

Mylene Martins Monteiro

**Glycemic control in type 2 diabetic patients with
periodontitis after nonsurgical periodontal therapy
associated or not to adjunctive therapies:
Systematic review with meta-analysis**

Brasília
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Trabalho de Conclusão de Curso apresentado ao Departamento de Odontologia da Faculdade de Ciências da Saúde da Universidade de Brasília, como requisito parcial para a conclusão do curso de Graduação em Odontologia.

Orientadora: Profa. Dra. Cristine Miron Stefani

Brasília
2019

À minha família que, com muito carinho, não mediu esforços para que eu concluísse mais essa etapa da minha vida.

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EPÍGRAFE

“O sucesso nasce do querer, da determinação e persistência em se chegar a um objetivo. Mesmo não atingindo o alvo, quem busca e vence obstáculos, no mínimo fará coisas admiráveis.”

José de Alencar

RESUMO

MONTEIRO, Mylene. Glycemic control in type 2 diabetic patients with periodontitis after nonsurgical periodontal therapy associated or not to adjunctive therapies: Systematic review with meta-analysis. 2019. Trabalho de Conclusão de Curso (Graduação em Odontologia) – Departamento de Odontologia da Faculdade de Ciências da Saúde da Universidade de Brasília.

A Este estudo teve como objetivo responder, por meio de uma revisão sistemática com meta-análise, à pergunta focada: há diferença entre o controle glicêmico e desfechos clínicos periodontais em pacientes diabéticos tipo 2 com periodontite submetidos a TPNC (terapia periodontal não cirúrgica) associada ou não a terapias periodontais adjuntas? Foram incluídos ensaios clínicos randomizados em que diabéticos tipo 2 com periodontite foram tratados com TPNC, ou com TPNC associada a terapias adjuntas. As bases de dados utilizadas foram PUBMED, Cochrane Library, LIVIVO, BVS, SCOPUS, Web of Science, e a literatura cinzenta. De 752 artigos recuperados, 17 foram incluídos. Sete usaram antibioticoterapia sistêmica associada à TPNC e dez outras terapias. Quatro artigos foram considerados com baixo risco de viés, onze com risco moderado e dois com risco elevado. Quinze artigos foram incluídos na meta-análise. Quando terapias adjuntas foram associadas a TPNC, comparada à TPNC sozinha, houve redução de 0,24% no nível de HbA1c ($p=0,003$) e 6,14% de sítios com sangramento à sondagem ($p = 0,02$) após 3 meses de acompanhamento; redução de 0,2 mm na profundidade de sondagem ($p=0,003$), 5,26% dos sítios com sangramento à sondagem ($p=0,02$) e ganho de inserção clínica de 0,23 mm ($p= 0,02$) após seis meses de acompanhamento. A associação de terapias adjuntas à TPNC

comparada a TPNC sozinha reduziu os níveis de HbA1c e melhorou os parâmetros clínicos periodontais em diabéticos tipo 2 com periodontite.

ABSTRACT

MONTEIRO, Mylene. Glycemic control in type 2 diabetic patients with periodontitis after nonsurgical periodontal therapy associated or not to adjunctive therapies: Systematic review with meta-analysis. Undergraduate Course Final Monograph (Undergraduate Course in Dentistry) – Department of Dentistry, School of Health Sciences, University of Brasília.

The aim of this study was to answer, through a systematic review with metaanalysis, the focused question: Is there any difference between the glycemic control and periodontal clinical outcomes of type 2 diabetic patients with periodontitis submitted to NSPT (non-surgical periodontal therapy) associated or not to adjunctive periodontal therapies? Randomized Clinical Trials in which type 2 diabetics patients with chronic periodontitis were treated with NSPT alone or NSPT + adjunctive therapies were included. Databases searched were PUBMED, Cochrane Library, LIVIVO, BVS, SCOPUS, Web of Science, and grey literature. Risk of bias was evaluated and metaanalysis performed. From 752 initially retrieved references, 17 were included. Seven used systemic antibiotic therapy associated to NSPT and ten used other therapies. Four articles were considered with low risk of bias, 11 moderate risk and two high risk. Fifteen articles were included on metaanalysis. When adjunctive therapies were associated with NSPT compared to NSPT alone, there was a 0.24% reduction in HbA1c level ($p = 0.003$) and 6.14% of sites with probing bleeding ($p = 0.02$) after 3 months follow up; 0.2 mm reduction in probing depth ($p = 0.003$), 5.26% of sites with probing bleeding ($p = 0.02$) and 0.23 mm clinic attachment gain ($p = 0.02$) after six months of follow-up. The use of adjunctive therapies with TPNC compared

to TPNC alone reduced HbA1c levels and improved periodontal clinical outcomes in type 2 diabetics with periodontitis.

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ARTIGO CIENTÍFICO

Este trabalho de Conclusão de Curso é baseado no artigo científico:

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FOLHA DE TÍTULO

Glycemic control in type 2 diabetic patients with periodontitis after nonsurgical periodontal therapy associated or not to adjunctive therapies: Systematic review with meta-analysis.

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ABSTRACT

Glycemic control in type 2 diabetic patients with periodontitis after nonsurgical periodontal therapy associated or not to adjunctive therapies: Systematic review with meta-analysis.

Abstract

The aim of this study was to answer, through a systematic review with metanalysis, the focused question: Is there any difference between the glycemic control and periodontal clinical outcomes of type 2 diabetic patients with periodontitis submitted to NSPT (non-surgical periodontal therapy) associated or not to adjunctive periodontal therapies? Randomized Clinical Trials in which type 2 diabetics patients with chronic periodontitis were treated with NSPT alone or NSPT + adjunctive therapies were included. Databases searched were PUBMED, Cochrane Library, LIVIVO, BVS, SCOPUS, Web of Science, and grey literature. Risk of bias was evaluated and metanalysis performed. From 752 initially retrieved references, 17 were included. Seven used systemic antibiotic therapy associated to NSPT and ten used other therapies. Four articles were considered with low risk of bias, 11 moderate risk and two high risk. Fifteen articles were included on metanalysis. When adjunctive therapies were associated with NSPT compared to NSPT alone, there was a 0.24% reduction in HbA1c level ($p = 0.003$) and 6.14% of sites with probing bleeding ($p = 0.02$) after 3 months follow up; 0.2 mm reduction in probing depth ($p = 0.003$), 5.26% of sites with probing bleeding ($p = 0.02$) and 0.23 mm clinic attachment gain ($p = 0.02$) after six months of follow-up. The use of adjunctive therapies with TPNC compared to TPNC alone reduced HbA1c levels and improved periodontal clinical outcomes in type 2 diabetics with periodontitis.

Keywords

Type 2 diabetes, periodontitis, nonsurgical periodontal therapy, antibiotic therapy, laser therapy, photodynamic therapy.

INTRODUCTION

As Periodontitis and type 2 diabetes mellitus are both common chronic conditions among people all over the world [1,2]. Periodontitis is defined as a “microbially-associated, host-mediated inflammation that results in loss of periodontal attachment” [3]. This inflammatory process begins and progresses with exacerbated tissue response to the pathogenic microorganisms such as bacteria and their byproducts within the dental biofilm [4,5].

Type 2 diabetes mellitus (T2D), formerly known as non-insulin dependent, is most commonly seen in older adults. T2D is a metabolic disorder characterized by high blood sugar (hyperglycemia) due to insulin resistance and decreased production of insulin by the pancreas [2]. Therefore, diabetes can lead to other health alterations, including Periodontal diseases [6].

The relationship between periodontitis and T2D is bidirectional and has been related in previous meta-analyses studies [7]. T2D causes impairment in glycemic control that can be associated to decreasing of polymorphonuclear leukocytes activity and damaging of the microvascular endothelium, both affecting the susceptibility to periodontal diseases. The presence of chronic inflammation within periodontal tissue can increase the circulating cytokines and prostaglandins which might trigger a systemic host response. These events are believed to decrease the action of insulin and impair the glycemic control [8].

The beneficial effect of periodontal treatment in glycemic control of type 2 diabetic patients is being studied since 1960. Periodontal treatment keystone is nonsurgical periodontal therapy (NSPT), mainly scaling and root planing, which have as most important goal the elimination of subgingival microorganism and reparation of support tissue [9]. It can therefore contribute to

control the inflammatory condition and decrease circulating CRP and TNF- α levels, leading to a reduction of HbA1c, otherwise improving glycemic control [6].

However, NSPT alone may not significantly eliminate pathogenic bacteria, that many times are inaccessible to periodontal instruments [10]. This way, adjunctive therapies such as systemic antimicrobial therapy, laser therapy, and phototherapy were tested aiming to improve the glycemic control after NSPT.

Systematic reviews with meta-analysis recently published have suggested that NSPT can contribute with the metabolic control in diabetics patients. However, the effects of the NSPT might be confused with the effects of additional therapies (local or systemic antibiotic therapy, laser therapy or others) [11,12].

Recently Cao et al. [13] compared the HbA1c reduction of NSPT with no treatment, NSPT with NSPT plus adjuvant therapy and NSPT plus adjuvant therapy with different adjuvant therapies. The meta-analysis showed an improvement in HbA1c% in all therapies comparing with no treatment, with 2 exceptions: subantimicrobial dose doxycycline and SRP plus local drugs [13]. Therefore, the present review was focused in comparing whether the introduction of adjunctive therapies into NSPT can improve the glycemic control and/or periodontal clinical outcomes of type 2 diabetic patients with periodontitis.

The aim of this study was to compare the effect of the non-surgical periodontal therapy (NSPT) alone or associated with adjunctive periodontal therapies in the metabolic control and periodontal clinical outcomes of type 2 diabetic patients (T2D) with periodontitis, through a systematic review of the literature with meta-analysis. The focused question answered was: Is there any difference between the glycemic control and periodontal clinical outcomes between type 2 diabetic patients with periodontitis submitted to NSPT associated to adjunctive periodontal therapies or NSPT alone?

