontal Diseases' OR Periodontitis OR Periodontitis OR Parodontosis OR 'Periodontal Pathology') AND TS=('Diabetes Mellitus, Type 2' OR 'Diabetes Mellitus, Noninsulin-Dependent' OR 'Diabetes Mellitus, Noninsulin Dependent' OR 'Diabetes Mellitus, Non Insulin Dependent' OR 'Diabetes Mellitus, Non-Insulin-Dependent' OR 'Non-Insulin-Dependent Diabetes Mellitus' OR 'Diabetes Mellitus, Type II' OR 'NIDDM' OR 'Type 2 Diabetes Mellitus' OR 'Type 2 Diabetes') AND TS=('Periodontal Debridement' OR 'Periodontal Debridement' OR 'Surgical Periodontal Debridement' OR 'Dental Scaling' OR 'Dental Scaling' OR 'Subgingival Scaling' OR 'Subgingival Curettage' OR 'Periodontal Pocket Debridement' OR 'Root Planing' OR 'Root Planing' OR 'Scaling and Root Planing' OR 'non-surgical periodontal therapy' OR 'non-surgical therapy' OR 'periodontal therapy' OR 'periodontal therapeutics' OR 'surgical periodontal therapy' OR 'periodontal treatment' OR 'periodontal intervention' OR 'Periodontitis Treatment' OR 'Intention-to-treat') AND TS=('Glycemic control' OR 'Glycated Hemoglobin A' OR 'glycated hemoglobin' OR HbA1c OR 'glucose levels' OR glycaemia OR 'hemoglobin A1c' OR A1C OR hemoglobin OR glucose OR 'blood sugar level')	345
LILACS/BIREME (though Biblioteca Virtual em Saúde)	((“periodontal diseases” OR “periodontal diseases” OR periodontitis OR periodontitis OR parodontosis OR “periodontal pathology” OR “doença periodontal” OR “enfermedad periodontal”)) AND ((“diabetes mellitus, type 2” OR “diabetes mellitus, noninsulin-dependent” OR “diabetes mellitus, noninsulin dependent” OR “diabetes mellitus, non insulin dependent” OR “diabetes mellitus, non-insulin-dependent” OR “non-insulin-dependent diabetes mellitus” OR “diabetes mellitus, type ii” OR “niddm” OR “type 2 diabetes mellitus” OR “type 2 diabetes” OR “diabetes mellitus tipo 2”)) AND ((“periodontal debridement” OR “periodontal debridement” OR “surgical periodontal debridement” OR “dental scaling” OR “dental scaling” OR “subgingival scaling” OR “subgingival curettage” OR “periodontal pocket debridement” OR “root planing” OR “root planing” OR “scaling AND root planing” OR “non-surgical periodontal therapy” OR “non-surgical therapy” OR “periodontal therapy” OR	7