METHODS

This Systematic Review and Meta-Analyses of intervention has been reported following PRISMA guidelines, as described in <http://www.prisma-statement.org/statement.htm>. The protocol of systematic review was registered in PROSPERO – International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO/), number CRD42016051549.

Eligibility Criteria

To define inclusion criteria, the acronym PICO was followed:

- Patients: adult patients with diabetes type 2 and periodontitis
- Intervention: NSPT (nonsurgical periodontal therapy) plus an adjunctive therapy (local or systemic antibiotics, laser therapy, phototherapy, etc.)
- Comparison: NSPT alone.
- Outcome: primary outcome was glycosylated hemoglobin (HbA1c) and secondary outcomes were periodontal clinical measurements: pocket probing depth (PPD), clinical attachment level (CAL) and bleeding on probing (BOP).
- Study designs: Randomized Clinical Trials.
- Follow-up: at least three months

Exclusion Criteria

- Reviews, Editorials, Letters, Conferences, Summaries, Books, Opinions;
- Observational Studies (Case-Control, Cohort and Cross-sectional), non-randomized or non-parallel study design;
- Studies whose sample included patients with diabetes type 1 or other periodontal disease besides periodontitis;
- Studies without considered primary outcome;

- Studies in which control group received any therapy other than NSPT alone, or remained untreated;
- Studies in which no adjunctive treatment to NSPT was tested;
- Studies with no available full text article or studies protocols;
- Studies written in non-Latin alphabet.

Search Strategy and Information Source

The PICO acronym was used to build the search strategy, with words related to P ("Diabetes Mellitus, Type 2" AND "Periodontitis"); I/C ("nonsurgical periodontal therapy" OR "antibiotic therapy" OR "laser therapy" OR "photodynamic therapy" OR "periodontal surgery") and O ("glycosylated hemoglobin A"). Descriptors of Medical Subject Headings (MeSH terms) were used to build the search strategy, and synonyms and terms variations were also used. The complete search strategy is available in appendix 1.

The electronic search was carried out in May 17th, 2019, using the following databases: PUBMED (National Center for Biotechnology Information), Cochrane Library, LIVIVO, BVS (LILACS), SCOPUS, Web of Science and the grey literature by PROQUEST, Open Grey and Google Scholar.

Study Selection

Studies eligibility was assessed independently by two reviewers (MMM e TGSN). After the database search, the duplicated references were removed using Rayyan QRCI (available at <https://rayyan.qcri.org/>), followed by manual removal. The articles selection was accomplished in two phases. In phase I, two independent reviewers analyzed title and abstract of the references, in accordance with the eligibility criteria, using Rayyan QRCI. The articles retrieved from grey literature were analyzed the same way.

In phase II, both reviewers read the full article, excluding those that did not meet the eligibility criteria. In the occurrence of

disagreements in any phase, a third reviewer (CMS) were consulted for a final decision. Manual search of included article's reference list was also performed.

Zotero Reference Manager (available at <https://www.zotero.org/>) was used to organize the review.

Data Extraction

The following data were extracted from included studies to build Table 1: author, country, publication year, case-definitions for periodontitis and T2D, samples (n, age, sex), treatment groups, results and main conclusions.

The Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomized Trials [14] was used to assess the risk of bias of included studies. Cochrane's Tool includes items regarding random sequence generation; allocation concealment; blinding of participants and personnel; blinding of participants assessment; incomplete outcome data; selective reporting and other bias. If three parameters were evaluated as unclear or two as high risk of bias, the study was considered at moderate risk, if three parameters were evaluated as high risk, the study was classified at high risk of bias. Otherwise, studies were considered at low risk of bias.

Data collection and risk of bias analysis were performed independently by two reviewers (MMM e TGSN) and checked by a third reviewer (CMS) for final decision.

Meta-analysis were performed using inverse variance, considering the mean difference as effect measure for glycosylated hemoglobin, pocket probing depth, clinical attachment level and bleeding on probing (final value – baseline value) for groups comparison (Adjunctive Therapies + NSPT versus NSPT alone), with a significance level of 95%, with two periods follow up: 3 and 6 months. Data heterogeneity was tested through I^2 test to define the type of effect (fixed or random)

adopted. The software Review Manager version 5.3.5 (Nordic Cochrane Center, Copenhagen, Denmark) was used.

RESULTS

Study selection

The Flow diagram for studies selection and inclusion process is shown in Figure1. The database search yielded a total of 722 articles and 30 additional from grey literature. After duplicate removal, 409 records remained. Phase 1 (title and abstract screening) identified 80 potentially relevant studies.

At Phase 2, the 80 full articles were retrieved and evaluated for inclusion. Sixty-three did not meet the inclusion criteria and were excluded as reported in appendix 2 (excluded articles and reason for exclusion). A total of 17 were included for qualitative analysis, 15 of whom were included for quantitative analysis.

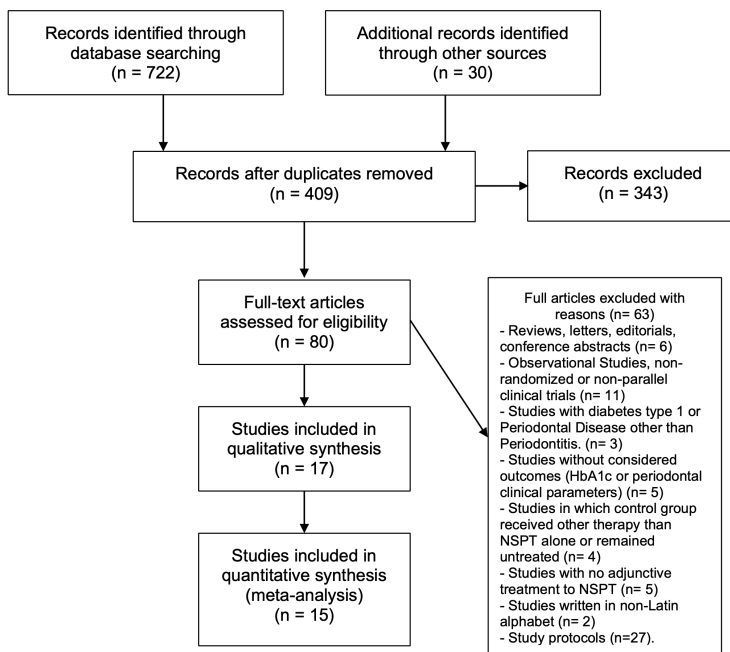


Figure 1: Flow diagram of studies selection and inclusion process (adapted from PRISMA 2009, available at www.prisma-statement.org)

Studies characteristics

Seventeen studies were included, four of which were conducted in Brazil [19,20,25,30], three in India [9,16,21], two in Egypt [28,29], two in Turkey, and seven in other countries (Greece [22], Iran [23], Poland [17], Saudi Arabia [15], United States [18] and Taiwan [24]). All of them were written in English.

Eight studies used systemic antibiotic therapy as adjunctive therapy [15-22]. Three studies used local antibiotic or antiseptic

[18,23,24,]. Five studies used diode laser or photodynamic therapy [9,15,25-27]. And three Studies used other therapies, like propolis intake [28]; omega 3 polyunsaturated fatty acids plus acetylsalicylic acid intake [29]; and homeopathic treatment [30]. Eight studies evaluated outcomes after 3 months follow up [9,15,17,18-21,27], one study after 4 months [16], eight after 6 months [22,23,24-26,28,29] and one after 12 months follow up [30].

For meta-analyses, studies were divided in two subgroups: NSPT + systemic antibiotics (doxycycline or amoxicillin plus clavulanic acid) and NSPT + Other therapies (subantimicrobial dose of doxycycline, local minocycline or chlorhexidine, diode laser application, photodynamic therapy, propolis intake, omega 3 polyunsaturated fatty acids plus acetylsalicylic acid intake, homeopathic therapy). And meta-analyses were performed for two follow up periods: 3 and 6 months, for each outcome (HbA1c, PPD, CAL and BOP).

All included studies (n=17) tested HbA1c as metabolic control indicator. Only four of them [21,27,28,30] showed significant difference for HbA1c when adjunctive therapies plus NSPT were compared to NSPT alone in any time period favoring the adjunctive therapy group. None of them used systemic antibiotics. And one [20] found significant difference favoring NSPT alone, compared to NSPT plus amoxicillin/clavulanic acid.

Also, all included studies evaluated PPD and CAL as periodontal clinical outcomes. Five studies [9,17,19,27,29] found significant difference for PPD and five [9,16,18,29,30] found significant difference for CAL favoring adjunctive therapy group at the end of the study.

Eight Studies tested bleeding on probing as outcome and two [25,26] found significant difference between groups, favoring adjunctive therapy group.

None included study found improved periodontal clinical outcomes for NSPT alone, when compared to NSPT plus

adjunctive therapies. Qualitative synthesis of included studies is presented in Table 1.

Table 1: Qualitative synthesis of included studies.

Author, year	Country	Age in years, Mean \pm SD and/or Range	Case definitions (PD and ZDM)	Groups (n) and treatments	Outcomes comparison between groups	Main Conclusions
Denizlek, Elbas et al., 2019 [26]	Turkey	30 to 60 years old TG: 50.6 \pm 7.25 CG: 48.05 \pm 6.05	PD: PPD 4-7mm in at least 4 teeth in the upper jaw, \geq 20 remaining teeth. ZDM: according to ADA, diagnosed 2 years before the study; HbA1C \geq 7%	TG (n=18): NSPT + diode laser application (with 810 nm wavelength, 1-watt power, contact mode using a 400 μ m fiber optic tip) CG (n=19): NSPT + placebo laser	Initial HbA1c (%) TG: 7.43 \pm 0.32 CG: 7.31 \pm 0.32 After 3 months HbA1c (%) (NS) TG: 7.06 \pm 0.31 CG: 7.00 \pm 0.29 BOP (%) TG1: 23.6 \pm 6.0 CG1: 30.15 \pm 8.63 p=0.008 After 6 months HbA1c (%) (NS) TG1: 6.88 \pm 0.34 CG: 7.09 \pm 0.29 BOP (%) TG1: 24.65 \pm 7.06 CG: 31.7 \pm 9.0 p=0.009 PDD and CAL: NS	The use of diode laser contributed to reducing pocket depth and local inflammation. However, it did not affect systemic inflammatory response. The diode laser use in periodontal therapy is beneficial for periodontal healing, but is not beneficial for metabolic control of diabetes
El-Sharkawy et al., 2016 [28]	Egypt	38 to 63 years old TG: 48.9 \pm 8.3 CG: 51.2 \pm 8.5	PD: PPD and CAL \geq 5 mm with BOP in at least one site/sexant; \geq 20 teeth. ZDM: for \geq 5 years; taking oral hypoglycemic drugs and/or insulin for \geq 5 months	TG (n=24) propolis + NSPT group (400 mg capsule orally, once daily for 6 months) CG (n=26) placebo + NSPT group	Initial HbA1c TG: 8.73 \pm 0.55 CG: 8.59 \pm 0.91 After 3 months HbA1c (%) (NS) TG: 8.71 \pm 0.56 CG: 8.68 \pm 0.82 After 6 months HbA1c (%) TG: 7.75 \pm 0.48 CG: 8.5 \pm 0.73 p<0.01 PDD and CAL: NS	Systemic propolis used as an adjunctive therapeutic agent to NSPT significantly improves periodontal therapy outcomes in individuals with ZDM and CP. In patients with ZDM, continuous daily intake of propolis after NSPT for 6 months yields significant reduction in levels of HbA1c, exhibiting additional health benefits for this category of patients.

Author, year	Country	Age in years Mean \pm SD and/or Range	Case definitions (PD and 2DM)	Groups (n) and treatments	Outcomes comparison between groups	Main Conclusions
Al-Zahrani et al., 2009 [15]	Saudi Arabia	TG1 51.42 \pm 6.24 TG2 51.92 \pm 7.28 CG 53.14 \pm 10.91 P>0.05	PD: CAL \geq 3 mm at \geq 30% of sites \geq 20 remaining teeth. 2DM: confirmed diagnosis (no further description)	TG 1 (n = 14): NSPT plus doxycycline 2x 100 mg for day 1 and then 100 mg once a day for 13 days TG2 (n= 14): NSPT plus PDT (photodynamic therapy with 0.01% methylene blue as photosensitizing agent and 670-nm non-thermal diode laser irradiation) CG (n = 15) NSPT	Initial HbA1c TG1: 8.42 \pm 1.65 TG2: 9.25 \pm 2.71 CG: 8.75 \pm 1.43 After 3 months HbA1c (%) (NS) TG1: 7.71 (1.77) TG2: 8.79 (2.85) CG: 8.22 \pm 0.95 BOP, PPD and CAL: NS	No added benefit of PDT on clinical periodontal parameters and glycemic control in patients with diabetes was found. Non- surgical periodontal treatment plus doxycycline showed an improvement in the glycemic control of patients with diabetes.
Barbosa et al., 2018 [25]	Brazil	35 to 65 years Mean age 52.2 years	PD: \geq 15 remaining teeth, moderate or severe chronic generalized periodontitis (no definition provided) 2DM: HbA1c <7%, under antidiabetic therapy	TG (n = 6): NSPT plus PDT (photodynamic therapy with methylene blue 10mg/ml as photosensitizing agent, 0.8J per site, six sites, 660nm red diode laser irradiation) CG (n = 6): NSPT	Initial HbA1c (%) TG: 8.8 \pm 1.7 CG: 7.91 \pm 1.9 After 3 months HbA1c (%) (NS) TG: 9.1 \pm 1.4 CG: 7.6 \pm 1.7 After 6 months HbA1c (%) (NS) TG: 9.1 \pm 2.0 CG: 7.5 \pm 1.3 BOP (%) TG1: 18.7 \pm 1.5 CG: 32.1 \pm 11.2 p=0.05 PDD and CAL: NS	When NSPT was combined with PDT, no additional benefits were observed for the periodontal and metabolic clinical parameters.

Author, year	Country	Age in years Mean \pm SD and/or Range	Case definitions (PD and 2DM)	Groups (n) and treatments	Outcomes comparison between groups	Main Conclusions
Chandra and Shashikum ar, 2019 [9]	India	30 to 60 years old TG: 50.6 \pm 7.25 CG: 48.05 \pm 6.05	PD: PPD \geq 4.7mm and CAL \geq 2mm, with at least 3 teeth per quadrant. \geq 20 remaining teeth. 2DM: confirmed diagnosis (no further description)	TG (n=18): NSPT Plus diode laser application (with a wavelength 808 nm and a power setting of 1.5 W-1.8 W were used in continuous, contact mode with a thin flexible fiber-optic cable (320 nm). CG (n=18): NSPT	Initial HbA1c (%) TG: 8.12 \pm 1.27 CG: 7.99 \pm 1.27 After 3 months: HbA1c (%) (NS) TG: 6.83 \pm .65 CG: 7.22 \pm 0.79 PPD (mm) TG: 1.8 \pm 0.3 CG: 2.63 \pm 0.39 p<0.001 CAL (mm) TG: 6.6511 \pm 0.5315 CG: 7.5011 \pm 0.5242 p<0.001	The use of diode laser therapy after NSPT is more effective than NSPT alone in the overall improvement of clinical and microbiological parameters. Also, the adjunctive use of soft tissue diode laser resulted in better improvement in HbA1c in NIDDM patients than NSPT alone after 3 months.

Author, year	Country	Age in years Mean \pm SD and/or Range	Case definitions (PD and 2DM)	Groups (n) and treatments	Outcomes comparison between groups	Main Conclusions
Grossi et al., 1997 [18]	USA	25 to 65 years (n = 113) Native Americans	PD: severe periodontal disease (no further description) 2DM: history of diabetes mellitus defined according to World Health Organization criteria.	TG 1: NSPT + topical H ₂ O and doxycycline 100 mg per day; TG2: NSPT + topical 0.12% Chlorhexidine (CHX) and doxycycline 100mg per day; TG3: NSPT + topical 0.05% povidone-iodine and doxycycline 100 mg per day TG4: NSPT + topical 0.12% chlorhexidine (CHX) and placebo CG: NSPT + topical H ₂ O and placebo	After 6 months All 5 study groups showed levels of HbA1c comparable to baseline levels. Only TG2 (NSPT + topical 0.12% Chlorhexidine + systemic doxycycline) showed statistically significant gain of attachment level (P< 0.05).	The reduction seen at 3 months in the HbA1c doxycycline-treated groups is the combined result of the antimicrobial effect and inhibition of the glycation process. This proposal suggests the need for effective treatment and long-term control of periodontal infection as part of the overall management of patients with diabetes mellitus.
Koçak et al., 2016 [27]	Turkey	35 to 60	PD: \geq 30 years old; \geq 17 teeth, \geq 8 sites with PPD \geq 5mm 2DM: 5.7 % \leq HbA1c \leq 8.5 %	TG (n = 30): NSPT + diode laser application (940-nm indium-gallium- aluminum-phosphate diode laser, 1.5 W pulse interval of 20 ms and pulse length 20 ms - 20 and 15 J/cm2 of energy, respectively) CG (n = 30): NSPT	After 3 months HbA1c (%) (Δ 0-3) TG: 0.41 \pm 0.19 CG: 0.22 \pm 0.25 P < 0.05 PPD (Δ 0-3) TG: 3.84 \pm 0.68 CG: 2.98 \pm 0.42 P < 0.05 CAL: NS	NSPT + DL (0.41 %) was superior in decreasing HbA1c levels compared to NSPT alone (0.22 %) in DM2 patients with periodontitis.
Lin et al., 2012 [24]	Taiwan	TG: 56.6 \pm 7.8 CG: 59.0 \pm 6.5	PD: \geq 20 remaining teeth and \geq 5 teeth with PPD \geq 5mm 2DM: HbA1c \geq 8.5% for more than 5 years	TG (n= 14): NSPT + subgingival 2% minocycline gel CG (n=14): NSPT	After 6 months HbA1c% reduction >0.66% TG: 57% (8 in 14 patients) CG: 64% (9 in 14 patients) NS PDD, CAL and BOP: NS.	Nonsurgical periodontal therapy with or without subgingival minocycline application may achieve significant periodontal improvement and moderate improvement in HbA1c, but had no significant effect on plasma levels of IL-6, CRP, or sRAGE in patients with poorly controlled 2DM.

Author, year	Country	Age in years Mean \pm SD and/or Range	Case definitions (PD and 2DM)	Groups (n) and treatments	Outcomes comparison between groups	Main Conclusions
Elwakeel e Hazaa, 2015 [29]	Egypt	24 to 58 years old; mean age 40.05 \pm 9	PD: \geq 14 natural teeth, of which at least five had a site with PPD \geq 5 mm and CAL \geq 4 mm. 2DM: HbA1c between 7% and 8%, type 2 DM for more than 2 years diagnosed according to the American Diabetes Association criteria).	TG (n = 20): NSPT + omega 3 polyunsaturated fatty acids (O3 PUFAs – 1g three times daily) + aspirin (75 mg of acetylsalicylic acid once daily) CG (n = 20): NSPT + placebo	Initial HbA1c TG: 7.6 \pm 0.4 CG: 7.59 \pm 0.33 After 3 months HbA1c (%) (NS) TG: 7.14 \pm 0.42 CG: 7.43 \pm 0.37 After 6 months HbA1c (%) (NS) TG: 6.99 \pm 0.51 CG: 7 \pm 0.4 PPD (mm): TG: 2.8 \pm 0.52 CG: 3.8 \pm 0.7 p<0.01 CAL (mm): TG: 3 \pm 1.78 CG: 4.2 \pm 0.52 p<0.01	Preliminary data about the value of the dietary use of Ω 3 PUFAs and aspirin in the prevention and management of patients with chronic periodontitis and type 2 DM, with better glycemic control.
Faramarzi et al., 2017 [23]	Iran	30 to 60 years old; mean age TG: 52.7 \pm 7.3 CG: 55.3 \pm 8.8	PD: moderate to severe. At least 8 teeth with PPD \geq 5mm 2DM: HbA1c over 6%	TG (n = 34): NSPT + subgingival CHX gel CG (n = 34): NSPT	Initial HbA1c (%) TG: 7.72 \pm 0.99 CG: 7.32 \pm 1.06 After 3 months HbA1c (%) (NS) TG: 6.20 \pm 0.97 CG: 6.53 \pm 1.06 After 6 months HbA1c (%) (NS) TG: 6.06 \pm 1.04 CG: 6.42 \pm 1.02 PDD and CAL: NS.	Nonsurgical periodontal therapy can effectively decrease FBS and HbA1c levels in diabetic patients. Higher improvements observed in metabolic parameters with application of CHX gel can be attributed to antimicrobial effects of this adhesive material.

Author, year	Country	Age in years Mean \pm SD and/or Range	Case definitions (PD and 2DM)	Groups (n) and treatments	Outcomes comparison between groups	Main Conclusions
Gaikwad et al., 2013 [16]	India	Aged 30 to 70 years	PD: chronic generalized periodontitis, no definition provided 2DM: receiving antidiabetic therapy, no further description	TG (n = 25): NSPT + antibiotic administration (doxycycline 100 mg once in day prescribed for 15 days) CG (n = 25): NSPT	Initial HbA1c (%) TG: 8.38 \pm 0.89 CG: 8.06 \pm 1.10 After 4 months HbA1c (%) (NS) TG: 7.00 \pm 0.76 CG: 7.11 \pm 0.99 CAL (mm): TG: 2.69 \pm 0.42 CG: 2.99 \pm 0.49 P = 0.042 PDD: NS	On intergroup comparison between the TG and CG, adjunctive use of systemic doxycycline showed improvement in the CAL and PPD, which was statistically significant, but the effect on the HbA1c level was not statistically significant.
Gilowski et al., 2012 [17]	Poland	36 to 68 years TG: 57.6 \pm 8.0 CG: 56.0 \pm 9.0 P=0.59	PD: at least 4 nonadjacent sites with PPD \geq 4mm 2DM: diagnosed at least 6 months before the study	TG (n = 17): NSPT+ SDD (Subantimicrobial dose doxycycline hydrochloride, 20 mg for 3 months, in 12h intervals) CG (n = 17): NSPT + placebo for 3 months (12h intervals)	Initial HbA1c (%) TG: 6.7 (6.3-7.0) CG: 6.2 (6.0-7.8) After 3 months HbA1c (%) (NS) TG: 6.7 (6.3-7.7) CG: 6.3 (5.5-7.3) PPD and CAL: NS, except for initial PPD \geq 4, when SDD group showed a greater reduction (P = 0.02).	SDD therapy in diabetic patients with CP leads to the reduction in GCF MMP-8 levels accompanied by significant improvement in PPD at tooth sites with moderate disease (PPD \geq 4mm).

Author, year	Country	Age in years Mean \pm SD and/or Range	Case definitions (PD and ZDM)	Groups (n) and treatments	Outcomes comparison between groups	Main Conclusions
Mourão et al., 2019 [30]	Brazil	32 to 70 years TG: 56.6 \pm 7.8 CG: 59.0 \pm 6.5	PD: severe with at least 2 proximal sites of 2 nonadjacent teeth with PPD \geq 6mm and CAL \geq 5mm ZDM: attested by an endocrinologist	TG (n= 40): NSPT + homeopathic therapy Berberis 6CH (two tablets, 2x/daily, 45 days), Mercurius solubilis /Belladonna / Hepar sulphur - 6CH (two tablets, 3x/daily, 15 days) and Pyrogenium - 200 CH, (single weekly dose, 2 weeks) CG (n=14): NSPT + placebos	Initial HbA1c (%) TG: 7.5 \pm 1.3 CG: 7.2 \pm 1.6 After 6 months HbA1c (%) TG: 5.6 \pm 1.9 CG: 6.2 \pm 1.9 p=0.001 After 12 months HbA1c (%) TG: 5.8 \pm 1.2 CG: 6.6 \pm 1.8 p< 0.001 CAL (mm) TG: 4.5 \pm 0.3 CG: 4.5 \pm 0.4 P = 0.03 PDD and BOP: NS.	Homeopathy as supplement of NSPT may further improve health condition, including glycemic control, in ZDM patients with periodontitis.
O'Connell et al., 2018 [19]	Brazil	TG: 52.3 \pm 6.3 CG: 53.5 \pm 13.6	PD: at least one site with PPD \geq 5mm and two teeth with attachment loss \geq 6 mm. ZDM: HbA1c >8%; diagnosed for >5 years	TG (n=15): NSPT + doxycycline 100 mg/day for 14 days. CG (n=15): NSPT + placebo	Initial HbA1c (%) TG: 11.8 \pm 1.6 CG: 10.7 \pm 2.0 After 3 months HbA1c (%) (NS) TG: 10.3 \pm 2.3 CG: 9.8 \pm 2.0 PPD (mm) TG: 1.9 \pm 0.3 CG: 2.1 \pm 0.3 P = 0.048 CAL and BOP: NS	Anti-infective periodontal therapy and adjunctive systemic doxycycline may influence the systemic conditions of patients with type 2 DM. However, it is possible that the observed improvements in glycemic control and in the reduction of inflammatory markers might be due to diet, which was not controlled in our study.

Author, year	Country	Age in years Mean \pm SD and/or Range	Case definitions (PD and ZDM)	Groups (n) and treatments	Outcomes comparison between groups	Main Conclusions
Rodrigues et al., 2005 [20]	Brazil	No description available	PD: ≥ 1 site with PPD ≥ 5 mm and 2 teeth with CAL \geq 6mm ZDM: no more than 5 years since diagnosis	TG (n=15): one-stage full- mouth NSPT + amoxicillin/clavulanic acid 875 mg twice daily for 2 weeks CG (n=15): one-stage full- mouth NSPT	Initial HbA1c (%): TG: 9.5 ± 2.4 CG: 8.8 ± 1.8 After 3 months HbA1c (%) TG: 9.2 ± 1.6 CG: 7.6 ± 1.4 p<0.05	Periodontal therapy improved glycemic control in patients with type 2 DM in both groups, however, the reduction in HbA1c values reached statistical significance only in the group receiving scaling and root planning alone.
Singh et al., 2008 [21]	India	≥ 30 years old	PD: $\geq 30\%$ of the teeth examined \geq 4mm PPD ZDMs: no description	TG (n=15): NSPT + systemic doxycycline (100mg daily for 14 days) CG (n=15): NSPT	Initial HbA1c (%): TG: 8.3 ± 0.7 CG: 7.9 ± 0.7 After 3 months HbA1c (%) TG: 7.5 ± 0.6 CG: 7.3 ± 0.6 p<0.05 PDD and CAL: NS	The results obtained appear to demonstrate a strong, statistically significant, association between clinical improvement in the periodontal condition and improved metabolic control of diabetes. Adjunctive doxycycline improves the periodontal and metabolic parameters to a statistically significant extent when compared to only periodontal therapy.
Tsalikis et al., 2014 [22]	Greece	TG: 62.9 ± 10 CG: 57.9 ± 8.2	PD: 6 pockets > 5 mm and CAL > 3 mm with radiographic bone loss ZDM: diagnosed >1 year, at least two consecutive values of HbA1c < 7.5%	TG (n = 31) NSPT + systemic doxycycline (200 mg as loading dose and 100 mg for 20 days) CG (n = 35) NSPT + placebo	Initial HbA1c (%): TG: 6.7 ± 0.61 CG: 6.89 ± 0.6 After 6 months HbA1c (%) (NS) TG: 6.48 ± 0.71 CG: 6.8 ± 0.87 PDD, CAL and BOP: NS	Well-controlled diabetic patients with periodontal disease display similar clinical, microbiological responses and MMP-8 levels, when treated by mechanical periodontal therapy alone compared to the adjunctive administration of systemic doxycycline.

PD: periodontitis; ZDM: Type 2 Diabetes Mellitus; PPD: periodontal probing depth; CAL: clinical attachment level; TG: Test Group; CG: Control Group; BOP: Bleeding on Probing;
HbA1c: Glycated Hemoglobin A; PDT: photodynamic therapy; NSPT: non-surgical periodontal therapy; ADA: American Diabetes Association.

Risk of Bias within Studies

The risk of Bias evaluation for the included Studies following reviewers' judgments is shown in Figure 2. Four Studies were considered at low risk of bias [22,28,29,30] and thirteen were considered at moderate risk of bias [9,15-21,23-27].

Barbosa et al. [25] and Koçak et al. [27] presented respectively four and three of seven domains with High risk of Bias, including selection, performance and detection bias. This may indicate high risk of bias.

Risk of bias of included studies is presented in figure 2.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Al-Zahrani et al. 2009	+	?	?	+	+	?	?
Barbosa et al. 2018	?	-	-	-	?	?	-
Chandra and Shashikumar 2019	+	+	?	?	?	?	-
Dengizek-Eltas et al. 2019	+	+	?	?	?	+	?
El-Sharkawy et al. 2016	+	+	+	+	+	+	+
Elwakeel et al. 2015	+	+	+	+	+	+	+
Faramarzi et al. 2017	+	-	?	?	+	+	?
Gaikwad et al. 2013	?	?	?	?	?	?	-
Gilowski et al. 2012	?	?	?	?	?	?	-
Grossi et al. 1997	?	?	?	?	?	?	?
Koçak et al. 2016	+	-	-	-	+	?	?
Lin et al. 2012	+	+	?	?	+	+	+
Mourão et al. 2019	+	+	+	+	+	+	+
O'Connell et al. 2008	?	?	?	?	+	+	?
Rodrigues et al. 2003	?	?	?	?	?	?	-
Singh et al. 2008	?	?	?	?	?	?	-
Tsalikis et al. 2014	+	+	+	+	+	+	+

Figure 2: Risk of bias analysis of included studies.

Studies individual characteristics and Synthesis of Results

Metabolic Control (HbA1c)

Fifteen Studies of 17 were included in meta-analysis of the effect of NSPT associated or not to adjunctive therapies on glycemic control (HbA1C% reduction) divided in two subgroups: Use of systemic antibiotics (n=6) and other therapies (n=10), including 333 patients. One study [15] comprised two adjunctive therapies groups (systemic doxycycline / phototherapy plus NSPT) compared to NSPT alone and was included in both subgroups, data from control group was duplicated in each subgroup comparison. Two studies were not included in meta-analysis, one [18] because provided no numeric data in tables, only graphs, and the other [24] because performed a logistic transformation of HbA1c results.

Al-Zahrani et al. [15], Grossi et al. [18], O'Connell et al. [19], and Singh et al. [21], found improvement in glycemic control and reduction in HbA1C with the adjunctive use of systemic doxycycline, while Gaikwad et al. [16] found no statistic difference and Tsalikis et al. [22] found similar responses compared to NSPT alone. Barbosa et al. [25] didn't observe additional benefits combining photodynamic therapy with NSPT. The association of diode laser described by Chandra et al. [9] and Koçak et al. [27] showed lower levels of HbA1C than NSPT, although, findings by Al-Zahrani et al. [15] and Dengizek et al. [26] showed no benefits for metabolic control.

El-Sharkawy et al. [28] showed that systemic propolis yields significant reduction in levels of HbA1c, the same result was found by Elwakeel et al. [29] using omega 3 and aspirin. Faramazi et al. [23] observed improvement of metabolic parameters using local Chlorhexidine gel. Gilowski et al. [17] observed that the use of doxycycline hydrochloride as adjunctive therapy favored the glicemic control.

Lin et al. [24] found improvements in HbA1C level using local

minoxicicline gel. Mourão et al. [30] observed significant improvements in laboratorial conditions when homeopathy was used as adjunctive therapy. Rodrigues et al. [20] found improvements using amoxicillin and clavulanic acid in HbA1C but reached statistical significance only in control group.

Statistic difference in HbA1c level was observed when other therapies were associated with NCPT was compared to NSPT alone ($p=0.03$) after 3 months follow up, but not when systemic antibiotics were associated (p=0.40) as showed in Figure 2. The overall effect of the use of adjunctive periodontal therapies associated with NSPT, compared to NSPT alone was significative ($p= 0.02$), mean difference -0.24% . Results can be observed in figure 3.

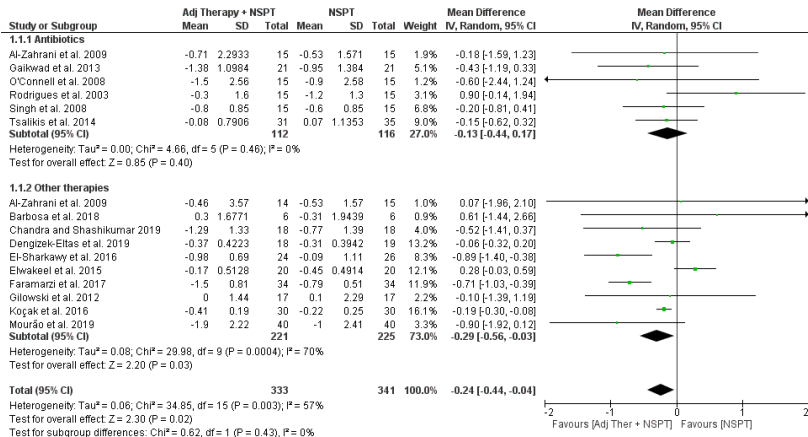


Figure 3: Forest plot of use of adjunctive therapies plus NSPT compared to NSPT alone on HbA1c level after 3 months follow up.

Six studies were included at the meta-analysis of six months follow up for HbA1c level. Besides the observed overall effect was slightly higher (-0,33%) it was not statistically significant ($p= 0.06$) (figure 4).

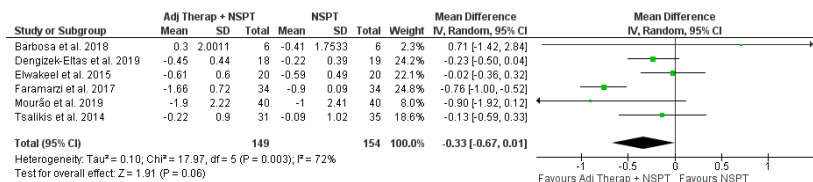


Figure 4: Forest plot of use of adjunctive therapies plus NSPT compared to NSPT alone on HbA1c level after 6 months follow up.

Periodontal Clinical Outcomes

Al-Zahrani et al. [15] showed no additional benefits on clinical periodontal parameters using systemic doxycycline as adjunctive therapy, while Tsalikis et al. [22] showed similar responses compared to NSPT alone. Gaikwad et al. [16], Singh et al. [21], Grossi et al. [18] and O'Connell et al. [19] showed improvement in the CAL and PPD. Barbosa et al. [25] found no additional benefit when photodynamic therapy was used as adjunctive therapy. Chandra et al. [9] and Koçak et al. [27] found improvement in clinical parameters using diode laser as adjunctive therapy, the same result was shown by Dengizek et al. [26], who found a reduction of PPD and local inflammation. Al-Zahrani et al. [15] observed no additional benefit.

EI-Sharkawy et al. [28] found improvements in periodontal parameters when propolis was used as adjunctive therapy. Omega 3 and aspirin tested by Elwakeel et al. [29] also showed better results. Faramazi et al. [23] showed that the use of CHX gel resulted in statistic significant improvement of clinical periodontal parameters. Gilowski et al. [17] observed significant improvement in PD using doxycycline hydrochloride.

Lin et al. [24] found no further improvement in clinical parameters using local minocycline gel as NSPT adjunctive, compared to NSPT alone. Mourão et al. [30] found significant improvement in periodontal conditions using homeopathy as adjunctive therapy. Rodrigues et al. [20] found improvement in periodontal

parameters using amoxicillin and clavulanic acid as adjunctive therapy to NSPT.

Pocket Probing Depth (PPD)

Fourteen of 17 studies were included in metanalysis for effect of adjunctive therapies plus NSPT versus NSPT alone on PPD after 3 months follow up. Two studies were not included in meta-analysis [18,28] because provided no numeric data in tables, only graphic representation of results, and one [17] because provided no standard deviation to mean values results.

Although there was difference when other therapies were associated to NSPT compared to NSPT alone (mean difference -0.34 mm, $p = 0.05$), the same was not observed when systemic antibiotics were used as adjunctive therapy ($p = 0.43$). Also, the overall effect was not significant ($p = 0.22$) (figure 5).

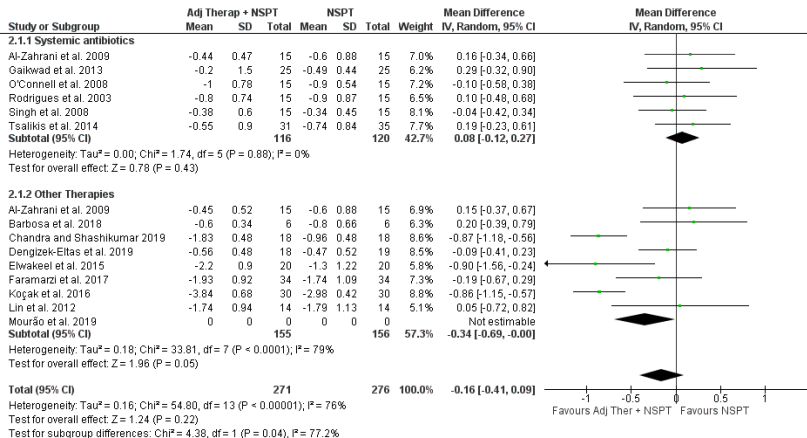


Figure 5: Forest plot of use of adjunctive therapies plus NSPT compared to NSPT alone on PPD after 3 months follow up.

Six studies were included at the meta-analysis of six months follow up for PPD. The observed overall effect was small (-0,20 mm), yet it was statistically significant ($p = 0,003$) (figure 6).

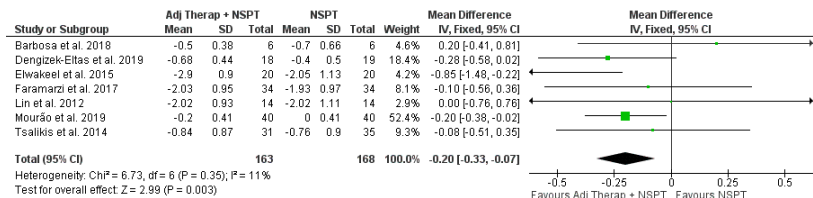


Figure 6: Forest plot of use of adjunctive therapies plus NSPT compared to NSPT alone on PPD after 6 months follow up.

Clinical Attachment Level (CAL)

Fourteen studies of 17 were included in meta-analysis for effect of adjunctive therapies plus NSPT versus NSPT alone on CAL after 3 months follow up. The studies not included in meta-analysis were the same as for PPD Meta-analysis [17, 18,28], for the same reasons. No significant difference was observed when systemic antibiotics ($p = 0.43$) or other therapies ($p = 0.30$) were used (overall effect mean difference -0.14 mm, $p = 0.11$) (figure 7).

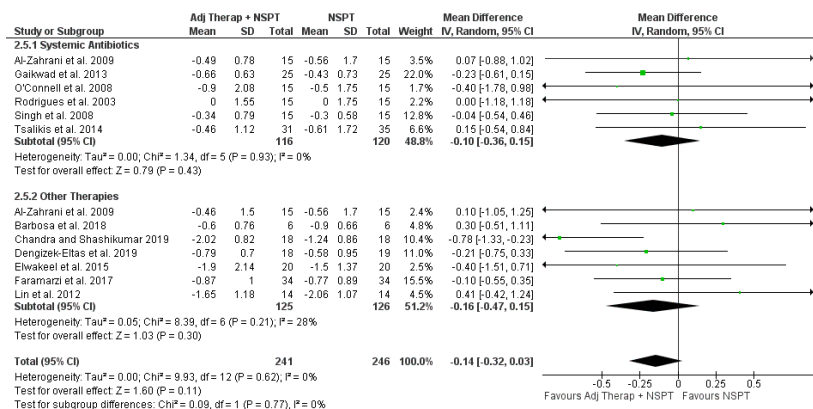


Figure 7: Forest plot of use of adjunctive therapies plus NSPT compared to NSPT alone on CAL after 3 months follow up.

Six studies were included at the meta-analysis of six months follow up for CAL. Like observed to PPD, besides overall effect

was small (mean difference -0,23 mm), it was statistically significant ($p= 0,02$) (figure 8).

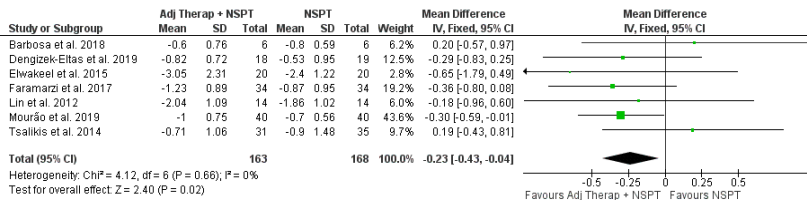


Figure 8: Forest plot of use of adjunctive therapies plus NSPT compared to NSPT alone on CAL after 6 months follow up.

Bleeding on Probing (BOP)

Only seven studies tested bleeding on probing and were included in meta-analysis for effect of adjunctive therapies plus NSPT versus NSPT alone on BOP after 3 months follow up. Four of them tested systemic antibiotics and four tested other adjunctive therapies (Al-Zahrani et al. [15] tested both). No significant difference was observed when systemic antibiotics ($p= 0.19$) or other therapies ($p= 0.35$) were used, however, overall effect mean difference -6.14% was statistically significant ($p= 0.02$) (figure 9).

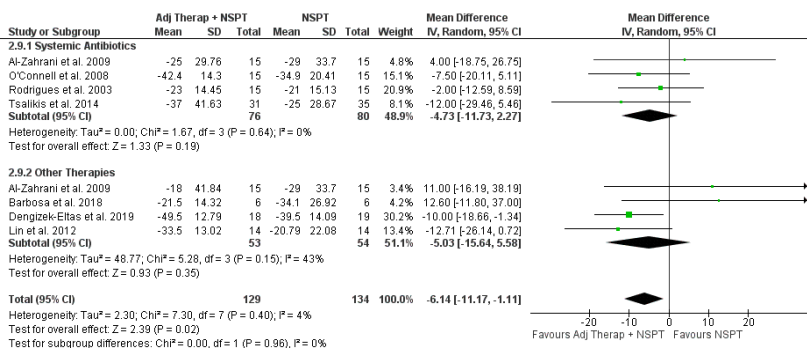


Figure 9: Forest plot of use of adjunctive therapies plus NSPT compared to NSPT alone on BOP after 3 months follow up.

Five studies were included at the meta-analysis of six months follow up for BOP. It was observed a statistically significant mean difference of -5.26% ($p = 0.02$) (figure 10).

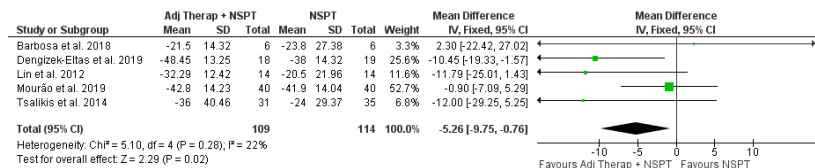


Figure 10: Forest plot of use of adjunctive therapies plus NSPT compared to NSPT alone on BOP after 6 months follow up.

DISCUSSION

This systematic review with meta-analysis evaluated the effect of non-surgical periodontal therapy (NSPT) alone or associated with adjunctive periodontal therapies on metabolic control and periodontal clinical outcomes in type 2 diabetic patients with periodontitis. Surprisingly, the use of systemic antibiotic therapy associated with NSPT in type 2 diabetic patients with chronic periodontitis was not more efficient than NSPT alone in reducing HbA1c levels after three months follow up ($p = 0.46$). Among the drug protocols tested, the use of doxycycline (100 mg / day for 14 to 20 days) associated with NSPT was more efficient than the combination of amoxicillin and clavulanic acid (875 mg twice daily for 14 days) with NSPT and NSPT alone in the reduction of HbA1c.

The use of systemic antibiotics in theory could contribute to the reduction of HbA1c not only on biofilm but also by acting in the body, reducing the risk associated with other systemic infections [11,21]. However, the reduction was not consistently observed. Similarly, for periodontal outcomes, systemic antibiotics associated to NSPT did not significantly contributed to PPD, CAL and BOP improvement. Furthermore, the use of antibiotics

could increase antimicrobial resistance and should often be avoided when possible.

The study design information and patients' characteristics were assessed to evaluate the similarity involving patient age, type of periodontitis and diabetes. The literature search followed the 1999 International Classification of Periodontal Diseases using "chronic periodontitis" as key word, which lead to studies that included preferably adult patients. Although, two of the authors also included younger patients in their study (< 30 years old) [18, 29]. In addition, seven studies included patients over 60 years old [16,1,18,22,25,28,30].

The meta-analysis found improvement in metabolic control after three months, but not after six months. This fact could be related to a lack of a follow-up evaluation, periodontal supportive therapy and patients' compliance during the course of the experiment. Also, visits reinforcing oral hygiene instructions should be performed, as stated by Elwakeel e Hazaa [29].

A non-expected phenomenon was the difference between three months meta-analysis and six months meta-analysis for two clinical parameters: pocket probing depth and clinical attachment level. The overall effect of both of them were statistically significant only after six months. This inconsistency may be attributed to periodontal wound healing, which may take a longer time.

The relation between periodontitis and diabetes mellitus was approached in recent studies, suggesting a bidirectional association between the two conditions, and the reciprocity of risk factors. The poor glycemic control triggered by T2D might improve the inflammatory process characteristic of periodontitis, while the inflammation associated to periodontitis tend to alter the glycemic control [31]. Also, the control of the inflammation triggered by periodontitis through periodontal therapy could be a tool to promote the metabolic control of patients with T2D [7].

Two recently published systematic reviews with meta-analysis have demonstrated that periodontal therapy alone contributed to metabolic control of diabetic patients, but the authors pointed that the effects of NSPT could confound with the effects of adjunctive therapies (local or systemic antibiotic therapy, phototherapy, etc.), that were not differentiated in the included studies [11,12].

Another meta-analysis published in 2019 [13] compared different treatments and their impact in HbA1C. Even though they found improvement in metabolic control within all therapies, they described SRP + aPDT + doxy as the most effective.

Geisinger et al. [32] published the clinical trial with the largest sample until today about the effects of NSPT without other adjunctive therapies on glycemic control in patients with DM2 and chronic periodontitis and didn't find significant difference after six months when compared to patients with untreated clinical conditions. According to the authors, considering that glycemic control is essential for a good prognosis of diabetes and is measured through glycated hemoglobin [33], more intensive periodontal approaches may be necessary for type 2 diabetic patients with periodontitis show reduction of HbA1c level.

Among other adjunctive therapies, the most frequent was the use of low-intensity laser. Three included studies used diode laser therapy (Koçak et al. [9]; Chandra et al. [26]; Dengizek et al. [27]). And two studies used photodynamic therapy (Al-Zahrani et al. [15] and Barbosa et al. [25]). None of the studies that used photodynamic therapy as adjunct to NSPT found any improvement on clinical periodontal parameters or glycemic control compared to NSPT. Similarly, only one of the studies with diode laser [9] found improvement in HbA1c level, while two found improvements in PPD [9,26], one in CAL [26] and one in BOP [27]. These inconsistent results are in agreement with findings of a recent systematic review [34], in which two of the five included articles that tested HbA1c after NSPT with low intensity laser compared to NSPT alone, showed significant

reduction of HbA1c for the laser-associated group, while three didn't presented significant statistical difference. Of these, four studies could be submitted to meta-analysis, but no significant statistical difference was observed in the effect of the laser associated to the TPNC neither on periodontal clinical outcomes nor on HbA1c [35].

Therapies that showed promising results were propolis intake [28], omega 3 polyunsaturated fatty acids plus acetylsalicylic acid intake [29] and homeopathic therapy [30], however these preliminary findings lack confirmation, and further studies are required.

Adjunctive therapies associated with NSPT (excluding systemic antibiotics) compared to NSPT alone presented statistical difference ($p= 0.03$), and the overall effect of all studies showed a statistical difference ($p= 0.02$) after three months follow up. This finding corroborates the observation that more intensive therapies may improve the metabolic control of type 2 diabetic patients [11,12,32].

CONCLUSION

The magnitude of reduction of glycated hemoglobin between groups after three months, however, was 0.24%, which clinically may not be significant. The association of adjunctive periodontal therapies to NSPT compared to NSPT alone contributed to the reduction of HbA1c and improvement of periodontal clinical outcomes in type 2 diabetic patients with periodontitis.

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APÊNDICES

APPENDIX 1. DATABASE SEARCH STRATEGY

Databas e	Search 2019-05-17	Referenc es
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PubMed	<p>#1 "glucose metabolism disorders"[All Fields] OR ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes mellitus type 2"[All Fields] OR "diabetes type 2"[All Fields] OR "diabetes mellitus, type II"[All Fields] OR "diabetes mellitus, type 2/therapy"[All Fields] OR "diabetes mellitus, type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields] OR "diabetes mellitus, type 2/blood"[All Fields] OR "diabetes mellitus, type 2/metabolism"[All Fields]</p> <p>#2 ("periodontitis"[MeSH Terms] OR "periodontitis"[All Fields] OR "Periodontal Diseases"[All Fields] OR "periodontal disease"[All Fields] OR "periodontal diseases/metabolism"[All Fields] OR "Chronic Periodontitis"[All Fields] OR "chronic periodontitis/therapy"[All Fields] OR "adult periodontitis"[All Fields] OR "loss, periodontal attachment"[All Fields] OR "attachment loss, periodontal"[All Fields] OR "Periodontitis, Adult"[All Fields] OR "Periodontitis, Chronic"[All Fields] OR "periodontal attachment loss"[All Fields])</p> <p>#3 ("non-surgical periodontal therapy"[All Fields] OR "nonsurgical periodontal therapy"[All Fields] OR "periodontal therapy"[All Fields] OR ("phase 1"[All Fields] AND "periodontal therapy"[All Fields]) OR "periodontal diseases/therapy"[All Fields] OR "chronic periodontitis/therapy"[All Fields] OR "scaling and root planing"[All Fields] OR "dental scaling"[All Fields] OR "dental scaling/methods"[All Fields] OR "root planing"[All Fields] OR "root planing/methods"[All Fields] OR "gingival curettage"[All Fields] OR "periodontal</p>	60
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<p>Cochrane</p>	<p>Trials matching "glucose metabolism disorders" OR diabetes OR "diabetes mellitus" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "diabetes mellitus, type II" OR "diabetes mellitus, type 2" OR "type 2 diabetes mellitus" in Title Abstract Keyword AND periodontitis OR "Periodontal Diseases" OR "periodontal disease" OR "Chronic Periodontitis" OR "adult periodontitis" OR "loss, periodontal attachment" OR "attachment loss, periodontal" OR "Periodontitis, Adult" OR "Periodontitis, Chronic" OR "periodontal attachment loss" in Title Abstract Keyword AND "non-surgical periodontal therapy" OR "nonsurgical periodontal therapy" OR "periodontal therapy" OR ("phase 1" AND "periodontal therapy") OR "periodontal diseases therapy" OR "chronic periodontitis therapy" OR "scaling and root planing" OR "dental scaling" OR "dental scaling methods" OR "root planing" OR "root planing methods" OR "gingival curettage" OR "periodontal treatment" OR "periodontal intervention" OR "subgingival curettage" OR "root scaling" OR "subgingival scaling" OR "supragingival scaling" OR "periodontal therapeutics" OR "periodontal debridement" OR "nonsurgical periodontal debridement" OR "low-level light therapy" OR "laser phototherapy" OR "laser therapy" OR phototherapy OR "anti-bacterial agents" OR (anti-bacterial AND agents) OR "antibacterial agents" OR antibiotics OR antibiotic OR "anti bacterial agents" OR bacteriocides OR "periodontal debridement methods" OR "chronic periodontitis surgery" OR "periodontal diseases surgery" OR "periodontal diseases therapy" OR "periodontal pocket surgery" in Title Abstract Keyword AND "advanced glycation end products" OR "glycosylated hemoglobin" OR "HbA1c" OR "hemoglobin A1c protein, human" OR "glycohemoglobin A" OR "hemoglobin A. glycosylated" OR</p>	<p>158</p>
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<p>LIVIVO</p>	<p>("glucose metabolism disorders" OR diabetes OR "diabetes mellitus" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "diabetes mellitus, type II" OR "diabetes mellitus, type 2" OR "type 2 diabetes mellitus") AND (periodontitis OR "Periodontal Diseases" OR "periodontal disease" OR "Chronic Periodontitis" OR "adult periodontitis" OR "loss, periodontal attachment" OR "attachment loss, periodontal" OR "Periodontitis, Adult" OR "Periodontitis, Chronic" OR "periodontal attachment loss") AND ("non-surgical periodontal therapy" OR "nonsurgical periodontal therapy" OR "periodontal therapy" OR ("phase 1" AND "periodontal therapy") OR "periodontal diseases therapy" OR "chronic periodontitis therapy" OR "scaling and root planing" OR "dental scaling" OR "dental scaling methods" OR "root planing" OR "root planing methods" OR "gingival curettage" OR "periodontal treatment" OR "periodontal intervention" OR "subgingival curettage" OR "root scaling" OR "subgingival scaling" OR "supragingival scaling" OR "periodontal therapeutics" OR "periodontal debridement" OR "nonsurgical periodontal debridement" OR "low-level light therapy" OR "laser phototherapy" OR "laser therapy" OR phototherapy OR "anti-bacterial agents" OR (anti-bacterial AND agents) OR "antibacterial agents" OR antibiotics OR antibiotic OR "anti bacterial agents" OR bacteriocides OR "periodontal debridement methods" OR "chronic periodontitis surgery" OR "periodontal diseases surgery" OR "periodontal diseases therapy" OR "periodontal pocket surgery") AND ("advanced glycation end products" OR "glycosylated hemoglobin" OR "HbA1c" OR "hemoglobin A1c protein, human" OR "glycohemoglobin A" OR "hemoglobin A, glycosylated" OR "hemoglobin A, glycosylated analysis" OR "hemoglobins,</p>	<p>33 (exceto Medline)</p>
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Scopus	<p>(TITLE-ABS-KEY (("glucose metabolism disorders" OR diabetes OR "diabetes mellitus" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "diabetes mellitus, type II" OR "diabetes mellitus, type 2" OR "type 2 diabetes mellitus")) AND TITLE-ABS-KEY ((periodontitis OR "Periodontal Diseases" OR "periodontal disease" OR "Chronic Periodontitis" OR "adult periodontitis" OR "loss, periodontal attachment" OR "attachment loss, periodontal" OR "Periodontitis, Adult" OR "Periodontitis, Chronic" OR "periodontal attachment loss")) AND TITLE-ABS-KEY (("non-surgical periodontal therapy" OR "nonsurgical periodontal therapy" OR "periodontal therapy" OR ("phase 1" AND "periodontal therapy") OR "periodontal diseases therapy" OR "chronic periodontitis therapy" OR "scaling and root planing" OR "dental scaling" OR "dental scaling methods" OR "root planing" OR "root planing methods" OR "gingival curettage" OR "periodontal treatment" OR "periodontal intervention" OR "subgingival curettage" OR "root scaling" OR "subgingival scaling" OR "supragingival scaling" OR "periodontal therapeutics" OR "periodontal debridement" OR "nonsurgical periodontal debridement" OR "low-level light therapy" OR "laser phototherapy" OR "laser therapy" OR phototherapy OR "anti-bacterial agents" OR (anti-bacterial AND agents) OR "antibacterial agents" OR antibiotics OR antibiotic OR "anti bacterial agents" OR bacteriocides OR "periodontal debridement methods" OR "chronic periodontitis surgery" OR "periodontal diseases surgery" OR "periodontal diseases therapy" OR "periodontal pocket surgery")) AND TITLE-ABS-KEY (("advanced glycation end products" OR "glycosylated hemoglobin" OR "HbA1c" OR "hemoglobin A1c protein, human" OR</p>	206
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<p>Web of Science</p>	<p>TÓPICO: (("glucose metabolism disorders" OR diabetes OR "diabetes mellitus" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "diabetes mellitus, type II" OR "diabetes mellitus, type 2" OR "type 2 diabetes mellitus")) AND TÓPICO: ((periodontitis OR "Periodontal Diseases" OR "periodontal disease" OR "Chronic Periodontitis" OR "adult periodontitis" OR "loss, periodontal attachment" OR "attachment loss, periodontal" OR "Periodontitis, Adult" OR "Periodontitis, Chronic" OR "periodontal attachment loss")) AND TÓPICO: (("non-surgical periodontal therapy" OR "nonsurgical periodontal therapy" OR "periodontal therapy" OR ("phase 1" AND "periodontal therapy") OR "periodontal diseases therapy" OR "chronic periodontitis therapy" OR "scaling and root planing" OR "dental scaling" OR "dental scaling methods" OR "root planing" OR "root planing methods" OR "gingival curettage" OR "periodontal treatment" OR "periodontal intervention" OR "subgingival curettage" OR "root scaling" OR "subgingival scaling" OR "supragingival scaling" OR "periodontal therapeutics" OR "periodontal debridement" OR "nonsurgical periodontal debridement" OR "low-level light therapy" OR "laser phototherapy" OR "laser therapy" OR phototherapy OR "anti-bacterial agents" OR (anti-bacterial AND agents) OR "antibacterial agents" OR antibiotics OR antibiotic OR "anti bacterial agents" OR bacteriocides OR "periodontal debridement methods" OR "chronic periodontitis surgery" OR "periodontal diseases surgery" OR "periodontal diseases therapy" OR "periodontal pocket surgery")) AND TÓPICO: (("advanced glycation end products" OR "glycosylated hemoglobin" OR "HbA1c" OR "hemoglobin A1c protein, human" OR "glycohemoglobin A" OR "hemoalobin A. dlvcosvlated" OR</p>	<p>163</p>
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BVS (Portuguese and Spanish)	<p>(tw:("transtornos do metabolismo de glucose" OR "trastornos del metabolismo de la glucosa" OR "diabetes mellitus" OR "diabetes mellitus tipo 2")) AND (tw: ("periodontite crônica" OR "periodontitis crónica" OR periodontite OR periodontitis OR "doenças periodontais" OR "enfermedades periodontales")) AND (tw: ("raspagem dentária" OR "raspado dental" OR "aplainamento radicular" OR "aplanamiento de la raíz" OR "curetagem subgingival" OR "curetaje subgingival" OR "desbridamento periodontal" OR "desbridamiento periodontal" OR cirurgia OR cirugía OR "terapia por láser" OR "terapia a laser" OR antibacterianos OR fototerapia)) AND (tw:("hemoglobina A glicosilada" OR "hemoglobina A glucosilada" OR "Hemoglobina A" OR "hemoglobinas"))</p>	102
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<p>ProQuest</p>	<p>noft(("glucose metabolism disorders" OR diabetes OR "diabetes mellitus" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "diabetes mellitus, type II" OR "diabetes mellitus, type 2" OR "type 2 diabetes mellitus")) AND noft((periodontitis OR "Periodontal Diseases" OR "periodontal disease" OR "Chronic Periodontitis" OR "adult periodontitis" OR "loss, periodontal attachment" OR "attachment loss, periodontal" OR "Periodontitis, Adult" OR "Periodontitis, Chronic" OR "periodontal attachment loss")) AND noft(("non-surgical periodontal therapy" OR "nonsurgical periodontal therapy" OR "periodontal therapy" OR ("phase 1" AND "periodontal therapy") OR "periodontal diseases therapy" OR "chronic periodontitis therapy" OR "scaling and root planing" OR "dental scaling" OR "dental scaling methods" OR "root planing" OR "root planing methods" OR "gingival curettage" OR "periodontal treatment" OR "periodontal intervention" OR "subgingival curettage" OR "root scaling" OR "subgingival scaling" OR "supragingival scaling" OR "periodontal therapeutics" OR "periodontal debridement" OR "nonsurgical periodontal debridement" OR "low-level light therapy" OR "laser phototherapy" OR "laser therapy" OR phototherapy OR "anti-bacterial agents" OR (anti-bacterial AND agents) OR "antibacterial agents" OR antibiotics OR antibiotic OR "anti bacterial agents" OR bacteriocides OR "periodontal debridement methods" OR "chronic periodontitis surgery" OR "periodontal diseases surgery" OR "periodontal diseases therapy" OR "periodontal pocket surgery")) AND noft(("advanced glycation end products" OR "glycosylated hemoglobin" OR "HbA1c" OR "hemoglobin A1c protein, human" OR "glycohemoglobin A" OR "hemoglobin A, glycosylated" OR "hemoglobin A, glycosylated analysis" OR "hemoglobins,</p>	<p>9</p>
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<p>Open Grey</p>	<p>("glucose metabolism disorders" OR diabetes OR "diabetes mellitus" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "diabetes mellitus, type II" OR "diabetes mellitus, type 2" OR "type 2 diabetes mellitus") AND (periodontitis OR "Periodontal Diseases" OR "periodontal disease" OR "Chronic Periodontitis" OR "adult periodontitis" OR "loss, periodontal attachment" OR "attachment loss, periodontal" OR "Periodontitis, Adult" OR "Periodontitis, Chronic" OR "periodontal attachment loss") AND ("non-surgical periodontal therapy" OR "nonsurgical periodontal therapy" OR "periodontal therapy" OR ("phase 1" AND "periodontal therapy") OR "periodontal diseases therapy" OR "chronic periodontitis therapy" OR "scaling and root planing" OR "dental scaling" OR "dental scaling methods" OR "root planing" OR "root planing methods" OR "gingival curettage" OR "periodontal treatment" OR "periodontal intervention" OR "subgingival curettage" OR "root scaling" OR "subgingival scaling" OR "supragingival scaling" OR "periodontal therapeutics" OR "periodontal debridement" OR "nonsurgical periodontal debridement" OR "low-level light therapy" OR "laser phototherapy" OR "laser therapy" OR phototherapy OR "anti-bacterial agents" OR (anti-bacterial AND agents) OR "antibacterial agents" OR antibiotics OR antibiotic OR "anti bacterial agents" OR bacteriocides OR "periodontal debridement methods" OR "chronic periodontitis surgery" OR "periodontal diseases surgery" OR "periodontal diseases therapy" OR "periodontal pocket surgery") AND ("advanced glycation end products" OR "glycosylated hemoglobin" OR "HbA1c" OR "hemoglobin A1c protein, human" OR "glycohemoglobin A" OR "hemoglobin A, glycosylated" OR "hemoglobin A, glycosylated analysis" OR "hemoglobins</p>	<p>2</p>
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Google Scholar	("diabetes mellitus" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "diabetes mellitus type II") AND (periodontitis OR "Chronic Periodontitis" OR "adult periodontitis" OR "periodontal attachment loss") AND ("non-surgical periodontal therapy" OR "scaling and root planing" OR "low-level light therapy" OR "laser therapy" OR phototherapy OR "anti-bacterial agents" OR antibiotics OR "chronic periodontitis/surgery" OR "periodontal surgery") AND ("glycosylated hemoglobin" OR "HbA1c")	19
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APPENDIX S2. EXCLUDED ARTICLES AND REASON FOR EXCLUSION. (N= 63).

Author, year	Reason for exclusion
Acharya et al., 2015	4
Alsheri et al., 2015	10
Al Mubarak et al., 2002	5
Al Mubarak et al., 2010	5
Alshorman, 2008	11
Borgnakke et al., 2014	1
Botero et al., 2013	5
Camargo et al., 2014	4
Campus et al., 2007	1
Chapple et al., 2014	1
Chee et al., 2006	1
Dodwad, et al., 2012	4
Engebretson and Hey-Hadavi, 2011	6
Fu et al., 2000	4
Guo and Zhu, 2004	4
Haerian Ardakani, A 2014	11
Hungund and Panseriya, 2012	4
Ivanaga, 2019	4
Javid et al., 2007	6

Javid et al., 2017	10
Kapellas et al., 2016	10
Katagiri et al., 2009	9
Long and Ru-Fan, 2011	4
Macedo et al., 2014	9
Masi, S., 2018	10
Matsumoto et al., 2009	6
Mendonça et al., 2012	6
Merchant et al., 2014	1
Munenaga et al., 2013	4
Navarro-Sanchez et al., 2007	4
Ramos et al., 2016	9
Santoso and Waspadji, 2008	9
Supraneni et al., 2018	10
Vergnes et al., 2014	1
Xu et al., 2013	4
Zare, Javid A., 2016	6
NCT00801164	12
NCT02735837	12
NCT02845024	12
NCT00016835	12
IRCT2016110430694N1	12

NCT03343366	12
IRCT2014082417587N7	12
IRCT2015010517587N	12
IRCT2015010517587N9	12
RBR-4tq9yq	12
RBR-9sq542	12
CTRI/2017/11/010348	12
CTRI/2018/01/011227	12
CTRI/2016/03/006764	12
IRCT2013092614774N1	12
IRCT2017011631993N1	12
IRCT2017030432874N1	12
NCT02794506	12
IRCT201411023690N5	12
NCT03444363	12
NCT02437747	12
ISRCTN11742127	12
ChiCTR1800018165	12
NCT02062047	12
CTRI/2017/11/010604	12
CTRI/2018/03/012726	12
CTRI/2018/03/012689	12

1- Review, letters, personal opinions, book chapters, panels, editorial and conference abstracts (n= 6), 2- In vitro studies or studies in animal models (n= 0), 3- Qualitative Research (n= 0), 4 - Observational Studies (Case-Control, Cohort and Cross-sectional), non-randomized or non-parallel clinical trials (n= 11), 5 - Studies that have considered diabetes type 1 or Periodontal Disease other than Chronic Periodontitis. (n= 3), 6 - Studies without considered outcomes (glycosylated hemoglobin A or periodontal clinical parameters) (n= 5), 7 - Studies that have included patients with comorbidities or metabolic syndrome (n= 0), 8 - Studies in which relevant systemic health conditions, such as hypertension and smoking, were not balanced between the groups (n= 0); 9 - Studies in which control group received any therapy other than NSPT alone or remained untreated (n= 4); 10 - Studies in which no adjunctive treatment to NSPT was tested (n= 5); 11- Studies written in non-Latin alphabet (n= 2); 12 - Study protocols (n=27).

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Park JC, Um YJ, Jung UW, Kim CS, Choi SH, Kim CK. Histological characteristics of newly formed cementum in surgically created one-wall intrabony defects in a canine model. *J Periodontal Implant Sci* 2010;40:3-10.

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Entire Book

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Lekholm U, Zarb GA. Patient selection and preparation. In: Branemark PI, Zarb GA, Albrektsson T, editors. Tissue-integrated prostheses: osseointegration in clinical dentistry. Chicago: Quintessence; 1985. p.199-220.

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