	“periodontal therapeutics” OR “surgical periodontal therapy” OR “periodontal treatment” OR “periodontal intervention”) OR (“periodontitis treatment” OR “intention-to-treat” OR “raspagem e alisamento radicular” OR “raspagem subgengival” OR “tratamento periodontal” OR “tratamento periodontal não cirúrgico” OR “tratamento periodontal cirúrgico” OR “terapia periodontal” OR “raspado y alisado radicular” OR “tratamiento periodontal” OR “tratamiento periodontal quirúrgico” OR “tratamiento periodontal no quirúrgico”))	
Dentistry and Oral Sciences Source (DOSS) + CINAHL (through EBSCO host)	('periodontal diseases' OR periodontitis OR parodontosis OR 'periodontal pathology') AND ('diabetes mellitus, type 2' OR 'diabetes mellitus, noninsulin-dependent' OR 'diabetes mellitus, noninsulin dependent' OR 'diabetes mellitus, non insulin dependent' OR 'diabetes mellitus, non-insulin-dependent' OR 'non-insulin-dependent diabetes mellitus' OR 'diabetes mellitus, type ii' OR 'niddm' OR 'type 2 diabetes mellitus' OR 'type 2 diabetes') AND ('periodontal debridement' OR 'surgical periodontal debridement' OR 'dental scaling' OR 'subgingival scaling' OR 'subgingival curettage' OR 'periodontal pocket debridement' OR 'root planing' OR 'scaling and root planing' OR 'non-surgical periodontal therapy' OR 'non-surgical therapy' OR 'periodontal therapy' OR 'periodontal therapeutics' OR 'surgical periodontal therapy' OR 'periodontal treatment' OR 'periodontal intervention' OR 'periodontitis treatment' OR 'intention-to-treat') AND ('glycemic control' OR 'glycated hemoglobin a' OR 'glycated hemoglobin' OR hba1c OR 'glucose levels' OR glycaemia OR 'hemoglobin a1c' OR a1c OR hemoglobin OR glucose OR 'blood sugar level') OBS: Duplicações excluídas pela própria base, total de 211 sem duplicações (285 com dupl)	223
LIVIVO	('periodontal diseases' OR periodontitis OR parodontosis OR 'periodontal pathology') AND ('diabetes mellitus, type 2' OR 'diabetes mellitus, noninsulin-dependent' OR 'diabetes mellitus, noninsulin dependent' OR 'diabetes mellitus, non insulin dependent' OR 'diabetes mellitus, non-insulin-dependent' OR 'non-insulin-dependent diabetes mellitus' OR 'diabetes mellitus, type ii' OR 'niddm' OR 'type 2 diabetes mellitus' OR 'type 2 diabetes') AND ('periodontal debridement' OR 'surgical periodontal debridement' OR 'dental scaling' OR 'subgingival scaling' OR 'subgingival curettage' OR 'periodontal pocket debridement' OR 'root planing' OR 'scaling and root planing' OR 'non-surgical periodontal therapy' OR 'non-surgical therapy' OR 'periodontal therapy' OR 'periodontal therapeutics' OR 'surgical periodontal therapy' OR 'periodontal treatment' OR 'periodontal intervention' OR 'periodontitis treatment' OR 'intention-to-treat') AND ('glycemic control' OR 'glycated hemoglobin a' OR 'glycated hemoglobin' OR hba1c OR 'glucose levels' OR glycaemia OR 'hemoglobin a1c' OR a1c OR hemoglobin OR glucose OR 'blood sugar level') Filtro: EXCLUIR MEDLINE	78
Cochrane Library	('periodontal diseases' OR periodontitis OR parodontosis OR 'periodontal pathology') AND ('diabetes mellitus, type 2' OR 'diabetes mellitus, noninsulin-dependent' OR 'diabetes mellitus, noninsulin dependent' OR 'diabetes mellitus, non insulin dependent' OR 'diabetes mellitus, non-insulin-dependent' OR 'non-insulin-dependent diabetes mellitus' OR 'diabetes mellitus, type ii' OR 'niddm' OR 'type 2 diabetes mellitus' OR 'type 2 diabetes') AND ('periodontal debridement' OR 'surgical periodontal debridement' OR 'dental scaling' OR 'subgingival scaling' OR 'subgingival curettage' OR 'periodontal pocket debridement' OR 'root planing' OR 'scaling and root planing' OR 'non-surgical periodontal therapy' OR 'non-surgical therapy' OR 'periodontal therapy' OR 'periodontal therapeutics' OR 'surgical	220

	periodontal therapy' OR 'periodontal treatment' OR 'periodontal intervention' OR 'periodontitis treatment' OR 'intention-to-treat') AND ('glycemic control' OR 'glycated hemoglobin a' OR 'glycated hemoglobin' OR hba1c OR 'glucose levels' OR glycaemia OR 'hemoglobin a1c' OR a1c OR hemoglobin OR glucose OR 'blood sugar level')	
Google Scholar	"Periodontal Diseases" AND "Type 2 Diabetes Mellitus" AND "Glycemic control" filetype:pdf Sem incluir patentes e citações	556
ProQuest	"Periodontal Diseases" AND "Type 2 Diabetes Mellitus" AND "Glycemic control" Document Type: Article	158
OpenGrey	“Type 2 Diabetes Mellitus” AND “Periodontitis”	3

LIST OF DATA EXTRACTED FROM ARTICLES

(1) Relevant methodological data: number of centers, ethical aspects, registration of protocol, funding, conflicts of interest, study location and recruitment of participants, duration of the study, inclusion and exclusion criteria for diabetic patients, demographics, sample size calculation, number of examiners, calibration, blinding, randomization, periodontal assessment, periodontitis and T2DM case definition, glycemic tests, T2DM treatment, intervention details, statistical analysis and controlled confounding factors.

(2) Relevant results with statistical measures: baseline and final HbA1c% levels, fasting plasma glucose (FPG), duration of T2DM and periodontal clinical measurements (gingival index, bleeding on probing, periodontal probing depth, clinical attachment level, and other parameters, such as oral biofilm index, dental calculus index, the involvement of furcation, suppuration, tooth mobility and tooth loss).

4 CONCLUSÃO GERAL

O estudo e a interpretação conjunta de informações de estudos primários, como os artigos selecionados nesta revisão, são necessários para o correto entendimento de como a terapia periodontal é capaz de influenciar no controle de índices glicêmicos em pacientes com periodontite e diabetes do tipo 2. Deste modo, tornar capaz a produção de evidência secundária, base para superar divergências e heterogeneidade metodológica em estudos futuros é essencial para guiar a tomada de decisões em saúde.

A presente revisão sistemática com meta-análise foi capaz de sumarizar evidência suficiente, para concluir que a instrumentação subgengival é capaz de reduzir índices glicêmicos em pacientes com periodontite e diabetes tipo 2, atuando como método terapêutico não farmacológico e complementar à terapia antidiabetes após 6 meses de tratamento.

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ANEXOS

Anexo 1 - Regime Interno do PPGO-UFC

Art. 46 – As dissertações e as teses apresentadas ao Programa de Pós-Graduação em Odontologia da Universidade Federal do Ceará poderão ser produzidas em formato alternativo ou tradicional. O formato

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FACULDADE DE FARMÁCIA, ODONTOLOGIA E ENFERMAGEM

alternativo estabelece: a critério do orientador e com a aprovação da Coordenação do Programa, que os capítulos poderão conter cópias de artigos e/ou relatórios de patentes de autoria ou coautoria do candidato, publicados ou submetidos para publicação em revistas científicas, escritos no idioma exigido pelo veículo de divulgação.

§1º - O orientador e o candidato deverão verificar junto às editoras a possibilidade de inclusão dos artigos na dissertação ou tese, em atendimento à legislação que rege o direito autoral, obtendo, se necessária, a competente autorização, deverão assinar declaração de que não estão infringindo o direito autoral transferido à editora.

§2º - A dissertação e a tese em formatos tradicionais ou formatos alternativos deverão seguir as normas preconizadas pelo Guia para Normalização de Trabalhos Acadêmicos da Biblioteca Universitária disponível no sítio http://www.biblioteca.ufc.br. As partes específicas do formato alternativo deverão ser feitas em concordância com o *Manual de Normalização para Defesa de dissertação de Mestrado e tese de Doutorado no formato Alternativo do PPGO*, disponível no sítio http://www.ppgo.ufc.br.

§3º - As dissertações defendidas no formato alternativo deverão constar de, no mínimo, 01(um) capítulo, enquanto que as teses no mesmo formato deverão constar de, no mínimo, 02 (dois) capítulos.

§4º - Admite-se que a dissertação ou a tese sejam escritas e/ou defendidas em língua estrangeira seguindo as diretrizes definidas no regimento interno do Programa;

Anexo 2 – Registro do Protocolo da Revisão Sistemática no PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Citation

Victor Bento Oliveira, Fábio Wildson Gurgel Costa, Rodrigo Otavio Rego. Effect of Subgingival Periodontal Therapy on Glycemic Control in Type 2 Diabetics Patients: a Systematic Review and Meta-Analysis of 6-month Follow-up Randomized Clinical Trials. PROSPERO 2021 CRD42021234864 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021234864

Review question

This systematic review aims to answer the following question: Is subgingival periodontal therapy (surgical or non-surgical) able to improve glycemic control by reducing glycated hemoglobin levels in type 2 diabetic patients compared to untreated diabetic patients after 6 months of follow-up?

The investigation question was designed using the PICOTS acronym:

Population (P) - Patients with Type 2 Diabetes Mellitus (T2DM) and Periodontitis

Intervention (I) - Subgingival therapy with or without surgical access for scaling

Comparator (C) - Diabetics patients without intervention or Non-Active Periodontal Therapy (oral hygiene instruction, prophylaxis, supragingival scaling)

Outcomes (O) - Glycemic control assessed by glycated hemoglobin (HbA1c%)

Time (T) - At least 6 months of follow-up

Studies Type (S) - Randomized Clinical Trials (RCTs)

Searches

Nine online databases will be accessed to collect primary information in the scientific literature from the initial indexing moment up to February 10th, 2021: MEDLINE (through PubMed), Scopus, Embase, Web of Science, Latin American and Caribbean Health Science Information - LILACS (through BVS), Livivo, DOSS (through EBSCO host), CINAHL (through EBSCO host) and Cochrane Library. The grey literature available on ProQuest, Google Scholar, and OpenGrey also will be searched. In addition, the reference list of selected RCTs will be searched manually for additional articles. The research will be updated soon after data extraction.

A search algorithm built by combining indexed terms, non-indexed terms and their synonyms will be individualized for each database. The sensitivity of the search algorithm was assessed in PubMed, whereupon at least seven of eight "sentinel articles" should be retrieved by the final search algorithm. Endnote X7 will be used for automatic exclusion of duplicate studies.

There will be a restriction on articles written in the alpha-Latin language.

Types of study to be included [1 change]

Inclusion: