

**UNIVERSIDADE DE BRASÍLIA**  
**Faculdade de Ciências de Saúde**  
**Programa de Pós-Graduação em Odontologia**



Dissertação de Mestrado

**Efficacy of adjunctive local antimicrobials to non-surgical periodontal therapy  
on pocket reduction and metabolic control of patients with type 2 diabetes: a  
network meta-analysis**

Eficácia dos antimicrobianos locais adjuvantes à terapia periodontal não cirúrgica na  
redução de bolsas periodontais e controle metabólico de pacientes com diabetes tipo  
2: meta-análise em rede

**Domitilla Marchiori Sant'Anna Leal de Oliveira**

Brasília, 10 de maio de 2023

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À minha família e a todos que participaram desta conquista.

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## RESUMO

Esta meta-análise em rede (MAR) investigou a eficácia do uso adjuvante de antimicrobianos locais administrados subgengivalmente à terapia periodontal não cirúrgica (TPNC) no controle metabólico e redução da profundidade de sondagem periodontal (PS) em pacientes com diabetes tipo 2 (DM2). Sete bases de dados, literatura cinzenta e plataformas de registros foram pesquisadas até fevereiro de 2022 para identificar ensaios clínicos randomizados (ECR) de acordo com os critérios de elegibilidade. O risco de viés foi avaliado por meio da ferramenta Cochrane Collaboration (RoB 2.0). Duas meta-análises em rede frequentistas foram realizadas utilizando o modelo de efeitos aleatórios para calcular as diferenças de médias como medida de efeito, e para avaliar quantitativamente a hemoglobina glicada (HbA1c) e a PS. A certeza da evidência foi avaliada por meio da abordagem GRADE para análise e interpretação dos resultados. Dez ECRs foram incluídos. No total, 261 pacientes foram tratados com oito diferentes antimicrobianos locais adjuvantes à TPNC (gel de azitromicina, gel de claritromicina, fibra ou pomada de tetraciclina, gel de clorexidina, nanoesferas de doxiciclina, gel de minociclina e gel de satranidazol), enquanto 249 pacientes receberam TPNC isoladamente ou associada a placebo. Considerando a redução da PS (8 estudos incluídos), os melhores resultados foram encontrados após 6 meses de uso do gel de satranidazol (certeza da evidência moderada). Para o controle da HbA1c (7 estudos incluídos), gel de doxiciclina, gel de clorexidina e fibra de tetraciclina apresentaram resultados promissores após 3 meses (baixa certeza de evidência). Em conclusão, o uso adjuvante do gel de satranidazol provavelmente reduz a PS após 6 meses de acompanhamento, enquanto o gel de doxiciclina, gel de clorexidina e fibra de tetraciclina podem reduzir os valores da HbA1c em pacientes com DM2 e periodontite tratados com TPNC após 3 meses de acompanhamento.

**Palavras-chave:** Antimicrobianos; Diabetes Mellitus Tipo 2; Periodontite; Terapia Periodontal Não Cirúrgica; Revisão Sistemática; Meta-análise em Rede.

## ABSTRACT

This network meta-analysis (NMA) investigated the efficacy of adjunctive use of subgingivally delivered antimicrobials to non-surgical periodontal therapy (NSPT) on the metabolic control and periodontal pocket depth (PPD) reduction in patients with type 2 diabetes (T2D). Seven databases, grey literature, and registry platforms were searched up to February 2022 to identify randomized clinical trials (RCT) fulfilling the eligibility criteria. The risk of bias was assessed through Cochrane's tool (RoB 2.0). Two frequentists NMA were performed using a random-effects model to calculate mean differences as effect measure and to quantitatively assess the glycated hemoglobin (HbA1c) and PPD. The certainty of evidence was evaluated through the GRADE approach and the partially contextualized framework for the interpretation of results. Ten RCTs were included. In total, 261 patients were treated with eight different local antimicrobials adjuvants to NSPT (azithromycin gel, clarithromycin gel, tetracycline fiber or ointment, chlorhexidine gel, doxycycline nanospheres, minocycline gel and satranidazole gel), while 249 patients received NSPT alone or associated to placebo. Considering PPD reduction (8 included studies), the best results were found after six months with the use of satranidazole gel (moderate evidence certainty). For HbA1c control (7 included studies), doxycycline gel, chlorhexidine gel, and tetracycline fiber showed promising results after three months (low evidence certainty). In conclusion, the adjunctive use of satranidazole gel probably reduces PPD after a 6-month follow-up, while doxycycline gel, chlorhexidine gel, and tetracycline fiber may decrease HbA1c values in patients with T2D and periodontitis treated with NSPT after a 3-month follow up.

**Keywords:** Antimicrobials; Type 2 Diabetes Mellitus; Periodontitis; Non-Surgical Periodontal Therapy; Systematic Review; Network Meta-Analysis

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## 1. INTRODUCTION

Several studies have described the bidirectional relationship between periodontitis and T2D [1–6]. While diabetes increases the risk for periodontitis by 2-3 times and is associated with increased disease severity [1,2,5], periodontitis may be related to poorer glycemic control and a higher risk for diabetic complications [1–3]. Therefore, previous studies have investigated the effect of conventional periodontal treatment on diabetes control, showing a reduction in glycated hemoglobin (HbA1c) levels in patients with T2D and periodontitis [1,2,5–7].

The cornerstone of periodontitis treatment consists of mechanical debridement of the root surface [8,9]. This procedure, also called non-surgical periodontal therapy (NSPT), includes mechanical removal of supra and subgingival bacterial plaque through scaling and root planing, using scalers, curettes, or ultrasonic devices [7]. However, NSPT presents some limitations, such as difficulty accessing deep pockets and furcation areas [8,9]. Therefore, in cases where NSPT alone cannot control periodontal disease, antimicrobial agents have been indicated to improve its results, especially in patients with systemic diseases that affect host resistance, as an alternative to surgical procedures [8,10].

Antimicrobials include antibiotics and antiseptics that eliminate or inactivate pathogens in sites where NSPT is not entirely effective [10,11]. These substances can be used locally or systemically as an adjunct to mechanical instrumentation [8,10]. However, although systemic antibiotics may improve periodontal health, they should be indicated only for particular situations due to their systemic and microbiological side effects (including intestinal effects and toxicity) and the risk of resistant organisms rising [8–10]. On the other hand, local antimicrobials present fewer adverse effects, better compliance, and a lower chance of bacterial resistance [8] usually indicated to localized pockets or nonresponding and recurrent sites [8,9]. Besides, locally (subgingivally delivered) antimicrobials can achieve levels that cannot be reached by the systemic route and allow antiseptics substances that would be considered toxic if administered systemically [10].

Literature has shown the benefits of subgingivally delivered antimicrobials used as adjuncts to NSPT in periodontitis treatment of normoglycemic patients [9,11,12] and patients with T2D [13]. The adjunctive use of these substances may improve

periodontal parameters in systemically healthy patients, reducing pathogenic bacterial load in biofilm and the release of proinflammatory mediators, which in diabetes could help control HbA1c levels [14,15]. Furthermore, it is noteworthy that HbA1c control in patients with T2D requires a previous periodontal control [16], and these patients have been considered poor candidates for surgical procedures due to their impaired healing [17,18]. So, adjunctive therapies can be beneficial to this population [19].

A previous systematic review evaluated the efficacy of local antibiotics in patients with either type 1 or type 2 diabetes and showed periodontal improvement, with periodontal pocket depth (PPD) reduction and clinical attachment level (CAL) gain, when these substances were associated with NSPT, especially in deep sites [13]. However, studies with antiseptics agents, such as chlorhexidine, were not included. In addition, the effects of local antibiotics on glycemic status and the certainty of evidence were not assessed. So, these results must be revisited.

Thus, this systematic review with network meta-analysis aimed to evaluate the effectiveness of subgingivally delivered local antimicrobials (including antibiotics and antiseptics) associated with NSPT in the glycemic control and periodontal parameters in patients with T2D and periodontitis.

## 2. METHODS

### 2.1 PROTOCOL AND REGISTRATION

This systematic review was carried out according to the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions [20]. It was registered under the number CRD42022308714 on the PROSPERO database (The International Prospective Register of Systematic Reviews, available at <http://www.crd.york.ac.uk/prospero/>). The PICO (Population, Intervention, Comparison, and Outcomes) question was “In patients with type 2 diabetes and periodontitis (P), does the adjunctive use of subgingivally delivered local antimicrobials to non-surgical periodontal therapy (I) improve the metabolic control and clinical periodontal parameters (O) when compared to conventional non-surgical periodontal therapy alone or associated to placebo (C)?

### 2.2 SEARCH STRATEGY AND ELIGIBILITY CRITERIA

The search was performed on February 04, 2022, using antimicrobials, T2D, and non-surgical periodontal therapy as main descriptors, with no language or publication period restrictions. The Medical Subject Headings (MeSH) Terms searched on PubMed were: ("Diabetes Mellitus" OR "Glycated Hemoglobin A") AND ("Antimicrobial") AND ("Chronic Periodontitis" OR "Periodontitis" OR "periodontal debridement"), including words variations and synonyms. The complete search strategy for each database is available in Supplementary file 1.

The PICO acronym was used to define the inclusion and exclusion criteria. Inclusion criteria consisted of randomized controlled clinical trials (RCT) evaluating (P) adult patients diagnosed with T2D (controlled or not) and untreated periodontitis who underwent (I) NSPT associated with subgingivally delivered local antimicrobials (including antibiotics and antiseptics) compared to (C) NSPT alone or associated to placebo. Metabolic control and clinical periodontal parameters, evaluated respectively through HbA1c and PPD levels change from baseline and at least 2-month follow up, were considered the primary outcomes (O). Periodontitis case definition was determined according to the Periodontal Diseases Classification [21]: patients with

interdental CAL detectable at  $\geq 2$  non-adjacent teeth, or buccal or oral CAL  $\geq 3$  mm with pocketing  $> 3$  mm detectable at  $\geq 2$  teeth. Diabetes case definition was determined according to the International Expert Committee [22], composed of members of the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation: HbA1c  $\geq 6.5\%$ .

Exclusion criteria comprised studies with non-RCT design, studies with no full text available, studies in which the sample included patients with type I diabetes or children and adolescents, studies in which subgingivally delivered local antibiotics/antimicrobials were combined with other active therapy (systemic antibiotics, anti-inflammatory drugs, etc.), studies not evaluating HbA1c or PPD as outcomes, studies using local antimicrobials/antibiotics with no low liberation vehicles use (e.g., with fluids or aqueous solutions as vehicles) and studies using non-absorbable delivery devices (e.g., plastic tubules) were also excluded.

The following electronic databases were searched: PubMed (MEDLINE), Cochrane (CENTRAL), Embase, LIVIVO, Scopus, Web of Science, and LILACS. Additionally, grey literature (non-peer-reviewed literature) was searched through ProQuest (Dissertation and Theses), OpenGrey, and Google Scholar. Clinical Trials Registry (available at <https://clinicaltrials.gov/>), International Clinical Trial Registry Platform (ICTRP WHO, available at <https://trialsearch.who.int/>), and hand search of reference lists from included studies were analyzed for additional references.

All results were imported into the reference manager Mendeley Desktop software (v.1.19.8, Elsevier, Amsterdam, The Netherlands), where duplicate references were identified and removed. Then, study selection was performed in Rayyan QCRI application [23] in two phases. In phase 1, two reviewers (DMSLO and ALMS) independently evaluated titles and abstracts according to previously established eligibility criteria, and disagreements were solved by a third evaluator (CMS). In phase 2, studies full texts were also analyzed by the same two independent reviewers to confirm eligibility, and once more, the same third evaluator solved disagreements.

## 2.3 DATA EXTRACTION AND RISK OF BIAS

Two independent reviewers performed data extraction (DMSLO and ALMS) with posterior comparison. Data extracted included authors, publication date, country,

participants (sample size and mean age), diabetes and periodontitis case definitions, information about antimicrobial substance tested, results regarding HbA1c and/or PPD before and after treatment for test and control groups, follow up, and main conclusions reported in the included study.

In the study performed by Lin et al. (2012) [24], the mean and standard deviation (mean $\pm$ SD) of HbA1c at 3 and 6 months were unavailable. Therefore, mean changes in plasma levels of HbA1c for each patient were extracted from the published plot using WebPlotDigitizer (v4.5, Ankit Rohatgi, Pacifica, CA, USA), and the standard deviations were calculated using an online app (<https://www.calculator.net/standard-deviation-calculator.html>, assessed on April 21, 2022).

The same two reviewers (DMSLO and ALMS) also assessed the risk of bias using Cochrane's risk of bias tool for RCT (RoB 2.0) [25], considering the "per protocol" approach for each outcome (HbA1c and PPD). PPD was the chosen periodontal outcome because it was a standard clinical periodontal parameter found in all the included studies and is considered a core outcome in periodontics [26]. For every included study, five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result) were analyzed and classified as "low risk", "some concerns" or "high risk". The worst classification among the domains was responsible for the overall risk of bias of the study. A third evaluator (CMS), once again, checked for disagreements.

## 2.4 DATA SYNTHESIS AND META-ANALYSIS

HbA1c and PPD level change from baseline to 12 and 24 weeks (3 and 6 months) after treatment mean scores (and standard deviations) were calculated for every included study. Using the MetaInsight software V3.1.14 [27] for continuous variables (available on <https://crsu.shinyapps.io/MetaInsight/>, accessed on June 17, 2022), a frequentist network meta-analysis (NMA) was performed to compare different local antimicrobials as adjuncts to NSPT. Random effects method model and inverse variance statistics were used to calculate mean differences (MD) with a 95% confidence interval. Diagrams were used to analyze the geometry of the network.

## 2.5 CERTAINTY OF EVIDENCE ASSESSMENT

Two reviewers (DMSLO and CMS) assessed the certainty of evidence following the GRADE approach with a Partially Contextualized Framework for Network Meta-analysis to interpret results [28,29]. Risk of bias, inconsistency, indirectness, and publication bias were evaluated for direct comparisons. For indirect comparisons, first-order loop comparison with the lowest certainty was considered, and intransitivity was assessed. Incoherence could not be evaluated due to the poorly connected network, but imprecision was assessed for the NMA effect estimate.

The partially contextualized framework considers the magnitude of the effect and the certainty of the evidence for interpreting the NMA results [30]. The magnitude of the effect followed the Minimal Important Difference (MID). The MID was the MD between groups, interpreted as the smallest beneficial difference that would mandate a therapy without troublesome adverse effects and excessive costs [31]. For HbA1c, a reduction of 0.5% was considered the MID; for PPD, the MID was a periodontal pocket reduction of  $\geq 1$  mm, or the change necessary to distinguish a periodontally diseased site from a healthy one (i.e., from 4mm to 3mm). Both MID values were decided by discussion within the review team, for no formal literature is available about this matter.

Detailed information on judgment criteria is available in Supplementary file 5 and Supplementary Tables S1, S2, S3, and S4.

### 3. RESULTS

#### 3.1 CHARACTERISTICS OF THE INCLUDED STUDIES

A total of 1,819 records were retrieved from the database search, resulting in 1,233 after removing duplicates. Titles and abstracts from the 1,233 records were analyzed according to the eligibility criteria, and then 1,206 were excluded. Twenty-seven full texts were read, and seventeen were excluded, resulting in 10 included studies (Fig. 1). A list of excluded articles and reasons for exclusion is available in Supplementary file 2.

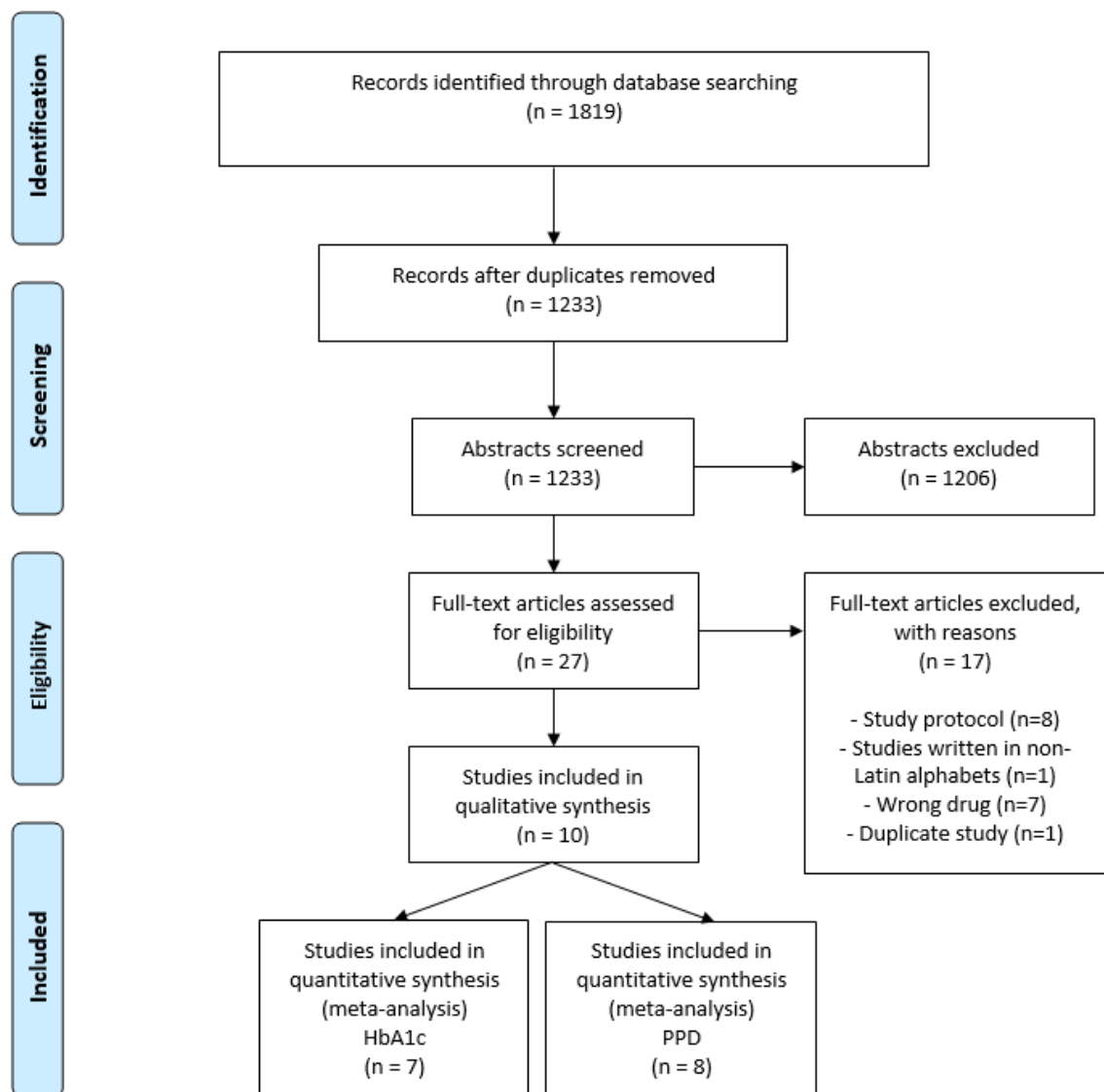


Figure 1: Flow diagram of the selection process according to the PRISMA statement for NMA.

Table 1 shows authors, date of publication, country, participants (number and average age), diabetes and periodontitis case definition, treatment delivered to test and control groups, results regarding HbA1c and/or PPD before and after treatment for test and control groups, follow-up, and main conclusions reported in the included study.

The studies were published between 2009 and 2019 from India [32–35], Iran [36], Brazil [37,38], Taiwan [24], and Japan [39,40]. In all included studies, a clinical periodontal examination confirmed the periodontitis and laboratory tests for HbA1c level, the T2D diagnoses. The intervention in test groups (TG) was subgingivally delivered antimicrobials as adjuncts to NSPT, and in control groups (CG), was NSPT alone [24,34,36,39,40] or associated to placebo [32,33,35,37,38].

Considering all included studies, 7 evaluated HbA1c [24,34,36–40], 9 PPD [24,32–39], and 6 both outcomes [24,34,36–39]. In total, 31 patients were treated with 0.5% azithromycin gel [32] injected into periodontal pockets after NSPT (maximum PPD, 1 site per patient); 32 with 0.5% clarithromycin gel [33] also injected into periodontal pockets after NSPT (maximum PPD, 1 site per patient); 20 with resorbable tetracycline fiber [34] inserted into selected periodontal pockets after NSPT and covered by a periodontal pack for 10 days; 34 with 1.5% chlorhexidine gel [36] inserted into periodontal pockets (8 teeth with 4-8mm PPD, minimum) after two sessions of NSPT (2 weeks apart) and covered by a periodontal pack for 7 days; 23 with 20% doxycycline-loaded PLGA nanospheres [37] applied into periodontal pockets (4 moderate and 2 deep pockets) after NSPT; 14 with 2% minocycline gel [24] inserted into periodontal pockets in a 4-week regimen, one month after NSPT; 14 with 2% minocycline gel [39] applied into periodontal pockets (every site with PPD  $\geq$ 4mm), after NSPT; 42 with tetracycline HCl ointment [40] applied into every periodontal pocket (once a week for 4 weeks) combined with sessions of NSPT; 32 with 3% satranidazole gel [35] injected into periodontal pockets after NSPT; and 19 with 1% chlorhexidine gel [38] applied into periodontal pockets, three times (repeated within 10 minutes), after two appointments of NSPT within 24h. In control groups, 114 patients underwent NSPT alone [24,34,36,39,40] while 135 received NSPT associated with a placebo [32,33,35,37,38].

Munenaga et al. (2013) [40] included six groups in the study, but according to the used periodontitis case-definition, only two groups (one test and one control) were analyzed in the NMA.

Table 1 - Summary of descriptive characteristics of included articles (n=10)

| Author,<br>year<br>Country          | Age in<br>years<br>mean<br>±SD or<br>range) | Case<br>definitions                                                                                                                                                                  | Groups<br>(n)                    | Treatments<br>TG<br>CG                                                                                                                                                     | Outcomes<br>comparison<br>between<br>groups<br>(Baseline)<br>Mean ± SD | Follow Up<br>(in<br>months) | Outcomes<br>comparison<br>between groups<br>(Final / P value)<br>Mean ± SD                                      | Main<br>Conclusions<br>reported in the<br>included study                                                                                                                                                                                       | Conflict of<br>interest and<br>funding<br>sources                                                                                                                                                        |
|-------------------------------------|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Agarwal<br>et al.,<br>2012<br>India | Age<br>range<br>30-50<br>years              | Periodontitis:<br>PPD ≥5 mm<br>and/or<br>CAL≥4mm and<br>vertical bone<br>loss≥3mm on<br>intraoral<br>periapical<br>radiographs<br><br>Diabetes:<br>HbA1c≥6.5%<br>and<br>FPG≥126mg/dl | TG<br>(n=31)<br><br>CG<br>(n=32) | TG: NSPT +<br>0.5%<br>azithromycin<br>gel injected<br>into<br>periodontal<br>pockets after<br>NSPT<br>(maximum<br>PPD, 1 site<br>per patient)<br><br>CG: NSPT +<br>placebo | PPD (mm)<br>TG 7.38±0.71<br>CG 7.27±0.73                               | 3<br>months                 | PPD (mm)<br>TG 5.88±0.94<br><b>(P&lt;0.05)</b><br>CG 6.03±0.90<br><b>(P&lt;0.05)</b><br><b>CBG: NS</b>          | Local delivery of<br>0.5%<br>azithromycin gel<br>into periodontal<br>pockets of CP<br>patients with<br>T2D stimulated<br>a significant<br>improvement in<br>clinical<br>improvement<br>compared to<br>placebo gel as<br>an adjunct to<br>NSPT. | No conflict of<br>interest.<br><br>Sources of<br>support: Micro<br>Labs<br>(pharmaceutical<br>company),<br>Bangalore, India<br>and Purac<br>Biomaterials<br>(PURASORB),<br>Gorinchem, the<br>Netherland. |
|                                     |                                             |                                                                                                                                                                                      |                                  |                                                                                                                                                                            |                                                                        | 6<br>months                 | PPD (mm)<br>TG 4.98±0.50<br><b>(P&lt;0.05)</b><br>CG 5.10±0.75<br><b>(P&lt;0.05)</b><br><b>CBG: (P&lt;0.05)</b> |                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |
|                                     |                                             |                                                                                                                                                                                      |                                  |                                                                                                                                                                            |                                                                        | 9<br>months                 | PPD (mm)<br>TG 3.96±0.57<br><b>(P&lt;0.05)</b><br>CG 4.51±1.25<br><b>(P&lt;0.05)</b><br><b>CBG: (P&lt;0.05)</b> |                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |
| Bajaj et<br>al., 2012<br>India      | Age<br>range<br>30-50<br>years              | Periodontitis:<br>PPD ≥5 mm<br>and/or<br>CAL≥4mm and<br>vertical bone<br>loss≥3mm on<br>intraoral<br>periapical<br>radiographs                                                       | TG<br>(n=32)<br><br>CG<br>(n=31) | TG: NSPT +<br>0.5%<br>clarithromycin<br>gel injected<br>into<br>periodontal<br>pockets after<br>NSPT<br>(maximum<br>PPD, 1 site<br>per patient)                            | PPD (mm)<br>TG 7.29±0.58<br>CG 7.23±0.69                               | 3 months                    | PPD (mm)<br>TG 4.93±0.39<br><b>NS</b><br>CG 5.88±0.84<br><b>NS</b><br><b>CBG: (P&lt;0.05)</b>                   | Local delivery of<br>0.5%<br>clarithromycin<br>gel into<br>periodontal<br>pockets of T2D<br>patients led to a<br>significant<br>reduction in<br>PPD and gain in<br>CAL as                                                                      | Conflict of<br>interest: not<br>informed.<br><br>Sources of<br>support: Micro<br>Labs<br>(pharmaceutical<br>company),<br>Bangalore, India<br>and Purac                                                   |
|                                     |                                             |                                                                                                                                                                                      |                                  |                                                                                                                                                                            |                                                                        | 6 months                    | PPD (mm)<br>TG 5.14±0.40<br><b>(P&lt;0.05)</b><br>CG 6.06±0.88                                                  |                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |

|                                    |                                                        | Diabetes:<br>HbA1c $\geq$ 6.5%<br>and<br>FPG $\geq$ 126mg/dl                                                                                     | CG: NSPT +<br>placebo            |                                                                                                                                                                                                                                                                     |                                                                                                                   |          | NS<br>CBG: (P<0.05)                                                                                                                                                                                                                           | compared to<br>placebo gel as<br>an adjunct to<br>NSPT.                                                                         | Biomaterials<br>(PURASORB),<br>Gorinchem, the<br>Netherland.                         |
|------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Dodwad<br>et al.,<br>2012<br>India | Age<br>range<br>35-70<br>years                         | Periodontitis:<br>At least 3 sites<br>with PPD<br>$\geq$ 4mm and<br>$\leq$ 7mm<br><br>Diabetes:<br>controlled or<br>moderately<br>controlled T2D | TG<br>(n=20)<br><br>CG<br>(n=20) | TG: NSPT +<br>Resorbable<br>tetracycline<br>fiber inserted<br>into selected<br>periodontal<br>pockets after<br>NSPT<br>(periodontal<br>pack for 10<br>days)<br><br>CG: NSPT<br>alone                                                                                | HbA1c (%)<br>TG 7.56 $\pm$ 0.23<br>CG 7.65 $\pm$ 0.23<br><br>PPD (mm)<br>TG 3.55 $\pm$ 0.81<br>CG 3.27 $\pm$ 0.88 | 3 months | HbA1c (%)<br>TG 6.87 $\pm$ 0.34<br><b>P=0.000</b><br>CG 7.58 $\pm$ 0.23<br><b>P=0.025</b><br><b>CBG: (P=0.000)</b><br><br>PPD (mm)<br>TG 2.14 $\pm$ 0.54<br><b>P=0.000</b><br>CG 2.78 $\pm$ 0.96<br><b>P=0.000</b><br><b>CBG: (P=0.015)</b>   | Locally delivered<br>tetracycline is a<br>better<br>treatment<br>modality<br>compared to<br>NSPT alone.                         | Conflict of<br>Interest: None<br>declared.<br><br>Source of<br>Support: Nil.         |
| Faramarzi<br>et al, 2017<br>Iran   | TG<br>52.7<br>$\pm$ 7.3<br><br>CG<br>55.3<br>$\pm$ 8.8 | Periodontitis:<br>At least 20<br>teeth;<br>minimum of 8<br>teeth with PPD<br>$\geq$ 5 mm<br><br>Diabetes:<br>HbA1c $\geq$ 6%                     | TG<br>(n=34)<br><br>CG<br>(n=34) | TG: NSPT +<br>subgingival<br>1.5%<br>xanthan-<br>based<br>chlorhexidine<br>gel inserted<br>into<br>periodontal<br>pockets (8<br>teeth with 4-8<br>mm PPD,<br>minimum)<br>after two<br>sessions of<br>NSPT (2<br>weeks apart)<br>(periodontal<br>pack for 7<br>days) | HbA1c (%)<br>TG 7.72 $\pm$ 0.99<br>CG 7.32 $\pm$ 1.06<br><br>PPD (mm)<br>TG 5.41 $\pm$ 0.80<br>CG 5.41 $\pm$ 0.76 | 3 months | HbA1c (%)<br>TG 6.20 $\pm$ 0.97<br><b>(P&lt;0.05)</b><br>CG 6.53 $\pm$ 1.06<br><b>(P&lt;0.05)</b><br><b>CBG: NS</b><br><br>PPD (mm)<br>TG 3.48 $\pm$ 0.56<br><b>(P&lt;0.05)</b><br>CG 3.67 $\pm$ 0.83<br><b>(P&lt;0.05)</b><br><b>CBG: NS</b> | The application<br>of chlorhexidine<br>gel might<br>improve the<br>effects of NSPT<br>in T2D patients<br>with<br>periodontitis. | No conflicts of<br>interest.<br><br>Financial<br>support and<br>sponsorship:<br>Nil. |
|                                    |                                                        |                                                                                                                                                  |                                  |                                                                                                                                                                                                                                                                     |                                                                                                                   | 6 months | HbA1c (%)<br>TG 6.06 $\pm$ 1.04<br><b>(P&lt;0.05)</b><br>CG 6.42 $\pm$ 1.02<br><b>(P&lt;0.05)</b><br><b>CBG: NS</b>                                                                                                                           |                                                                                                                                 |                                                                                      |

|                             |                                        |                                                                                                               |                            |                                                                                                                                                                      |                                                                                   |          |                                                                                                                                                                                                   |                                                                                       |                                                                                                                        |
|-----------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
|                             |                                        |                                                                                                               |                            | CG: NSPT alone                                                                                                                                                       |                                                                                   |          | PPD (mm)<br>TG 3.38±0.55<br><b>(P&lt;0.05)</b><br>CG 3.48±0.67<br><b>(P&lt;0.05)</b><br><b>CBG: NS</b>                                                                                            |                                                                                       |                                                                                                                        |
| Lecio et al, 2019<br>Brazil | TG<br>58.6±12.4<br><br>CG<br>53.1±10.2 | Periodontitis:<br>At least 8 single-rooted teeth with PPD ≥5 and BoP<br><br>Diabetes:<br>History T2D> 5 years | TG (n=23)<br><br>CG (n=21) | TG: NSPT + 20% doxycycline-loaded PLGA nanospheres applied into periodontal pockets (4 moderate and 2 deep pockets) after NSPT<br><br>CG: NSPT + placebo nanospheres | HbA1c (%)<br>TG 8.1±1.0<br>CG 8.4±1.2<br><br>PPD (mm)<br>TG 5.6±0.5<br>CG 5.5±0.5 | 3 months | HbA1c (%)<br>TG 6.9±1.2<br><b>(P≤0.05)</b><br>CG 8.0±0.9<br><b>NS</b><br><b>CBG: (P≤0.05)</b><br><br>PPD (mm)<br>TG 3.5±0.7<br><b>(P≤0.05)</b><br>CG 3.4±0.7<br><b>(P≤0.05)</b><br><b>CBG: NS</b> | DOXY nanospheres may be considered a potential adjunct to NSPT in the therapy of T2D. | No conflicts of interest.<br><br>Funding: support from Research Support Foundation of the State of São Paulo – FAPESP. |
|                             |                                        |                                                                                                               |                            |                                                                                                                                                                      |                                                                                   | 6 months | HbA1c (%)<br>TG 8.2±1.5<br><b>NS</b><br>CG 8.5±1.6<br><b>NS</b><br><b>CBG: NS</b><br><br>PPD (mm)<br>TG 3.3±0.7<br><b>(P≤0.05)</b><br>CG 3.1±0.7<br><b>(P≤0.05)</b><br><b>CBG: NS</b>             |                                                                                       |                                                                                                                        |
| Lin et al., 2012<br>Taiwan  | TG<br>56.6±7.8                         | Periodontitis:<br>At least 20 teeth and five or more teeth                                                    | TG (n=14)                  | TG: NSPT + 2% minocycline gel inserted into periodontal                                                                                                              | HbA1c (%)<br>TG 9.3±0.8<br>CG 9.9±2.2                                             | 3 months | HbA1c (%)<br>TG 9.11±1.13<br><b>NS</b><br>CG 9.83±1.42                                                                                                                                            | NSPT alone or associated with minocycline may improve                                 | No conflicts of interest.                                                                                              |

|                                    |                                      |                                                                                                                  |                                  |                                                                                                                                                                              |                                                        |          |                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                    |                                                                                                                                                                             |
|------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    | CG<br>59.0±6.5                       | with<br>PPD≥5mm<br><br>Diabetes:<br>HbA1c≥8.5%<br>for more than 5<br>years                                       | CG<br>(n=14)                     | pockets (4-<br>week regimen)<br>one month after<br>NSPT<br><br>CG: NSPT<br>alone                                                                                             | PPD (mm)<br>TG 5.13±0.47<br>CG 5.15±0.52               |          | <b>NS</b><br><b>CBG: NS</b><br><br>PPD (mm)<br>TG 3.39±0.91<br><b>(P&lt;0.05)</b><br>CG 3.36±1.12<br><b>(P&lt;0.05)</b><br><b>CBG NS</b><br><br>6 months<br>HbA1c (%)<br>TG 8.09±2.60<br><b>NS</b><br>CG 8.75±1.31<br><b>NS</b><br><b>CBG: NS</b><br><br>PPD (mm)<br>TG 3.11±0.92<br><b>(P&lt;0.05)</b><br>CG 3.13±1.10<br><b>(P&lt;0.05)</b><br><b>CBG NS</b> | glycemic control<br>in patients with<br>poorly controlled<br>T2D.                                                  | Supported by<br>funds SKH-<br>TMU-96-12 from<br>grants of<br>cooperative<br>projects of Shin-<br>Kong Wu Ho-Su<br>Memorial<br>Hospital and<br>Taipei Medical<br>University. |
| Matsumoto<br>et al., 2009<br>Japan | TG<br>61.5±7.9<br><br>CG<br>56.4±7.0 | Periodontitis:<br>At least 10<br>sites with<br>PPD≥4mm<br><br>Diabetes:<br>HbA1c≥5.5%<br>and<br>FPG≥126mg/<br>dl | TG<br>(n=14)<br><br>CG<br>(n=13) | TG: NSPT +<br>2%<br>minocycline<br>hydrochloride<br>gel applied<br>into<br>periodontal<br>pockets<br>(every site<br>with PPD<br>≥4mm) after<br>NSPT<br><br>CG: NSPT<br>alone | HbA1c (%)<br>TG 7.1±0.9<br>CG 7.4±1.1<br><br>PPD<br>NA | 2 months | HbA1c (%)<br>TG 7.4±0.88<br><b>NS</b><br>CG 7.8±1.27<br><b>NS</b><br><b>CBG: NS</b><br><br>PPD<br>After 2 months, the<br>percentage of sites<br>with PPD≥4mm in<br>TG reduced by<br>8.3% (P≤0.05) and<br>by 5.0% in CG<br>(P≤0.05).                                                                                                                            | Minocycline<br>improves<br>periodontal<br>disease but has<br>not contributed<br>to a reduction of<br>HbA1c values. | No conflicts of<br>interest.<br><br>Supported by<br>Grant-in-<br>Aids from<br>Ministry of<br>Education,<br>Culture,<br>Sports, Science<br>and Technology<br>of Japan.       |

|                                |                                       |                                                                                                                                                          |                            |                                                                                                                                                           |                                             |                          |                                                                                                                                                                                                          |                                                                                                                                                                                                                               |                                                                                                                                                                         |
|--------------------------------|---------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Munenaga et al., 2013<br>Japan | Age range<br>54-75 years              | Periodontitis: High sensitivity c-reactive protein (hsCRP)>500 ng/ml and bone score over 25% constitute mid-to severe-periodontitis.<br><br>Diabetes: NA | TG (n=42)<br><br>CG (n=33) | TG: NSPT + tetracycline-HCl ointment applied into every periodontal pocket (once a week for 4 weeks) combined with sessions of NSPT<br><br>CG: NSPT alone | HbA1c (%)<br>TG: 7.40±1.17<br>CG: 7.43±1.17 | 3 months                 | HbA1c (%)<br>TG: 6.91±0.86 ( <b>P≤0.001</b> )<br>CG: 7.13±0.96 ( <b>P≤0.05</b> )<br><b>CBG: NA</b>                                                                                                       | Treatment using antibiotics is recommended for better metabolic control in subjects with T2D and periodontitis (hsCRP>500 ng/ml).                                                                                             | No conflicts of interest.<br><br>Supported by 8020 Research fund (2008) from 8020 Promotion Foundation, and Grant-in-Aid by Japan Society for the Promotion of Science. |
| Priyanka et al., 2015<br>India | TG<br>40.3±10.2<br><br>CG<br>42.2±8.2 | Periodontitis: PPD≥5mm and/or CAL≥4mm and vertical bone loss ≥ 3mm on intraoral periapical radiographs<br><br>Diabetes: controlled disease with HbA1c<8% | TG (n=32)<br><br>CG (n=32) | TG: NSPT + 3% satranidazole gel injected into periodontal pockets after NSPT<br><br>CG: NSPT + placebo                                                    | PPD (mm)<br>TG 8.31±1.42<br>CG 8.24±1.32    | 3 months<br><br>6 months | PPD (mm)<br>TG 5.32±1.25 ( <b>P≤0.001</b> )<br>CG 6.55±1.22 ( <b>P≤0.001</b> )<br><b>CBG: NA</b><br><br>PPD (mm)<br>TG 3.58±1.22 ( <b>P≤0.001</b> )<br>CG 6.15±1.11 ( <b>P≤0.001</b> )<br><b>CBG: NA</b> | Local delivery of 3% Satranidazole into the periodontal pocket stimulated a significant increase in the PPD reduction and CAL gain, compared to placebo gel as an adjunct to NSPT in T2D patients with chronic periodontitis. | No conflicts of interest.<br><br>Supported by Alkem Laboratories Ltd., Mumbai, India.                                                                                   |
| Santos et al., 2013<br>Brazil  | TG<br>50.3±9.5<br><br>CG<br>53.9±10.8 | Periodontitis: More than 30% of the sites with PPD and CAL≥4mm                                                                                           | TG (n=19)<br><br>CG (n=19) | TG: NSPT + 1% chlorhexidine gel applied into periodontal                                                                                                  | HbA1c (%)<br>TG 10.0±2.41<br>CG 10.4±2.9    | 3 months                 | HbA1c (%)<br>TG 9.3±2.75 <b>NS</b><br>CG 9.7±2.9 <b>NS</b>                                                                                                                                               | Treatments did not differ concerning clinical parameters for                                                                                                                                                                  | No conflicts of interest.                                                                                                                                               |

|                                      |                                                                                                                    |                                      |              |                                                                                                    |                                    |                                                                      |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------|----------------------------------------------------------------------------------------------------|------------------------------------|----------------------------------------------------------------------|
| Diabetes:<br>History T2D> 5<br>years | pockets three<br>times<br>(repeated<br>within 10<br>minutes) after<br>two<br>appointments<br>of NSPT within<br>24h | PPD (mm)<br>TG 3.4±0.5<br>CG 3.7±0.8 |              | <b>CBG: NS</b>                                                                                     | up to 12 months<br>post-treatment. | Funding:<br>provided by São<br>Paulo State<br>Research<br>Foundation |
|                                      | CG: NSPT +<br>placebo gel                                                                                          |                                      | 6<br>months  | HbA1c (%)<br>TG 9.9±2.40<br><b>NS</b><br>CG 9.6±3.2<br><b>NS</b><br><b>CBG: NS</b>                 |                                    |                                                                      |
|                                      |                                                                                                                    |                                      |              | PPD (mm)<br>TG 2.9±0.4<br><b>(P&lt;0.05)</b><br>CG 2.9±0.5<br><b>(P&lt;0.05)</b><br><b>CBG: NS</b> |                                    |                                                                      |
|                                      |                                                                                                                    |                                      | 12<br>months | HbA1c (%)<br>TG 9.7±2.54<br><b>NS</b><br>CG 8.9±2.5<br><b>NS</b><br><b>CBG: NS</b>                 |                                    |                                                                      |
|                                      |                                                                                                                    |                                      |              | PPD (mm)<br>TG 3.0±0.4<br><b>(P&lt;0.05)</b><br>CG 2.9±0.6<br><b>(P&lt;0.05)</b><br><b>CBG: NS</b> |                                    |                                                                      |

Legend: TG: teste group; CG: Control Group; HbA1c: glycated hemoglobin; NA: not available; FPG: Fasting plasma glucose; PPD: Probing pocket depth; CAL: Clinical attachment level; BoP: Bleeding on probing; T2D: Type 2 Diabetes Mellitus; NSPT: non-surgical periodontal therapy; CBG: Comparison between groups; NS: Non-significant

### 3.2 RISK OF BIAS

Regarding HbA1c, two studies [37,38] presented a “low” risk of bias, and five studies [24,34,36,39,40] “some concerns” (Fig. 2 and 3). In the studies classified as “some concerns” the risk of bias occurred mainly because the authors did not properly describe the randomization process, allocation concealment, or the lack of operator blinding.

Considering PPD, three studies [32,37,38] presented a “low” risk of bias, four studies [33–36] were considered with “some concerns” and two studies [24,39] had a “high” risk of bias (Fig. 4 and 5). Once again, lack of information about the randomization process, concealment of allocation, and clarity on operator or outcome assessor blinding were the main criteria for increasing the risk of bias. In addition, one study [24] did not report missing outcome data about PPD.

We emphasize that in the study performed by Matsumoto et al. (2009) [39], test and control groups presented statistical differences concerning PPD at baseline but not regarding HbA1c, which justifies the different classifications in domain 1 (randomization process), according to Cochrane’s RoB 2.0 algorithm.

|                                                        |                     | Risk of bias domains |    |    |    |    |                 |
|--------------------------------------------------------|---------------------|----------------------|----|----|----|----|-----------------|
|                                                        |                     | D1                   | D2 | D3 | D4 | D5 | Overall         |
| Study                                                  | Dodwad 2012 (34)    | ⊖                    | ⊖  | ⊕  | ⊕  | ⊕  | ⊖               |
|                                                        | Faramarzi 2017 (36) | ⊖                    | ⊖  | ⊕  | ⊕  | ⊕  | ⊖               |
|                                                        | Lecio 2019 (37)     | ⊕                    | ⊕  | ⊕  | ⊕  | ⊕  | ⊕               |
|                                                        | Lin 2012 (24)       | ⊕                    | ⊖  | ⊕  | ⊕  | ⊕  | ⊖               |
|                                                        | Matsumoto 2009 (39) | ⊖                    | ⊖  | ⊕  | ⊕  | ⊕  | ⊖               |
|                                                        | Munenaga 2013 (40)  | ⊖                    | ⊖  | ⊕  | ⊕  | ⊕  | ⊖               |
|                                                        | Santos 2013 (38)    | ⊕                    | ⊕  | ⊕  | ⊕  | ⊕  | ⊕               |
| Domains:                                               |                     |                      |    |    |    |    | Judgement       |
| D1: Bias arising from the randomization process.       |                     |                      |    |    |    |    | ⊖ Some concerns |
| D2: Bias due to deviations from intended intervention. |                     |                      |    |    |    |    | ⊕ Low           |
| D3: Bias due to missing outcome data.                  |                     |                      |    |    |    |    |                 |
| D4: Bias in measurement of the outcome.                |                     |                      |    |    |    |    |                 |
| D5: Bias in selection of the reported result.          |                     |                      |    |    |    |    |                 |

Figure 2: Risk of bias assessment of included studies (for HbA1c outcome) considering each Cochrane’s RoB 2.0 tool domain and overall risk of bias.

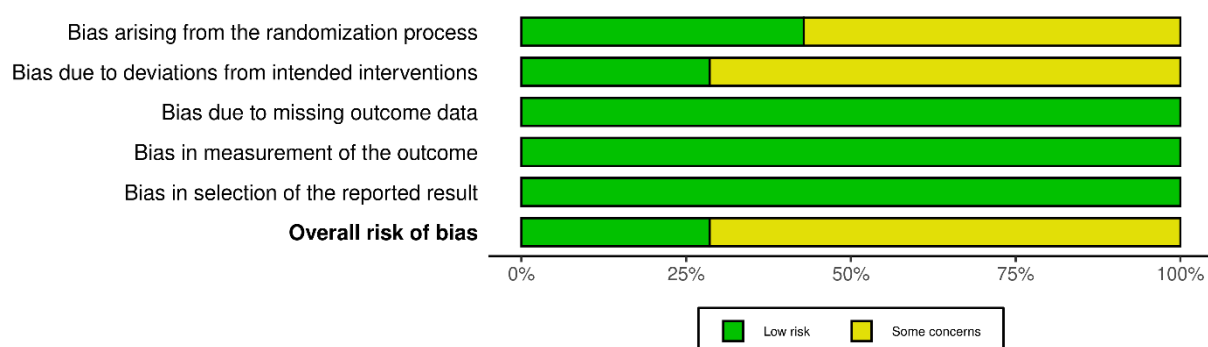


Figure 3: Weighted bars plot of Risk of bias evaluation of included studies (for HbA1c outcome) (Cochrane's RoB 2.0 tool).

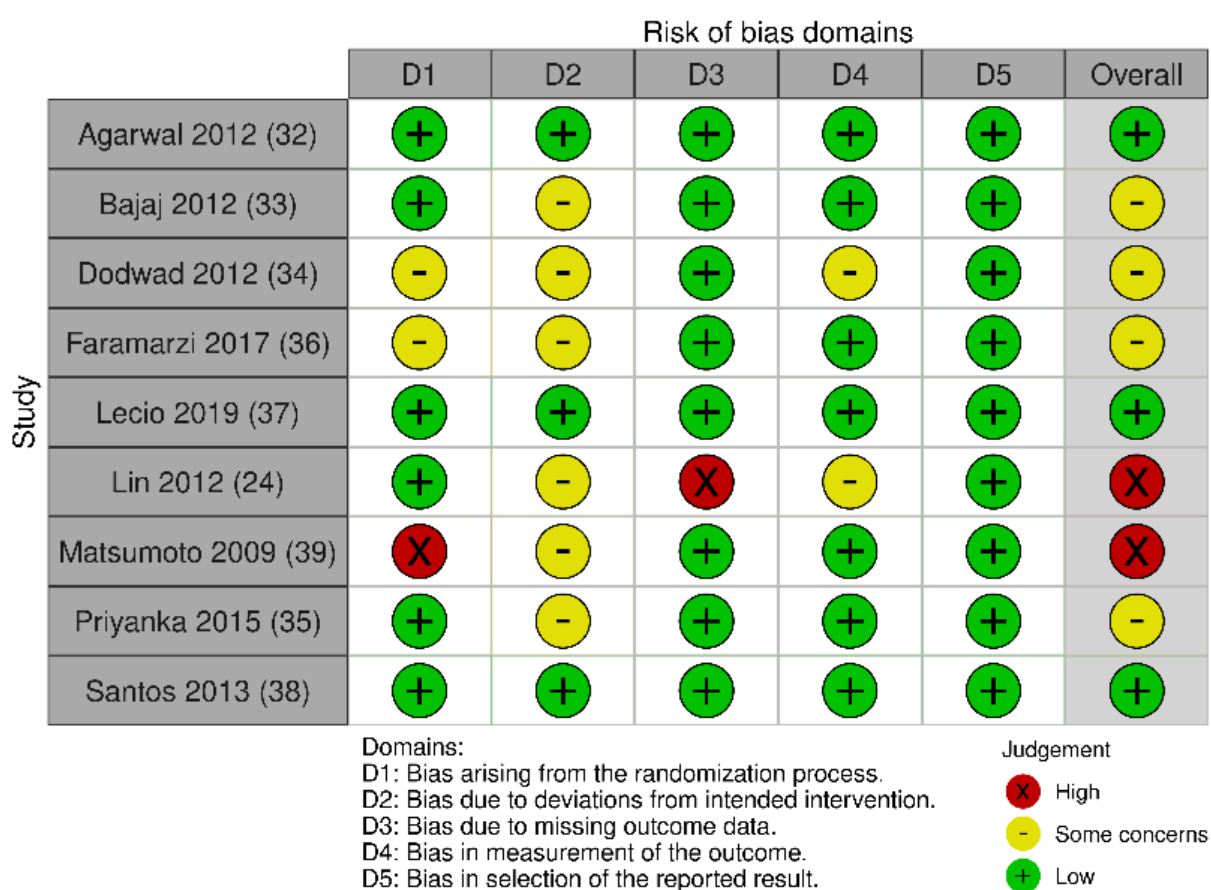


Figure 4: Risk of bias assessment of included studies (for PPD outcome) considering each Cochrane's RoB 2.0 tool domain and overall risk of bias.

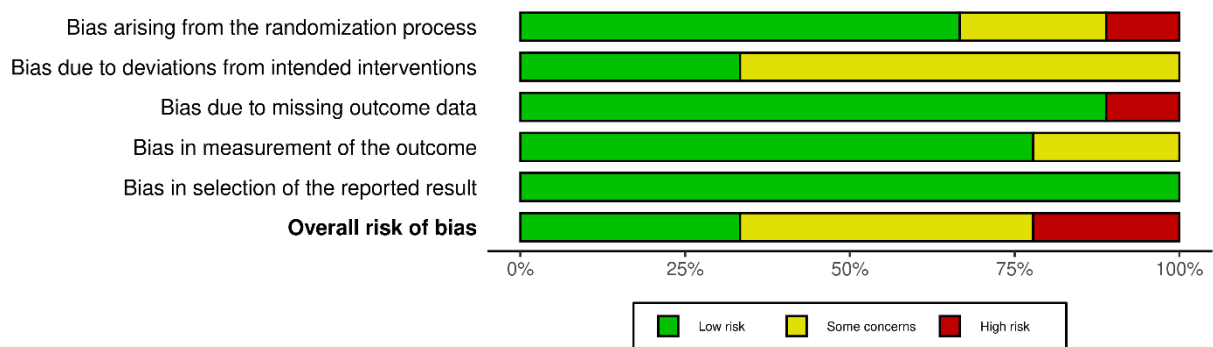


Figure 5: Weighted bars plot of Risk of bias evaluation of included studies (for PPD outcome) (Cochrane's RoB 2.0 tool).

### 3.3 NETWORK META-ANALYSIS RESULTS

Seven studies were included in the NMA for HbA1c, while eight were for PPD. The study performed by Matsumoto et al. (2009) [39] was not included in the meta-analysis for PPD because the authors mentioned the improvement in PPD after using minocycline gel adjunct to NSPT, but mean $\pm$ SD was not available either at baseline or after the treatment, and further information was not obtained after contact with the authors. Fig. 6 (HbA1c) and Fig. 7 (PPD) show the network plot with the number of interventions and studies included for each outcome (HbA1c and PPD) at different follow-up periods (3 and 6 months). The league table for all effect estimates comparisons is available in Supplementary file 3. Tables 2 and 3 present the effect estimates for each comparison, considering the outcomes and different follow-up periods (3 and 6 months). The results were interpreted using the GRADE partially contextualized framework.

At 3 months, doxycycline nanospheres (MD: -0.80%; 95%CI: -1.70, 0.10), chlorhexidine gel (MD: -0.68%; 95%CI: -1.34, -0.02), and tetracycline fiber (MD: -0.62%; 95%CI: -0.85, -0.39) reached the MID in HbA1c reduction, when compared to NSPT, all with low certainty of evidence. At 6 months, only the chlorhexidine gel (MD: -0.53%; 95%CI: -1.57, 0.51) was more effective than NSPT, achieving the MID, yet, with very low certainty of evidence (Table 2).

At 3 months, satranidazole gel (MD: -1.30mm; 95%CI: -2.22, -0.38) and clarithromycin gel (MD: -1.01mm; 95%CI: -1.50, -0.52) reached the MID in PPD reduction, when compared to NSPT (low certainty of the evidence). The best result was found for satranidazole gel after 6 months, which reduced PPD by 2.64 mm (about 2.5x the MID) compared to NSPT with moderate certainty of evidence (MD: -2.64mm;

95%CI: -3.56, -1.72) (Table 3).

The forest plot comparing all local antimicrobials and NSPT alone is shown in Fig. 8 (HbA1c) and Fig. 9 (PPD). Inconsistency test results are shown in Supplementary file 4.

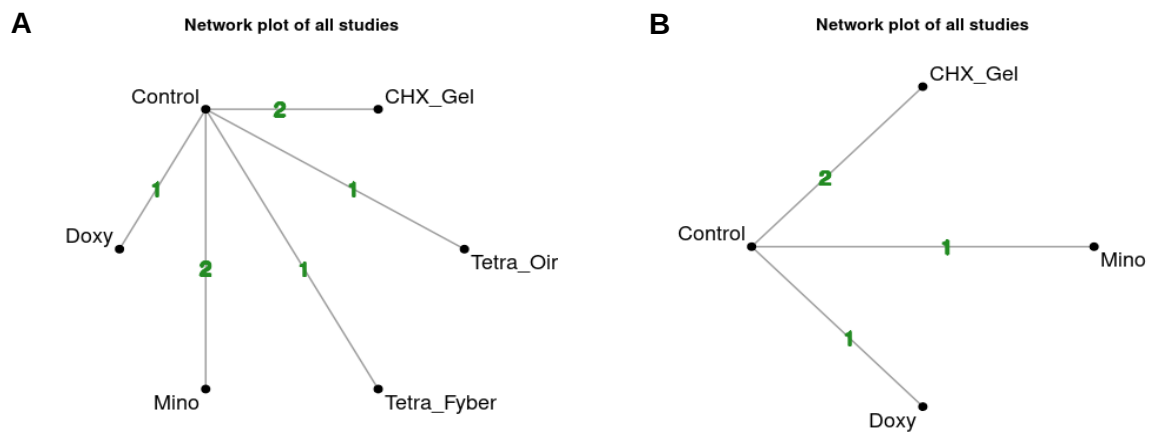


Figure 6: Network plot for included studies for HbA1c. Numbers in lines show the number of included studies in direct comparisons (CHX\_Gel: chlorhexidine gel; Doxy: doxycycline gel; Mino: minocycline gel; Tetra\_Fyber: tetracycline fiber; Tetra\_Oin: tetracycline ointment). **A**: network plot at 3 months; **B**: network plot at 6 months.

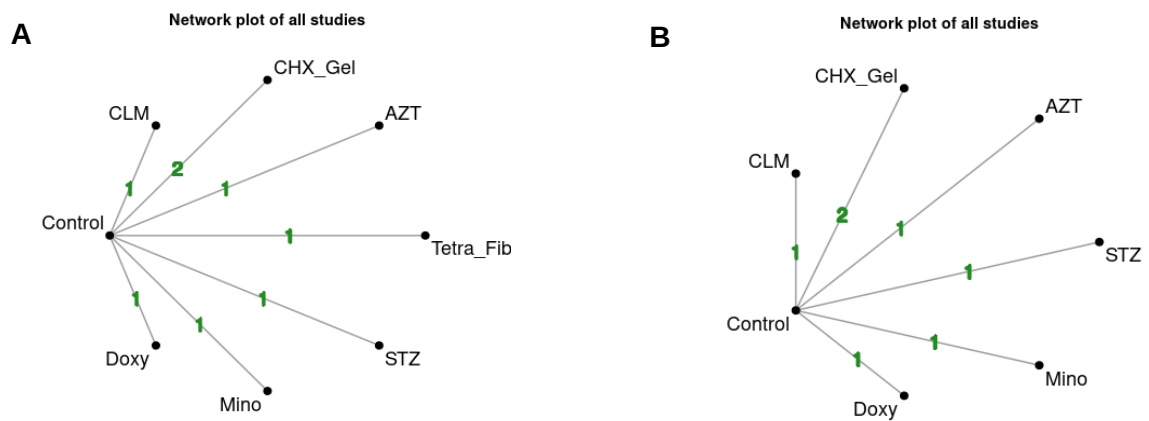


Figure 7: Network plot for included studies for PPD. Numbers in lines show the number of included studies in direct comparisons (AZT: azithromycin gel; CLM: clarithromycin gel; CHX\_Gel: chlorhexidine gel; Doxy: doxycycline gel; Mino: minocycline gel; Tetra\_Fib: tetracycline fiber; STZ: satranidazole gel). **A**: network plot at 3 months; **B**: network plot at 6 months.

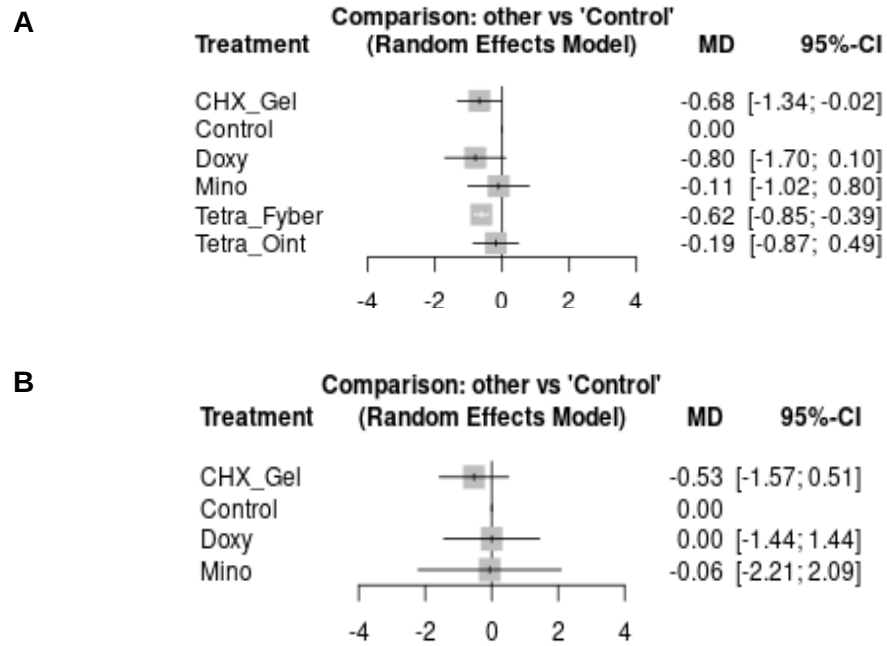


Figure 8: Forest plot showing the performance of different local antimicrobials used as adjuncts to NSPT, compared to NSPT alone after different follow-up periods. **A:** HbA1c assessment at 3 months; **B:** HbA1c assessment at 6 months.

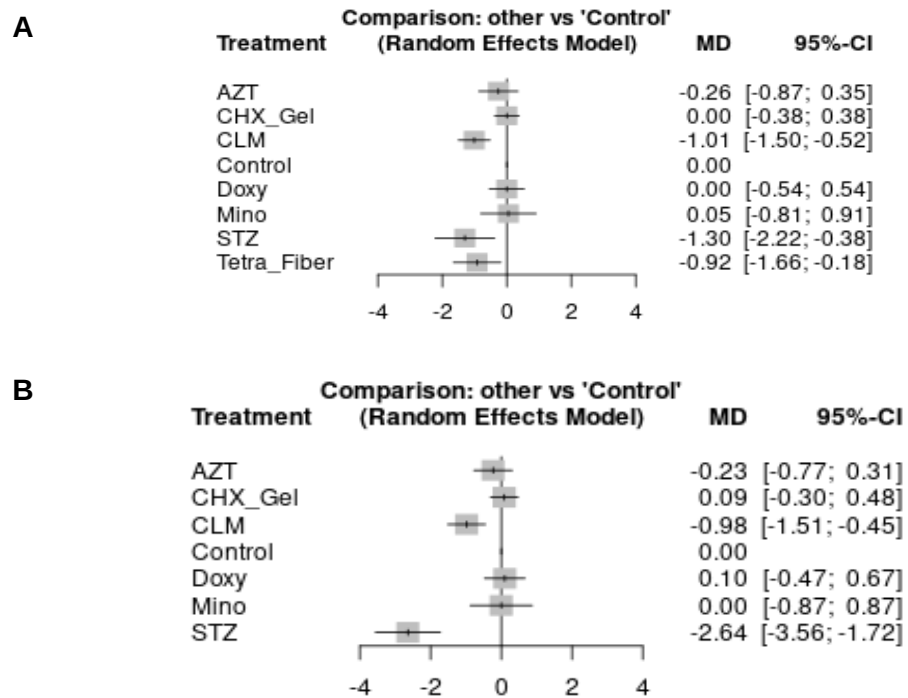


Figure 9: Forest plot showing the performance of different local antimicrobials used as adjuncts to NSPT, compared to NSPT alone after different follow-up periods. **A:** PPD assessment at 3 months; **B:** PPD assessment at 6 months.

Table 2. Classification of interventions for HbA1c control at 3 months and performances after 6 months in patients with type 2 diabetes mellitus and periodontitis following the partially contextualized framework for NMA

| <b>Intervention<sup>1</sup></b> | <b>HbA1c reduction<sup>2</sup><br/>MD [95% CI] after<br/>3 months</b> | <b>Certainty<br/>of<br/>Evidence</b> | <b>HbA1c reduction<sup>2</sup><br/>MD [95% CI] after<br/>6 months</b> | <b>Certainty<br/>of<br/>Evidence</b> |
|---------------------------------|-----------------------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------------|--------------------------------------|
| Doxy gel                        | -0.80 [-1.70; 0.10]                                                   | Low                                  | 0.00 [-1.44; 1.44]                                                    | Low                                  |
| CHX gel                         | -0.68 [-1.34; -0.02]                                                  | Low                                  | -0.53 [-1.57; 0.51]                                                   | Very low                             |
| Tetra fiber                     | -0.62 [-0.85; -0.39]                                                  | Low                                  | -                                                                     | -                                    |
| Tetra ointment                  | -0.19 [-0.87; 0.49]                                                   | Very low                             | -                                                                     | -                                    |
| Minocycline gel                 | -0.11 [-1.02; 0.80]                                                   | Very low                             | -0.06 [-2.21; 2.09]                                                   | Low                                  |

Notes: Doxy gel: doxycycline gel; CHX gel: chlorhexidine gel; Tetra fiber: tetracycline fiber; Tetra ointment: tetracycline ointment; MD: mean difference; CI: Confidence Interval.

<sup>1</sup>Used as an adjunct of NSPT and compared to NSPT alone.

<sup>2</sup>Results in % HbA1c. MID was considered 0.5%. Negative values mean that the intervention was more effective in reducing HbA1c. Positive values mean that the comparator (NSPT) was more effective.

Table 3. Classification of interventions for PPD improvement at 3 months and performances after 6 months in patients with type 2 diabetes mellitus and periodontitis following the partially contextualized framework for NMA

| <b>Intervention<sup>1</sup></b> | <b>PPD reduction<sup>2</sup><br/>MD [95% CI] after<br/>3 months</b> | <b>Certainty<br/>of<br/>Evidence</b> | <b>PPD reduction<sup>2</sup><br/>MD [95% CI] after<br/>6 months</b> | <b>Certainty<br/>of<br/>Evidence</b> |
|---------------------------------|---------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------|--------------------------------------|
| STZ gel                         | -1.30 [-2.22; -0.38]                                                | Low                                  | <b>-2.64 [-3.56; -1.72]</b>                                         | <b>Moderate</b>                      |
| CLM gel                         | -1.01 [-1.50; -0.52]                                                | Low                                  | -0.98 [-1.51; -0.45]                                                | Low                                  |
| Tetra fiber                     | -0.92 [-1.66; -0.18]                                                | Very low                             | -                                                                   | -                                    |
| AZT gel                         | -0.26 [-0.87; 0.35]                                                 | Low                                  | -0.23 [-0.77; 0.31]                                                 | Low                                  |
| Minocycline gel                 | 0.05 [-0.81; 0.91]                                                  | Very low                             | 0.00 [-0.87; 0.87]                                                  | Very low                             |
| Doxy gel                        | 0.00 [-0.54; 0.54]                                                  | Moderate                             | 0.10 [-0.47; 0.67]                                                  | Moderate                             |
| CHX gel                         | 0.00 [-0.38; 0.38]                                                  | Very low                             | 0.09 [-0.30; 0.48]                                                  | Very low                             |

Notes: STZ gel: satranidazole gel; CLM gel: clarithromycin gel; Tetra fiber: tetracycline fiber; AZT gel: azithromycin gel; Doxy gel: doxycycline gel; CHX gel: chlorhexidine gel; MD: mean difference; CI: Confidence Interval.

<sup>1</sup>Used as an adjunct of NSPT and compared to NSPT alone.

<sup>2</sup>Results in mm. MID was considered  $\geq 1$ mm. Negative values mean that the intervention was more effective in reducing PPD. Positive values mean that the comparator (NSPT) was more effective.

### 3.4 CERTAINTY OF EVIDENCE

At 3 and 6 months, the certainty of the evidence for HbA1c varied from “low” to “very low”, while for PPD, from “moderate” to “very low” (Supplementary file 3). Downgrading occurred mainly because of the risk of bias and imprecision. Detailed results for each comparison judgment are available in Supplementary file 5.

#### 4. Discussion

The results of the NMA were analyzed considering the effect magnitude and the certainty of the evidence. The most promising subgingivally delivered local antimicrobials (used as adjuncts to NSPT and compared to NSPT alone) for HbA1c reduction after 3 months were doxycycline gel, chlorhexidine gel, and tetracycline fibers. All of them reached the MID for HbA1c, nevertheless, all with low evidence certainty. After 6 months, chlorhexidine gel kept showing promising effects despite the very low certainty.

Concerning PPD, satranidazole gel was the most effective treatment compared to NSPT after 6-months of follow-up (large effect with moderate certainty).

Satranidazole is a novel nitroimidazole, an alternative to metronidazole, presenting four-fold more potency against gram-negative bacteria [41]. This substance has been considered more active against aerobic, anaerobic, and microaerophilic bacteria, being an interesting alternative to eliminate deep pockets when combined with NSPT. Satranidazole has the potential to reduce sites infected by periodontopathogens such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans* [42]. The subgingival use of 3% satranidazole gel in systemically healthy subjects with chronic periodontitis showed a more significant PPD reduction and CAL gain than NSPT alone and metronidazole gel [42,43]. A more recent study compared the efficacy of 0.25% satranidazole gel versus 1% metronidazole gel subgingival use in association with NSPT in the treatment of periodontitis, showing that even at lower concentrations, satranidazole gel presented good results [41]. The literature is still scarce in evaluating the benefits of local satranidazole in diabetic patients, and our search retrieved only one study [35], which was considered with “some concerns” regarding the risk of bias due to the lack of operator blinding. Although the NMA showed a large effect with moderate certainty for PPD reduction after 6 months of follow-up, the effect of satranidazole gel on HbA1c was not tested in this study. Thus, although promising, further studies are necessary to interlink the periodontal results to glycemic control and confirm the effects on the periodontal parameters of patients with T2D.

Doxycycline belongs to the tetracycline family, and is a broad-spectrum antibiotic with additional benefits like anti-oxidant properties and the capacity to inhibit

matrix metalloproteinases (MMPs) that induce the release of various inflammatory mediators [44,45]. There are studies demonstrating the benefits of local doxycycline for improving periodontal status in systemically healthy subjects [46–49], patients with type 1 diabetes [50], and smokers [51]. In the same way, some studies have already described an HbA1c reduction [45,52,53] and periodontal improvement [45,53] in patients with T2D, but with the systemic use of the drug. Gomaa et al. (2018) [54] treated T2D patients with systemic doxycycline 20 mg and subgingivally delivered doxycycline gel 10% into the periodontal pockets. The patients exhibited a more significant reduction of PPD and CAL ( $P < 0.05$ ) when compared to the control group (NSPT alone) [54]. However, this study was excluded from the present review due to the concomitant use of systemic antibiotics. Our search returned only one study evaluating the local use of doxycycline in patients with T2D and periodontitis [37], and it presented a “low” risk of bias. However, the NMA showed an important effect with low certainty, so these findings need further confirmation.

Chlorhexidine is an effective antiseptic against a broad spectrum of microorganisms. When administered in gel-based presentations, higher concentrations (up to 15 times) are reached than liquid carriers [55]. Chlorhexidine gel as an adjuvant to NSPT can improve the periodontal status, reducing PPD, and increasing CAL gain in patients with chronic periodontitis [55–57]. In the study by Srirangarajan et al. (2016) [56] patients with T2D, with and without chronic periodontitis, were treated with NSPT in a comparative clinical trial. Those with chronic periodontitis also received subgingivally delivered chlorhexidine 1% gel in all periodontal pockets. After the treatment, all periodontal parameters (plaque index, gingival index, and PPD) significantly improved. All patients presented a statistically significant reduction in fasting glucose, suggesting that decreasing periodontal inflammation reduces insulin resistance, improving metabolic control [56]. Two studies evaluating the efficacy of chlorhexidine were included in the present network meta-analysis [36,38], one [38] considered as “low” risk of bias and the other one [36] presenting “some concerns”. The NMA showed an important and consistent effect for CHX gel on HbA1c reduction after 3 and 6-months follow-up; however, with low certainty of evidence after 3 months and very low after 6 months. Therefore, these results must be analyzed cautiously due to considerable uncertainty and demand confirmation with further studies.

Tetracyclines are a common antibiotic family with antimicrobial, anti-

inflammatory, and anti-collagenase properties, besides the ability to inhibit bone resorption and promote the attachment of fibroblasts to root surfaces [44,58]. Tetracyclines are bacteriostatic agents effective against many gram-negative species, such as *A. actinomycetemcomitans*. Due to their antimicrobial and immunomodulatory effects, tetracyclines are a good adjunctive option in managing periodontal disease [44,58]. The effects of tetracycline fibers have been studied since 1983, indicating that these devices could produce effects on the periodontal microbiota and signs of clinical improvement [59]. Some studies tested the efficacy of subgingivally inserted tetracycline fiber as an adjunct to NSPT compared to NSPT alone, and showed a greater PPD reduction and CAL gain [60–62]. Other methods for subgingival delivery of tetracyclines include irrigation and the subgingival application of an ointment or gel [63]. There is evidence that the delivery through fibers is more efficient than irrigation [64], although there is no comparison with other formulations (gel or ointment). We included only one study using tetracyclines fiber in patients with T2D [34] and one with tetracycline ointment [40]. The tetracycline ointment showed a slight reduction in HbA1c with very low certainty. In contrast, the tetracycline fiber showed an important effect, with low certainty for the HbA1c decrease after 3 months follow-up. Furthermore, no additional studies were found to reinforce these findings. Therefore, these results require further confirmation.

Periodontitis control favors glycemic control and decreases systemic inflammation in patients with T2D [65]. The presence of chronic infections, including periodontitis, might induce an increase of circulating cytokines and factors such as C-reactive protein, interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha and prostaglandin-E2 [66]. As a result, the systemic inflammatory burden increases, which eventually induces insulin resistance in T2D, impairing glycemic control [7,66]. Patients with T2D and periodontitis have higher levels of systemic inflammatory markers compared with people with periodontitis only, and NSPT results in a greater reduction of these markers in subjects with T2D compared with those with periodontitis and systemically healthy [67]. In this context, periodontal therapy may improve insulin sensitivity and consequently the HbA1c values by decreasing inflammatory cytokines and markers levels [65,67]. Since any improvement in glycemic status has the potential to reduce the risk of diabetic complications and to improve the quality of life of people with T2D [67,68], any effort to control periodontal inflammation is valuable. Therefore, the use of subgingival antimicrobials as adjuncts to NSPT in patients with T2D and

periodontitis should be further investigated.

#### 4.1 LIMITATIONS AND STRENGTHS

This study presents limitations, such as the small number of included studies, which resulted in a poorly connected network. Furthermore, only some of the studies evaluated both clinical periodontal parameters and HbA1c value, preventing the inclusion of the ten included studies in both NMA (HbA1c and PPD).

Despite it was not an objective of this study, clinicians have the interest to know the adverse effects of the tested substances. However, none of the studies evaluating the local antimicrobials with promising results reported these data.

This study's strengths comprise the highly rigorous methodologic approach used to assess the certainty of the evidence and interpret the results through the GRADE partially contextualized framework with MID that can avoid spurious and misleading conclusions [30].

#### 4.2 IMPLICATIONS FOR FUTURE RESEARCH AND CLINICAL PRACTICE

The effectiveness of adjunctive local antimicrobials to NSPT on reducing both HbA1c levels and improving clinical periodontal parameters (PPD) in patients with T2D and periodontitis is still unclear. So, further intervention trials are required to confirm these NMA findings. These might include larger sample sizes, longer follow-ups, and rigorous methods to reduce the risk of bias and increase the validity of the results. Besides that, we recommend that future research focus on the antimicrobials that achieved MID thought with low and very low certainty, as future research may change the current evidence [69]. The antimicrobials with promising results that should be included in future trials are satranidazole, doxycycline, chlorhexidine, tetracycline, and clarithromycin.

## 5. Conclusion

The subgingival (local) use of satranidazole gel probably results in PPD reduction after 6-month follow-up compared to NSPT alone (moderate evidence certainty) in patients with T2D; however, the effect in HbA1c was not tested yet. The use of doxycycline gel, chlorhexidine gel, and tetracycline fiber as adjuncts to NSPT may reduce the HbA1c values in patients with T2D (low evidence certainty) after 3 months of follow-up, but these short-term findings require further confirmation.

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## **PRESS RELEASE**

Esta dissertação de mestrado visa contribuir com a pesquisa na área da periodontia, apresentando as evidências disponíveis na literatura científica sobre o uso de antimicrobianos locais em pacientes com diabetes tipo 2 e periodontite. Os estudos analisados favorecem o desenvolvimento de novos protocolos terapêuticos com o objetivo de melhorar o controle glicêmico e a condição clínica periodontal desses pacientes. Os resultados da presente dissertação podem nortear estudos futuros, além de auxiliar na tomada de decisão sobre as substâncias que podem ser incorporadas na prática clínica, como uma estratégia complementar a terapia convencional, visando uma melhoria na qualidade dos tratamentos oferecidos.

## ANNEX

## SUPPLEMENTARY FILE 1 - COMPLETE SEARCH STRATEGY FOR EACH DATABASE

| Database      | Search 2022-02-04                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | References |
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| <b>Cochrane</b> | <p>("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Diabetes" OR "Metabolic Diseases" OR "Hyperglycemia" OR "Glucose Metabolism Disorders" OR "Metabolic Control" OR "Glycated Hemoglobin A" OR "Glycated Hemoglobin" OR "HbA1" OR "Glycosylated Hemoglobin A" OR "Blood Glucose" OR "Glycemic Index" OR "Fasting blood glucose" OR "Post-prandial blood glucose" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "type II diabetes mellitus" OR "type 2 diabetes" OR "type II diabetes" OR "advanced glycation end products" OR "HbA1c" OR "human hemoglobin A1c protein" OR "glycohemoglobin A" OR "glycosylated analysis hemoglobin A" OR "glycated hemoglobins" OR "glycated hemoglobin" OR "blood glucose metabolism" OR "blood glucose analysis")):ti,ab,kw AND ("local" OR "subgingival" OR "subgingivally delivered" OR "subgingival delivery" OR "subgingival application" OR "locally delivered" OR "local use" OR "gel" OR "topical" OR "delivery vehicle" OR "nanospheres") AND ("antibiotic" OR "antibiotics" OR "antimicrobial" OR "antimicrobials" OR "anti-bacterial" OR "agents" OR "anti-bacterial agents" OR "antibacterial agents" OR "disinfection" OR "amoxicillin" OR "amox" OR "amoxicilline" OR "penicillin" OR "Azithromycin" OR "clarithromycin" OR "doxycycline" OR "doxycyclin" OR</p> | 129 |

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|               | <p>'bleeding index' OR 'periodontal inflammation' OR 'Gingival Bleeding on Probing' OR 'gingival bleeding' OR 'Gingival Index' OR 'Gingival Indices' OR 'Gingival Indexes' OR 'Dental Plaque Index' OR 'Dental Plaque Indexes' OR 'Dental Plaque Indices' OR 'Dental Plaque' OR 'dental biofilm' OR 'dental biofilms' OR 'Periodontal probing depth' OR 'Clinical attachment loss' OR 'Periodontal Debridement' OR 'Periodontal Debridements' OR 'Periodontal Pocket Debridement' OR 'periodontal therapy' OR 'Dental Scaling' OR 'Root Scaling' OR 'Subgingival Scaling' OR 'periodontal treatment' OR 'periodontal therapy' OR 'nonsurgical periodontal treatment' OR 'non-surgical periodontal treatment' OR 'non-surgical mechanical therapy' OR 'Root Planing' OR 'Root Planings' OR 'periodontal attachment loss' OR 'clinical attachment level' OR 'attachment gain' OR 'periodontal healing' OR 'periodontal diseased sites' OR 'periodontal parameters' OR 'periodontal clinical parameters' OR 'pocket closure' OR 'pocket depth reduction' OR 'residual pockets' OR 'periodontal recession' OR 'Gingival Recession' OR 'Gingival Recessions' OR 'periodontal re-instrumentation' OR 'pocket re-instrumentation' OR 'periodontal residual sites')</p> |     |
| <b>LIVIVO</b> | <p>("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Diabetes" OR "Metabolic Diseases" OR "Hyperglycemia" OR "Glucose Metabolism Disorders" OR "Metabolic Control" OR "Glycated Hemoglobin A" OR "Glycated Hemoglobin" OR "HbA1" OR "Glycosylated Hemoglobin A" OR "Blood Glucose" OR "Glycemic Index" OR "Fasting blood glucose" OR "Post-prandial blood glucose" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "type II diabetes mellitus" OR "type 2 diabetes" OR "type II diabetes" OR "advanced glycation end products" OR "HbA1c" OR "human hemoglobin A1c protein" OR "glycohemoglobin A" OR "glycosylated analysis hemoglobin A" OR "glycated hemoglobins" OR "glycated hemoglobin" OR "blood glucose metabolism" OR "blood glucose analysis") AND ("local" OR "subgingival" OR "subgingivally delivered" OR "subgingival delivery" OR "subgingival application" OR "locally delivered" OR "local use" OR "gel" OR "topical" OR "delivery vehicle" OR "nanospheres") AND ("antibiotic" OR "antibiotics" OR "antimicrobial" OR "antimicrobials" OR "anti-bacterial" OR "agents" OR "anti-bacterial agents" OR "antibacterial agents" OR "disinfection"</p>                                                                                  | 194 |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
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|  | <p>OR "amoxicillin" OR "amox" OR "amoxicilline" OR "penicillin" OR "Azithromycin" OR "clarithromycin" OR "doxycycline" OR "doxycyclin" OR "Tetracycline" OR "minocycline" OR "clindamycin" OR "Fluoroquinolones" OR "metronidazole" OR "Chlorhexidine" OR "triclosan" OR "Cetylpyridinium" OR "Cetylpyridinium chloride" OR "CPC" OR "povidone iodine") AND ("Chronic Periodontitis" OR "Chronic Periodontitides" OR "Adult Periodontitis" OR "Adult Periodontitides" OR "Periodontal treatment" OR "Periodontal therapy" OR "nonsurgical periodontal therapy" OR "non-surgical periodontal therapy" OR "Periodontitis" OR "Periodontitides" OR "Periodontal Diseases" OR "Periodontal Disease" OR "Parodontosis" OR "Parodontoses" OR "Pyorrhea Alveolaris" OR "scaling and root planing" OR "Periodontal Pocket" OR "periodontal pockets" OR "pocket depth" OR "pocket probing" OR "probing depth" OR "periodontal health" OR "Alveolar Bone Loss" OR "Alveolar Bone Losses" OR "Alveolar Resorption" OR "Periodontal Bone Losses" OR "Periodontal Bone Loss" OR "Periodontal Resorption" OR "phase 1 periodontal therapy" OR "initial periodontal therapy" OR "Periodontal Index" OR "Periodontal Indices" OR "Periodontal Indexes" OR "bleeding on probing" OR "bleeding index" OR "periodontal inflammation" OR "Gingival Bleeding on Probing" OR "gingival bleeding" OR "Gingival Index" OR "Gingival Indices" OR "Gingival Indexes" OR "Dental Plaque Index" OR "Dental Plaque Indexes" OR "Dental Plaque Indices" OR "Dental Plaque" OR "dental biofilm" OR "dental biofilms" OR "Periodontal probing depth" OR "Clinical attachment loss" OR "Periodontal Debridement" OR "Periodontal Debridements" OR "Periodontal Pocket Debridement" OR "periodontal therapy" OR "Dental Scaling" OR "Root Scaling" OR "Subgingival Scaling" OR "periodontal treatment" OR "periodontal therapy" OR "nonsurgical periodontal treatment" OR "non-surgical periodontal treatment" OR "non-surgical mechanical therapy" OR "Root Planing" OR "Root Planings" OR "periodontal attachment loss" OR "clinical attachment level" OR "attachment gain" OR "periodontal healing" OR "periodontal diseased sites" OR "periodontal parameters" OR "periodontal clinical parameters" OR "pocket closure" OR "pocket depth reduction" OR "residual pockets" OR "periodontal recession" OR "Gingival Recession"</p> |  |
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|               | OR "Gingival Recessions" OR "periodontal re-instrumentation" OR "pocket re-instrumentation" OR "periodontal residual sites")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |     |
| <b>Scopus</b> | <p>TITLE-ABS-KEY(("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Diabetes" OR "Metabolic Diseases" OR "Hyperglycemia" OR "Glucose Metabolism Disorders" OR "Metabolic Control" OR "Glycated Hemoglobin A" OR "Glycated Hemoglobin" OR "HbA1" OR "Glycosylated Hemoglobin A" OR "Blood Glucose" OR "Glycemic Index" OR "Fasting blood glucose" OR "Post-prandial blood glucose" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "type II diabetes mellitus" OR "type 2 diabetes" OR "type II diabetes" OR "advanced glycation end products" OR "HbA1c" OR "human hemoglobin A1c protein" OR "glycohemoglobin A" OR "glycosylated analysis hemoglobin A" OR "glycated hemoglobins" OR "glycated hemoglobin" OR "blood glucose metabolism" OR "blood glucose analysis") AND ("local" OR "subgingival" OR "subgingivally delivered" OR "subgingival delivery" OR "subgingival application" OR "locally delivered" OR "local use" OR "gel" OR "topical" OR "delivery vehicle" OR "nanospheres") AND ("antibiotic" OR "antibiotics" OR "antimicrobial" OR "antimicrobials" OR "anti-bacterial" OR "agents" OR "anti-bacterial agents" OR "antibacterial agents" OR "disinfection" OR "amoxicillin" OR "amox" OR "amoxicilline" OR "penicillin" OR "Azithromycin" OR "clarithromycin" OR "doxycycline" OR "doxycyclin" OR "Tetracycline" OR "minocycline" OR "clindamycin" OR "Fluoroquinolones" OR "metronidazole" OR "Chlorhexidine" OR "triclosan" OR "Cetylpyridinium" OR "Cetylpyridinium chloride" OR "CPC" OR "povidone iodine") AND ("Chronic Periodontitis" OR "Chronic Periodontitides" OR "Adult Periodontitis" OR "Adult Periodontitides" OR "Periodontal treatment" OR "Periodontal therapy" OR "nonsurgical periodontal therapy" OR "non-surgical periodontal therapy" OR "Periodontitis" OR "Periodontitides" OR "Periodontal Diseases" OR "Periodontal Disease" OR "Parodontosis" OR "Parodontoses" OR "Pyorrhea Alveolaris" OR "scaling and root planing" OR "Periodontal Pocket" OR "periodontal pockets" OR "pocket depth" OR "pocket probing" OR "probing depth" OR "periodontal health" OR "Alveolar Bone Loss" OR "Alveolar Bone Losses" OR "Alveolar Resorption"</p> | 215 |

|                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
|                       | <p>OR "Periodontal Bone Losses" OR "Periodontal Bone Loss" OR "Periodontal Resorption" OR "phase 1 periodontal therapy" OR "initial periodontal therapy" OR "Periodontal Index" OR "Periodontal Indices" OR "Periodontal Indexes" OR "bleeding on probing" OR "bleeding index" OR "periodontal inflammation" OR "Gingival Bleeding on Probing" OR "gingival bleeding" OR "Gingival Index" OR "Gingival Indices" OR "Gingival Indexes" OR "Dental Plaque Index" OR "Dental Plaque Indexes" OR "Dental Plaque Indices" OR "Dental Plaque" OR "dental biofilm" OR "dental biofilms" OR "Periodontal probing depth" OR "Clinical attachment loss" OR "Periodontal Debridement" OR "Periodontal Debridements" OR "Periodontal Pocket Debridement" OR "periodontal therapy" OR "Dental Scaling" OR "Root Scaling" OR "Subgingival Scaling" OR "periodontal treatment" OR "periodontal therapy" OR "nonsurgical periodontal treatment" OR "non-surgical periodontal treatment" OR "non-surgical mechanical therapy" OR "Root Planing" OR "Root Planings" OR "periodontal attachment loss" OR "clinical attachment level" OR "attachment gain" OR "periodontal healing" OR "periodontal diseased sites" OR "periodontal parameters" OR "periodontal clinical parameters" OR "pocket closure" OR "pocket depth reduction" OR "residual pockets" OR "periodontal recession" OR "Gingival Recession" OR "Gingival Recessions" OR "periodontal re-instrumentation" OR "pocket re-instrumentation" OR "periodontal residual sites"))</p> |    |
| <b>Web of Science</b> | <p>("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Diabetes" OR "Metabolic Diseases" OR "Hyperglycemia" OR "Glucose Metabolism Disorders" OR "Metabolic Control" OR "Glycated Hemoglobin A" OR "Glycated Hemoglobin" OR "HbA1" OR "Glycosylated Hemoglobin A" OR "Blood Glucose" OR "Glycemic Index" OR "Fasting blood glucose" OR "Post-prandial blood glucose" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "type II diabetes mellitus" OR "type 2 diabetes" OR "type II diabetes" OR "advanced glycation end products" OR "HbA1c" OR "human hemoglobin A1c protein" OR "glycohemoglobin A" OR "glycosylated analysis hemoglobin A" OR "glycated hemoglobins" OR "glycated hemoglobin" OR "blood glucose metabolism" OR "blood glucose analysis") AND ("local" OR "subgingival" OR "subgingivally"</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 78 |

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|  | <p> delivered" OR "subgingival delivery" OR<br/> "subgingival application" OR "locally delivered" OR<br/> "local use" OR "gel" OR "topical" OR "delivery<br/> vehicle" OR "nanospheres") AND ("antibiotic" OR<br/> "antibiotics" OR "antimicrobial" OR "antimicrobials"<br/> OR "anti-bacterial" OR "agents" OR "anti-bacterial<br/> agents" OR "antibacterial agents" OR "disinfection"<br/> OR "amoxicillin" OR "amox" OR "amoxicilline" OR<br/> "penicillin" OR "Azithromycin" OR "clarithromycin"<br/> OR "doxycycline" OR "doxycyclin" OR<br/> "Tetracycline" OR "minocycline" OR "clindamycin"<br/> OR "Fluoroquinolones" OR "metronidazole" OR<br/> "Chlorhexidine" OR "triclosan" OR "Cetylpyridinium"<br/> OR "Cetylpyridinium chloride" OR "CPC" OR<br/> "povidone iodine") AND ("Chronic Periodontitis" OR<br/> "Chronic Periodontitides" OR "Adult Periodontitis"<br/> OR "Adult Periodontitides" OR "Periodontal<br/> treatment" OR "Periodontal therapy" OR<br/> "nonsurgical periodontal therapy" OR "non-surgical<br/> periodontal therapy" OR "Periodontitis" OR<br/> "Periodontitides" OR "Periodontal Diseases" OR<br/> "Periodontal Disease" OR "Parodontosis" OR<br/> "Parodontoses" OR "Pyorrhea Alveolaris" OR<br/> "scaling and root planing" OR "Periodontal Pocket"<br/> OR "periodontal pockets" OR "pocket depth" OR<br/> "pocket probing" OR "probing depth" OR<br/> "periodontal health" OR "Alveolar Bone Loss" OR<br/> "Alveolar Bone Losses" OR "Alveolar Resorption"<br/> OR "Periodontal Bone Losses" OR "Periodontal<br/> Bone Loss" OR "Periodontal Resorption" OR<br/> "phase 1 periodontal therapy" OR "initial<br/> periodontal therapy" OR "Periodontal Index" OR<br/> "Periodontal Indices" OR "Periodontal Indexes" OR<br/> "bleeding on probing" OR "bleeding index" OR<br/> "periodontal inflammation" OR "Gingival Bleeding<br/> on Probing" OR "gingival bleeding" OR "Gingival<br/> Index" OR "Gingival Indices" OR "Gingival Indexes"<br/> OR "Dental Plaque Index" OR "Dental Plaque<br/> Indexes" OR "Dental Plaque Indices" OR "Dental<br/> Plaque" OR "dental biofilm" OR "dental biofilms"<br/> OR "Periodontal probing depth" OR "Clinical<br/> attachment loss" OR "Periodontal Debridement"<br/> OR "Periodontal Debridements" OR "Periodontal<br/> Pocket Debridement" OR "periodontal therapy" OR<br/> "Dental Scaling" OR "Root Scaling" OR<br/> "Subgingival Scaling" OR "periodontal treatment"<br/> OR "periodontal therapy" OR "nonsurgical<br/> periodontal treatment" OR "non-surgical periodontal<br/> treatment" OR "non-surgical mechanical therapy"<br/> OR "Root Planing" OR "Root Planings" OR </p> |  |
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|                                                | "periodontal attachment loss" OR "clinical attachment level" OR "attachment gain" OR "periodontal healing" OR "periodontal diseased sites" OR "periodontal parameters" OR "periodontal clinical parameters" OR "pocket closure" OR "pocket depth reduction" OR "residual pockets" OR "periodontal recession" OR "Gingival Recession" OR "Gingival Recessions" OR "periodontal re-instrumentation" OR "pocket re-instrumentation" OR "periodontal residual sites")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |
| <b>LILACS<br/>(Portuguese<br/>and Spanish)</b> | ("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Diabetes" OR "Metabolic Diseases" OR "Hyperglycemia" OR "Glucose Metabolism Disorders" OR "Metabolic Control" OR "Glycated Hemoglobin A" OR "Glycated Hemoglobin" OR "HbA1" OR "Glycosylated Hemoglobin A" OR "Blood Glucose" OR "Glycemic Index" OR "Fasting blood glucose" OR "Post-prandial blood glucose" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "type II diabetes mellitus" OR "type 2 diabetes" OR "type II diabetes" OR "advanced glycation end products" OR "HbA1c" OR "human hemoglobin A1c protein" OR "glycohemoglobin A" OR "glycosylated analysis hemoglobin A" OR "glycated hemoglobins" OR "glycated hemoglobin" OR "blood glucose metabolism" OR "blood glucose analysis" OR "Diabetes Mellitus" OR "Diabetes mellitus tipo 2" OR "doenças metabólicas" OR "enfermedades metabólicas" OR "Hiperglicemia" OR "hiperglucemia" OR "Transtornos do metabolismo de glucose" OR "Transtornos del metabolismo de la glucosa" OR "Hemoglobina A Glicada" OR "Hemoglobina A Glucada" OR "glicemia" OR "glucemia" OR "índice glicêmico" OR "índice glucêmico" OR "produtos finais de glicação avançada" OR "productos finales de glicación avanzada") AND ("local" OR "subgingival" OR "subgingivally delivered" OR "subgingival delivery" OR "subgingival application" OR "locally delivered" OR "local use" OR "gel" OR "topical" OR "delivery vehicle" OR "nanospheres" OR "subgingival" OR "subgingival" OR "Nanosferas") AND ("antibiotic" OR "antibiotics" OR "antimicrobial" OR "antimicrobials" OR "anti-bacterial" OR "agents" OR "anti-bacterial agents" OR "antibacterial agents" OR "disinfection" OR "amoxicillin" OR "amox" OR "amoxicilline" OR "penicillin" OR "Azithromycin" OR "clarithromycin" OR "doxycycline" OR "doxycyclin" OR "Tetracycline" OR "minocycline" OR | 19 |

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|  | <p> "clindamycin" OR "Fluoroquinolones" OR<br/> "metronidazole" OR "Chlorhexidine" OR "triclosan"<br/> OR "Cetylpyridinium" OR "Cetylpyridinium chloride"<br/> OR "CPC" OR "povidone iodine" OR<br/> "antibacterianos" OR "Anti-Infeciosos" OR<br/> "Antimicrobianos" OR "Antiinfeciosos" OR<br/> "desinfecção" OR "desinfección" OR "Amoxicilina"<br/> OR "Penicilina" OR "Azitromicina" OR<br/> "Claritromicina" OR "Doxiciclina" OR "Tetraciclina"<br/> OR "Minociclina" OR "Clindamicina" OR<br/> "Fluoroquinolonas" OR "Metronidazol" OR<br/> "clorexidina" OR "clorhexidina" OR "triclosano" OR<br/> "triclosán" OR "cetilpiridínio" OR "cloreto de<br/> cetilpiridínio" OR "Cloruro de Cetilpiridino" OR<br/> "Povidona-Iodo" OR "Povidona Yodada") AND<br/> ("Chronic Periodontitis" OR "Chronic<br/> Periodontitides" OR "Adult Periodontitis" OR "Adult<br/> Periodontitides" OR "Periodontal treatment" OR<br/> "Periodontal therapy" OR "nonsurgical periodontal<br/> therapy" OR "non-surgical periodontal therapy" OR<br/> "Periodontitis" OR "Periodontitides" OR<br/> "Periodontal Diseases" OR "Periodontal Disease"<br/> OR "Parodontosis" OR "Parodontoses" OR<br/> "Pyorrhea Alveolaris" OR "scaling and root planing"<br/> OR "Periodontal Pocket" OR "periodontal pockets"<br/> OR "pocket depth" OR "pocket probing" OR<br/> "probing depth" OR "periodontal health" OR<br/> "Alveolar Bone Loss" OR "Alveolar Bone Losses"<br/> OR "Alveolar Resorption" OR "Periodontal Bone<br/> Losses" OR "Periodontal Bone Loss" OR<br/> "Periodontal Resorption" OR "phase 1 periodontal<br/> therapy" OR "initial periodontal therapy" OR<br/> "Periodontal Index" OR "Periodontal Indices" OR<br/> "Periodontal Indexes" OR "bleeding on probing" OR<br/> "bleeding index" OR "periodontal inflammation" OR<br/> "Gingival Bleeding on Probing" OR "gingival<br/> bleeding" OR "Gingival Index" OR "Gingival<br/> Indices" OR "Gingival Indexes" OR "Dental Plaque<br/> Index" OR "Dental Plaque Indexes" OR "Dental<br/> Plaque Indices" OR "Dental Plaque" OR "dental<br/> biofilm" OR "dental biofilms" OR "Periodontal<br/> probing depth" OR "Clinical attachment loss" OR<br/> "Periodontal Debridement" OR "Periodontal<br/> Debridements" OR "Periodontal Pocket<br/> Debridement" OR "periodontal therapy" OR "Dental<br/> Scaling" OR "Root Scaling" OR "Subgingival<br/> Scaling" OR "periodontal treatment" OR<br/> "periodontal therapy" OR "nonsurgical periodontal<br/> treatment" OR "non-surgical periodontal treatment"<br/> OR "non-surgical mechanical therapy" OR "Root </p> |  |
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|                 | <p>Planing" OR "Root Planings" OR "periodontal attachment loss" OR "clinical attachment level" OR "attachment gain" OR "periodontal healing" OR "periodontal diseased sites" OR "periodontal parameters" OR "periodontal clinical parameters" OR "pocket closure" OR "pocket depth reduction" OR "residual pockets" OR "periodontal recession" OR "Gingival Recession" OR "Gingival Recessions" OR "periodontal re-instrumentation" OR "pocket re-instrumentation" OR "periodontal residual sites" OR "Periodontite crônica" OR "periodontitis crônica" OR "desbridamento periodontal" OR "Desbridamiento Periodontal" OR "aplainamento radicular" OR "aplanamiento de la raíz" OR "raspagem dentária" OR "raspado dental" OR "curetagem subgingival" OR "curetaje subgingival" OR "Periodontite" OR "Periodontitis" OR "doenças periodontais" OR "enfermedades periodontales" OR "bolsa periodontal" OR "índice periodontal" OR "Índice de Placa Dentária" OR "Índice de Placa Dental" OR "Placa Dentária" OR "Placa Dental" OR "perda da inserção periodontal" OR "pérdida de la inserción periodontal" OR "Retração Gingival" OR "Recesión Gingival")</p>                                                                        |    |
| <b>ProQuest</b> | <p>noft(("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Diabetes" OR "Metabolic Diseases" OR "Hyperglycemia" OR "Glucose Metabolism Disorders" OR "Metabolic Control" OR "Glycated Hemoglobin A" OR "Glycated Hemoglobin" OR "HbA1" OR "Glycosylated Hemoglobin A" OR "Blood Glucose" OR "Glycemic Index" OR "Fasting blood glucose" OR "Post-prandial blood glucose" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "type II diabetes mellitus" OR "type 2 diabetes" OR "type II diabetes" OR "advanced glycation end products" OR "HbA1c" OR "human hemoglobin A1c protein" OR "glycohemoglobin A" OR "glycosylated analysis hemoglobin A" OR "glycated hemoglobins" OR "glycated hemoglobin" OR "blood glucose metabolism" OR "blood glucose analysis") AND ("local" OR "subgingival" OR "subgingivally delivered" OR "subgingival delivery" OR "subgingival application" OR "locally delivered" OR "local use" OR "gel" OR "topical" OR "delivery vehicle" OR "nanospheres") AND ("antibiotic" OR "antibiotics" OR "antimicrobial" OR "antimicrobials" OR "anti-bacterial" OR "agents" OR "anti-bacterial agents" OR "antibacterial agents" OR "disinfection" OR "amoxicillin" OR "amox" OR "amoxicilline" OR</p> | 12 |

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|  | <p> "penicillin" OR "Azithromycin" OR "clarithromycin"<br/> OR "doxycycline" OR "doxycyclin" OR<br/> "Tetracycline" OR "minocycline" OR "clindamycin"<br/> OR "Fluoroquinolones" OR "metronidazole" OR<br/> "Chlorhexidine" OR "triclosan" OR "Cetylpyridinium"<br/> OR "Cetylpyridinium chloride" OR "CPC" OR<br/> "povidone iodine") AND ("Chronic Periodontitis" OR<br/> "Chronic Periodontitides" OR "Adult Periodontitis"<br/> OR "Adult Periodontitides" OR "Periodontal<br/> treatment" OR "Periodontal therapy" OR<br/> "nonsurgical periodontal therapy" OR "non-surgical<br/> periodontal therapy" OR "Periodontitis" OR<br/> "Periodontitides" OR "Periodontal Diseases" OR<br/> "Periodontal Disease" OR "Parodontosis" OR<br/> "Parodontoses" OR "Pyorrhea Alveolaris" OR<br/> "scaling and root planing" OR "Periodontal Pocket"<br/> OR "periodontal pockets" OR "pocket depth" OR<br/> "pocket probing" OR "probing depth" OR<br/> "periodontal health" OR "Alveolar Bone Loss" OR<br/> "Alveolar Bone Losses" OR "Alveolar Resorption"<br/> OR "Periodontal Bone Losses" OR "Periodontal<br/> Bone Loss" OR "Periodontal Resorption" OR<br/> "phase 1 periodontal therapy" OR "initial<br/> periodontal therapy" OR "Periodontal Index" OR<br/> "Periodontal Indices" OR "Periodontal Indexes" OR<br/> "bleeding on probing" OR "bleeding index" OR<br/> "periodontal inflammation" OR "Gingival Bleeding<br/> on Probing" OR "gingival bleeding" OR "Gingival<br/> Index" OR "Gingival Indices" OR "Gingival Indexes"<br/> OR "Dental Plaque Index" OR "Dental Plaque<br/> Indexes" OR "Dental Plaque Indices" OR "Dental<br/> Plaque" OR "dental biofilm" OR "dental biofilms"<br/> OR "Periodontal probing depth" OR "Clinical<br/> attachment loss" OR "Periodontal Debridement"<br/> OR "Periodontal Debridements" OR "Periodontal<br/> Pocket Debridement" OR "periodontal therapy" OR<br/> "Dental Scaling" OR "Root Scaling" OR<br/> "Subgingival Scaling" OR "periodontal treatment"<br/> OR "periodontal therapy" OR "nonsurgical<br/> periodontal treatment" OR "non-surgical periodontal<br/> treatment" OR "non-surgical mechanical therapy"<br/> OR "Root Planing" OR "Root Planings" OR<br/> "periodontal attachment loss" OR "clinical<br/> attachment level" OR "attachment gain" OR<br/> "periodontal healing" OR "periodontal diseased<br/> sites" OR "periodontal parameters" OR "periodontal<br/> clinical parameters" OR "pocket closure" OR<br/> "pocket depth reduction" OR "residual pockets" OR<br/> "periodontal recession" OR "Gingival Recession"<br/> OR "Gingival Recessions" OR "periodontal re- </p> |  |
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|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|
|                  | instrumentation" OR "pocket re-instrumentation" OR "periodontal residual sites"))                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |   |
| <b>Open Grey</b> | ("Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Diabetes" OR "Metabolic Diseases" OR "Hyperglycemia" OR "Glucose Metabolism Disorders" OR "Metabolic Control" OR "Glycated Hemoglobin A" OR "Glycated Hemoglobin" OR "HbA1" OR "Glycosylated Hemoglobin A" OR "Blood Glucose" OR "Glycemic Index" OR "Fasting blood glucose" OR "Post-prandial blood glucose" OR "diabetes mellitus type 2" OR "diabetes type 2" OR "type II diabetes mellitus" OR "type 2 diabetes" OR "type II diabetes" OR "advanced glycation end products" OR "HbA1c" OR "human hemoglobin A1c protein" OR "glycohemoglobin A" OR "glycosylated analysis hemoglobin A" OR "glycated hemoglobins" OR "glycated hemoglobin" OR "blood glucose metabolism" OR "blood glucose analysis") AND ("local" OR "subgingival" OR "subgingivally delivered" OR "subgingival delivery" OR "subgingival application" OR "locally delivered" OR "local use" OR "gel" OR "topical" OR "delivery vehicle" OR "nanospheres") AND ("antibiotic" OR "antibiotics" OR "antimicrobial" OR "antimicrobials" OR "anti-bacterial" OR "agents" OR "anti-bacterial agents" OR "antibacterial agents" OR "disinfection" OR "amoxicillin" OR "amox" OR "amoxicilline" OR "penicillin" OR "Azithromycin" OR "clarithromycin" OR "doxycycline" OR "doxycyclin" OR "Tetracycline" OR "minocycline" OR "clindamycin" OR "Fluoroquinolones" OR "metronidazole" OR "Chlorhexidine" OR "triclosan" OR "Cetylpyridinium" OR "Cetylpyridinium chloride" OR "CPC" OR "povidone iodine") AND ("Chronic Periodontitis" OR "Chronic Periodontitides" OR "Adult Periodontitis" OR "Adult Periodontitides" OR "Periodontal treatment" OR "Periodontal therapy" OR "nonsurgical periodontal therapy" OR "non-surgical periodontal therapy" OR "Periodontitis" OR "Periodontitides" OR "Periodontal Diseases" OR "Periodontal Disease" OR "Parodontosis" OR "Parodontoses" OR "Pyorrhea Alveolaris" OR "scaling and root planing" OR "Periodontal Pocket" OR "periodontal pockets" OR "pocket depth" OR "pocket probing" OR "probing depth" OR "periodontal health" OR "Alveolar Bone Loss" OR "Alveolar Bone Losses" OR "Alveolar Resorption" OR "Periodontal Bone Losses" OR "Periodontal Bone Loss" OR "Periodontal Resorption" OR | 0 |

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|                                | "phase 1 periodontal therapy" OR "initial periodontal therapy" OR "Periodontal Index" OR "Periodontal Indices" OR "Periodontal Indexes" OR "bleeding on probing" OR "bleeding index" OR "periodontal inflammation" OR "Gingival Bleeding on Probing" OR "gingival bleeding" OR "Gingival Index" OR "Gingival Indices" OR "Gingival Indexes" OR "Dental Plaque Index" OR "Dental Plaque Indexes" OR "Dental Plaque Indices" OR "Dental Plaque" OR "dental biofilm" OR "dental biofilms" OR "Periodontal probing depth" OR "Clinical attachment loss" OR "Periodontal Debridement" OR "Periodontal Debridements" OR "Periodontal Pocket Debridement" OR "periodontal therapy" OR "Dental Scaling" OR "Root Scaling" OR "Subgingival Scaling" OR "periodontal treatment" OR "periodontal therapy" OR "nonsurgical periodontal treatment" OR "non-surgical periodontal treatment" OR "non-surgical mechanical therapy" OR "Root Planing" OR "Root Planings" OR "periodontal attachment loss" OR "clinical attachment level" OR "attachment gain" OR "periodontal healing" OR "periodontal diseased sites" OR "periodontal parameters" OR "periodontal clinical parameters" OR "pocket closure" OR "pocket depth reduction" OR "residual pockets" OR "periodontal recession" OR "Gingival Recession" OR "Gingival Recessions" OR "periodontal re-instrumentation" OR "pocket re-instrumentation" OR "periodontal residual sites") |     |
| <b>Google Scholar</b>          | ("Type 2 Diabetes mellitus" OR "diabetes mellitus") AND ("periodontitis" OR "chronic periodontitis") AND ("non-surgical periodontal therapy" OR "scaling and root planing") AND ("antimicrobials") AND ("local" OR "subgingival") AND ("HbA1c")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 210 |
| <b>Clinical Trial registry</b> | Condition or disease: Periodontitis<br>Other terms: Antimicrobials AND diabetes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 20  |
| <b>ICTRP WHO</b>               | periodontitis AND diabetes AND antimicrobials                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0   |

## SUPPLEMENTARY FILE 2 - EXCLUDED ARTICLES AND REASONS FOR EXCLUSION (N=17)

| Author, year                   | Reason for exclusion |
|--------------------------------|----------------------|
| Engebretson & Hey-Hadavi. 2011 | 8                    |
| Grossi et al. 1997             | 8                    |
| Haerian-Ardakani et al. 2014a  | 5                    |
| Haerian-Ardakani et al. 2014b  | 11                   |
| Hincapié et al. 2014           | 8                    |
| Miranda et al. 2014            | 8                    |
| Peña Sisto et al. 2018         | 8                    |
| Qureshi et al. 2021            | 8                    |
| Torkzaban & Rabienejad. 2018   | 8                    |
| CTRI/2019/02/017389            | 4                    |
| CTRI/2019/07/020326            | 4                    |
| CTRI/2021/05/033474            | 4                    |
| IRCT2013092614774N1            | 4                    |
| IRCT2015010517587N8            | 4                    |
| IRCT2015010517587N9            | 4                    |
| NCT02062047                    | 4                    |
| NCT02735837                    | 4                    |

1- Reviews, letters, personal opinions, books or book chapters, panel and conference abstracts (n=0), 2- Wrong design studies. (n=0), 3- Wrong sample studies. (n=0), 4- Study Protocols (n=8), 5- Studies written in non-Latin alphabets (n=1), 6- Wrong outcome (n=0), 7- Wrong population (n=0), 8- Wrong drug (systemic use or wrong vehicle) (n=7), 9-Confused effects (n=0), 10- No full text available (n=0), 11- duplicate study (n=1)

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2. Grossi SG, Skrepchinsk FB, DeCaro T, et al. Treatment of Periodontal Disease in Diabetics Reduces Glycated Hemoglobin. *J Periodontol* 1997;68(8):713-19.
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- non surgical periodontal therapy on Hba1c and lipid profile in type 2 diabetic patients: a clinico-biochemical study. *J Shahid Sadoughi Univ Med Sci* 2014; 22(4):1387-95.
4. Haerian-Ardakani A, Asadi Y, Afkhami M, et al. Effect of topical tetracycline gel with non surgical periodontal therapy on Hba1c and lipid profile in type 2 diabetic patients. *J Shahid Sadoughi Univ Med Sci* 2014; 22(4):1387-95.
  5. Hincapié JP, Castrillón CA, Yepes FL, et al. Microbiological effects of periodontal therapy plus azithromycin in patients with diabetes: results from a randomized clinical trial. *Acta Odontol Latinoam.* 2014;27(2):89-95. doi: 10.1590/S1852-48342014000200008.
  6. Miranda TS, Feres M, Perez-Chaparro PJ, et al. Metronidazole and amoxicillin as adjuncts to scaling and root planing for the treatment of type 2 diabetic subjects with periodontitis: 1-year outcomes of a randomized placebo-controlled clinical trial. *J Clin Periodontol.* 2014 Sep;41(9):890-9. doi: 10.1111/jcpe.12282.
  7. Peña Sisto M, Silva MC, Avalo WS, et al. Efectividad del tratamiento periodontal en el control metabólico de pacientes con diabetes mellitus. *MEDISAN.* 2018;22(3):240-247.
  8. Qureshi A., Bokhari SAH, Haque Z, et al. Clinical efficacy of scaling and root planing with and without metronidazole on glycemic control: three-arm randomized controlled trial. *BMC Oral Health.* 2021;21(1):253. doi: 10.1186/s12903-021-01620-1.
  9. Torkzaban P & Rabienejad N. Effect of non-surgical periodontal therapy with and without 0.2% chlorhexidine rinse on metabolic control of type 2 diabetic patients. *Avicenna J Dent Res.* 2018;10(3):83-88. doi: 10.34172/ajdr.2018.18.
  10. CTRI/2019/02/017389, To evaluate the effectiveness of chlorhexidine chip as an adjunct to scaling and root planing in patient with type 2 diabetes mellitus. <https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2019/02/017389> - Volume 0, Issue 0, pp. – published 2019-02-01.
  11. CTRI/2019/07/020326, Comparison of glycated hemoglobin levels after cleaning of teeth with and without application of chlorhexidine metronidazole gel on gums in chronic periodontitis patient with type 2 diabetes mellitus. <https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2019/07/020326> - Volume 0, Issue 0, pp. – published 2019-07-23.
  12. CTRI/2021/05/033474, Benefits of two locally delivered agents on cytokine level in diabetic patients with chronic periodontitis. <https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2021/05/033474> - Volume 0,

Issue 0, pp. – published 2021-05-07.

13. IRCT2013092614774N1, Effects of SRP on blood glucose level reduction in diabetic patients.

<https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT2013092614774N1> - Volume 0, Issue 0, pp. - published 2014-02-06.

14. IRCT2015010517587N8, A randomized, placebo controlled trial The effect of non-surgical periodontal therapy with adjunctive topical doxycycline gel on HbA1c in patients with type 2 diabetes mellitus (DM).

<https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT2015010517587N8> – Volume 0, Issue 0, pp. – published 2015-02-10.

15. IRCT2015010517587N9, A randomized double-blind placebo-controlled, clinical trial the effect of non-surgical periodontal therapy plus subgingivally azithromycin gel on HbA1c in patients with type 2 diabetes mellitus (DM).

<https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT2015010517587N9> - Volume 0, Issue 0, pp. - published 2015-02-18.

16. NCT02062047, Full-mouth and Partial-mouth Scaling and Root Planing in Type 2 Diabetic Subjects. <https://clinicaltrials.gov/show/NCT02062047> - Volume 0, Issue 0, pp. – published 2014-02-13.

17. NCT02735837, The Effect of Topical Doxycycline Gel on HbA1c in Patients With Type 2 Diabetes Mellitus (DM)®. <https://clinicaltrials.gov/show/NCT02735837> - Volume 0, Issue 0, pp. – published 2016-04-13.

### SUPPLEMENTARY FILE 3 - LEAGUE TABLE FOR EACH COMPARISON (MEAN DIFFERENCES)

League table showing the effect estimates (in Mean Difference) and 95%CI for each comparison. The lower triangle shows the results of mixed comparisons; the upper triangle shows direct comparisons. Negative results favor treatments showed in the columns, positive results favor treatment in the rows. Bold results indicate that the treatment in the column was more effective compared to the intervention in the line. The colors show the certainty of evidence for each comparison, according to the legend on the lower left (green: high certainty; yellow: moderate certainty; orange: low certainty; light red: very low certainty).

#### Comparisons for HbA1c at 3 months

|                     |                      |                      |                     |                     |                      |
|---------------------|----------------------|----------------------|---------------------|---------------------|----------------------|
| Doxy                | .                    | .                    | .                   | .                   | -0.80 [-1.70; 0.10]  |
| -0.12 [-1.24; 1.00] | CHX_Gel              | .                    | .                   | .                   | -0.68 [-1.34; -0.02] |
| -0.18 [-1.11; 0.75] | -0.06 [-0.75; 0.64]  | Tetra_Fyber          | .                   | .                   | -0.62 [-0.85; -0.39] |
| -0.61 [-1.74; 0.52] | -0.49 [-1.43; 0.46]  | -0.43 [-1.14; 0.28]  | Tetra_Oint          | .                   | -0.19 [-0.87; 0.49]  |
| -0.69 [-1.98; 0.59] | -0.57 [-1.70; 0.55]  | -0.51 [-1.45; 0.43]  | -0.08 [-1.22; 1.05] | Mino                | -0.11 [-1.02; 0.80]  |
| -0.80 [-1.70; 0.10] | -0.68 [-1.34; -0.02] | -0.62 [-0.85; -0.39] | -0.19 [-0.87; 0.49] | -0.11 [-1.02; 0.80] | Control (NSPT)       |

#### Comparisons for HbA1c at 6 months

|                     |                     |                    |                     |
|---------------------|---------------------|--------------------|---------------------|
| CHX_Gel             | .                   | .                  | -0.53 [-1.57; 0.51] |
| -0.47 [-2.86; 1.92] | Mino                | .                  | -0.06 [-2.21; 2.09] |
| -0.53 [-2.31; 1.24] | -0.06 [-2.65; 2.53] | Doxy               | -0.00 [-1.44; 1.44] |
| -0.53 [-1.57; 0.51] | -0.06 [-2.21; 2.09] | 0.00 [-1.44; 1.44] | Control (NSPT)      |

### Comparisons for PPD at 3 months

|                         |                         |                         |                        |                        |                        |                         |                        |
|-------------------------|-------------------------|-------------------------|------------------------|------------------------|------------------------|-------------------------|------------------------|
| STZ                     | .                       | .                       | .                      | .                      | .                      | -1.30 [-2.22;<br>-0.38] | .                      |
| -0.29 [-1.34;<br>0.76]  | CLM                     | .                       | .                      | .                      | .                      | -1.01 [-1.50;<br>-0.52] | .                      |
| -0.38 [-1.56;<br>0.80]  | -0.09 [-0.97;<br>0.79]  | Tetra_Fiber             | .                      | .                      | .                      | -0.92 [-1.66;<br>-0.18] | .                      |
| -1.04 [-2.15;<br>0.07]  | -0.75 [-1.53;<br>0.03]  | -0.66 [-1.61;<br>0.29]  | AZT                    | .                      | .                      | -0.26 [-0.87;<br>0.35]  | .                      |
| -1.30 [-2.37;<br>-0.23] | -1.01 [-1.74;<br>-0.28] | -0.92 [-1.83;<br>-0.01] | -0.26 [-1.07;<br>0.55] | Doxy                   | .                      | -0.00 [-0.54;<br>0.54]  | .                      |
| -1.30 [-2.30;<br>-0.30] | -1.01 [-1.63;<br>-0.39] | -0.92 [-1.75;<br>-0.09] | -0.26 [-0.98;<br>0.46] | -0.00 [-0.67;<br>0.66] | CHX_Gel                | 0.00 [-0.38;<br>0.38]   | .                      |
| -1.30 [-2.22;<br>-0.38] | -1.01 [-1.50;<br>-0.52] | -0.92 [-1.66;<br>-0.18] | -0.26 [-0.87;<br>0.35] | 0.00 [-0.54;<br>0.54]  | 0.00 [-0.38;<br>0.38]  | Control<br>(NSPT)       | -0.05 [-0.91;<br>0.81] |
| -1.35 [-2.61;<br>-0.09] | -1.06 [-2.05;<br>-0.07] | -0.97 [-2.10;<br>0.16]  | -0.31 [-1.36;<br>0.74] | -0.05 [-1.06;<br>0.96] | -0.05 [-0.99;<br>0.89] | -0.05 [-0.91;<br>0.81]  | Mino                   |

### Comparisons for PPD at 6 months

|                      |                      |                     |                     |                      |                     |                     |
|----------------------|----------------------|---------------------|---------------------|----------------------|---------------------|---------------------|
| STZ                  | .                    | .                   | .                   | -2.64 [-3.56; -1.72] | .                   | .                   |
| -1.66 [-2.72; -0.60] | CLM                  | .                   | .                   | -0.98 [-1.51; -0.45] | .                   | .                   |
| -2.41 [-3.47; -1.35] | -0.75 [-1.51; 0.01]  | AZT                 | .                   | -0.23 [-0.77; 0.31]  | .                   | .                   |
| -2.64 [-3.91; -1.37] | -0.98 [-2.00; 0.04]  | -0.23 [-1.26; 0.80] | Mino                | -0.00 [-0.87; 0.87]  | .                   | .                   |
| -2.64 [-3.56; -1.72] | -0.98 [-1.51; -0.45] | -0.23 [-0.77; 0.31] | 0.00 [-0.87; 0.87]  | Control (NSPT)       | -0.10 [-0.67; 0.47] | -0.09 [-0.48; 0.30] |
| -2.74 [-3.82; -1.66] | -1.08 [-1.86; -0.30] | -0.33 [-1.12; 0.46] | -0.10 [-1.14; 0.94] | -0.10 [-0.67; 0.47]  | Doxy                | .                   |
| -2.73 [-3.72; -1.73] | -1.07 [-1.73; -0.41] | -0.32 [-0.98; 0.35] | -0.09 [-1.05; 0.87] | -0.09 [-0.48; 0.30]  | 0.01 [-0.68; 0.70]  | CHX_Gel             |

### Certainty of Evidence

|          |
|----------|
| High     |
| Moderate |
| Low      |
| Very Low |

## SUPPLEMENTARY FILE 4 - ASSESSMENT OF INCONSISTENCY FOR ALL STUDIES (MD)

### Results NMA HbA1c 3 months

| Comparison                 | N. Studies | NMA   | Direct | Indirect | Difference | Diff_95CI_lower | Diff_95CI_upper | p-Value |
|----------------------------|------------|-------|--------|----------|------------|-----------------|-----------------|---------|
| CHX_Gel:Control            | 2          | -0.68 | -0.68  | NA       | NA         | NA              | NA              | NA      |
| CHX_Gel:Doxy               | 0          | 0.12  | NA     | 0.12     | NA         | NA              | NA              | NA      |
| CHX_Gel:Mino               | 0          | -0.57 | NA     | -0.57    | NA         | NA              | NA              | NA      |
| CHX_Gel:Tetra_Fyber        | 0          | -0.06 | NA     | -0.06    | NA         | NA              | NA              | NA      |
| CHX_Gel:Tetra_Oint         | 0          | -0.49 | NA     | -0.49    | NA         | NA              | NA              | NA      |
| Doxy:Control               | 1          | -0.80 | -0.80  | NA       | NA         | NA              | NA              | NA      |
| Mino:Control               | 2          | -0.11 | -0.11  | NA       | NA         | NA              | NA              | NA      |
| Tetra_Fyber:Control        | 1          | -0.62 | -0.62  | NA       | NA         | NA              | NA              | NA      |
| Tetra_Oint:Control         | 1          | -0.19 | -0.19  | NA       | NA         | NA              | NA              | NA      |
| Doxy:Mino                  | 0          | -0.69 | NA     | -0.69    | NA         | NA              | NA              | NA      |
| Doxy:Tetra_Fyber           | 0          | -0.18 | NA     | -0.18    | NA         | NA              | NA              | NA      |
| Doxy:Tetra_Oint            | 0          | -0.61 | NA     | -0.61    | NA         | NA              | NA              | NA      |
| Mino:Tetra_Fyber           | 0          | 0.51  | NA     | 0.51     | NA         | NA              | NA              | NA      |
| Mino:Tetra_Oint            | 0          | 0.08  | NA     | 0.08     | NA         | NA              | NA              | NA      |
| Tetra_Fyber:<br>Tetra_Oint | 0          | -0.43 | NA     | -0.43    | NA         | NA              | NA              | NA      |

### Results NMA HbA1c 6 months

| Comparison      | N. Studies | NMA   | Direct | Indirect | Difference | Diff_95CI_lower | Diff_95CI_upper | p-Value |
|-----------------|------------|-------|--------|----------|------------|-----------------|-----------------|---------|
| CHX_Gel:Control | 2          | -0.53 | -0.53  | NA       | NA         | NA              | NA              | NA      |
| CHX_Gel:Doxy    | 0          | -0.53 | NA     | -0.53    | NA         | NA              | NA              | NA      |
| CHX_Gel:Mino    | 0          | -0.47 | NA     | -0.47    | NA         | NA              | NA              | NA      |
| Doxy:Control    | 1          | 0.00  | -0.00  | NA       | NA         | NA              | NA              | NA      |
| Mino:Control    | 1          | -0.06 | -0.06  | NA       | NA         | NA              | NA              | NA      |
| Doxy:Mino       | 0          | 0.06  | NA     | 0.06     | NA         | NA              | NA              | NA      |

### Results NMA PPD 3 months

| Comparison      | N. Studies | NMA   | Direct | Indirect | Difference | Diff_95CI_lower | Diff_95CI_upper | p-Value |
|-----------------|------------|-------|--------|----------|------------|-----------------|-----------------|---------|
| AZT:CHX_Gel     | 0          | -0.26 | NA     | -0.26    | NA         | NA              | NA              | NA      |
| AZT:CLM         | 0          | 0.75  | NA     | 0.75     | NA         | NA              | NA              | NA      |
| AZT:Control     | 1          | -0.26 | -0.26  | NA       | NA         | NA              | NA              | NA      |
| AZT:Doxy        | 0          | -0.26 | NA     | -0.26    | NA         | NA              | NA              | NA      |
| AZT:Mino        | 0          | -0.31 | NA     | -0.31    | NA         | NA              | NA              | NA      |
| AZT:STZ         | 0          | 1.04  | NA     | 1.04     | NA         | NA              | NA              | NA      |
| AZT:Tetra_Fiber | 0          | 0.66  | NA     | 0.66     | NA         | NA              | NA              | NA      |
| CHX_Gel:CLM     | 0          | 1.01  | NA     | 1.01     | NA         | NA              | NA              | NA      |
| CHX_Gel:Control | 2          | 0.00  | 0.00   | NA       | NA         | NA              | NA              | NA      |
| CHX_Gel:Doxy    | 0          | 0.00  | NA     | 0.00     | NA         | NA              | NA              | NA      |
| CHX_Gel:Mino    | 0          | -0.05 | NA     | -0.05    | NA         | NA              | NA              | NA      |

|                     |   |       |       |       |    |    |    |    |
|---------------------|---|-------|-------|-------|----|----|----|----|
| CHX_Gel:STZ         | 0 | 1.30  | NA    | 1.30  | NA | NA | NA | NA |
| CHX_Gel:Tetra_Fiber | 0 | 0.92  | NA    | 0.92  | NA | NA | NA | NA |
| CLM:Control         | 1 | -1.01 | -1.01 | NA    | NA | NA | NA | NA |
| CLM:Doxy            | 0 | -1.01 | NA    | -1.01 | NA | NA | NA | NA |
| CLM:Mino            | 0 | -1.06 | NA    | -1.06 | NA | NA | NA | NA |
| CLM:STZ             | 0 | 0.29  | NA    | 0.29  | NA | NA | NA | NA |
| CLM:Tetra_Fiber     | 0 | -0.09 | NA    | -0.09 | NA | NA | NA | NA |
| Doxy:Control        | 1 | 0.00  | -0.00 | NA    | NA | NA | NA | NA |
| Mino:Control        | 1 | 0.05  | 0.05  | NA    | NA | NA | NA | NA |
| STZ:Control         | 1 | -1.30 | -1.30 | NA    | NA | NA | NA | NA |
| Tetra_Fiber:Control | 1 | -0.92 | -0.92 | NA    | NA | NA | NA | NA |
| Doxy:Mino           | 0 | -0.05 | NA    | -0.05 | NA | NA | NA | NA |
| Doxy:STZ            | 0 | 1.30  | NA    | 1.30  | NA | NA | NA | NA |
| Doxy:Tetra_Fiber    | 0 | 0.92  | NA    | 0.92  | NA | NA | NA | NA |
| Mino:STZ            | 0 | 1.35  | NA    | 1.35  | NA | NA | NA | NA |
| Mino:Tetra_Fiber    | 0 | 0.97  | NA    | 0.97  | NA | NA | NA | NA |
| STZ:Tetra_Fiber     | 0 | -0.38 | NA    | -0.38 | NA | NA | NA | NA |

### Results NMA PPD 6 months

| Comparison  | N. Studies | NMA   | Direct | Indirect | Difference | Diff_95CI_lower | Diff_95CI_upper | p-Value |
|-------------|------------|-------|--------|----------|------------|-----------------|-----------------|---------|
| AZT:CHX_Gel | 0          | -0.32 | NA     | -0.32    | NA         | NA              | NA              | NA      |
| AZT:CLM     | 0          | 0.75  | NA     | 0.75     | NA         | NA              | NA              | NA      |
| AZT:Control | 1          | -0.23 | -0.23  | NA       | NA         | NA              | NA              | NA      |

|                 |   |       |       |       |    |    |    |    |
|-----------------|---|-------|-------|-------|----|----|----|----|
| AZT:Doxy        | 0 | -0.33 | NA    | -0.33 | NA | NA | NA | NA |
| AZT:Mino        | 0 | -0.23 | NA    | -0.23 | NA | NA | NA | NA |
| AZT:STZ         | 0 | 2.41  | NA    | 2.41  | NA | NA | NA | NA |
| CHX_Gel:CLM     | 0 | 1.07  | NA    | 1.07  | NA | NA | NA | NA |
| CHX_Gel:Control | 2 | 0.09  | 0.09  | NA    | NA | NA | NA | NA |
| CHX_Gel:Doxy    | 0 | -0.01 | NA    | -0.01 | NA | NA | NA | NA |
| CHX_Gel:Mino    | 0 | 0.09  | NA    | 0.09  | NA | NA | NA | NA |
| CHX_Gel:STZ     | 0 | 2.73  | NA    | 2.73  | NA | NA | NA | NA |
| CLM:Control     | 1 | -0.98 | -0.98 | NA    | NA | NA | NA | NA |
| CLM:Doxy        | 0 | -1.08 | NA    | -1.08 | NA | NA | NA | NA |
| CLM:Mino        | 0 | -0.98 | NA    | -0.98 | NA | NA | NA | NA |
| CLM:STZ         | 0 | 1.66  | NA    | 1.66  | NA | NA | NA | NA |
| Doxy:Control    | 1 | 0.10  | 0.10  | NA    | NA | NA | NA | NA |
| Mino:Control    | 1 | 0.00  | -0.00 | NA    | NA | NA | NA | NA |
| STZ:Control     | 1 | -2.64 | -2.64 | NA    | NA | NA | NA | NA |
| Doxy:Mino       | 0 | 0.10  | NA    | 0.10  | NA | NA | NA | NA |
| Doxy:STZ        | 0 | 2.74  | NA    | 2.74  | NA | NA | NA | NA |
| Mino:STZ        | 0 | 2.64  | NA    | 2.64  | NA | NA | NA | NA |

## SUPPLEMENTARY FILE 5 - GRADE EXPLANATIONS AND RESULTS

### GRADE Approach result for HbA1c at 3 months:

Criteria used to assess certainty of evidence was based on the Cochrane Training - <https://training.cochrane.org/resource/grade-approach-rate-certainty-evidence-network-meta-analysis-and-summary-findings-tables> and apropos literature (listed below).

| Criteria      | Rated down direct estimate if:                                                                                                                                                                                                                                                                                                                                                                                                                                               | Analysis                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk of bias  | When at least one study on the direct comparison presented high risk or some concerns due to problems in the randomization process and lack of blinding.                                                                                                                                                                                                                                                                                                                     | We rated down the certainty in one level due to some concerns and two levels due to high risk of bias in the randomization process.<br>On the other hand, since glycated hemoglobin is assessed through an automatic laboratory process, no problems with blinding were considered and we did not rate down the certainty.                                                                                                                             |
| Inconsistency | <ul style="list-style-type: none"> <li>• If effect estimates were similar across studies (Guyatt et al. 2011b);</li> <li>• Overlap of 95%CI (Guyatt et al. 2011b);</li> <li>• <math>I^2</math> for direct comparisons if was either moderate (30-60%), substantial (50-90%) or considerable (75%-100%) (Schunemann et al., 2021).</li> <li>• If only one study contributed to the direct effect estimate, the certainty was not rated down (Guyatt et al. 2011b).</li> </ul> | We did not rate down the certainty for single studies forming the effect estimate.<br>Two comparisons had 2 studies included (CHX_Gel vs NSPT – Faramarzi et al., 2017 and Santos et al., 2013; Mino vs NSPT – Lin et al., 2012 and Matsumoto et al., 2009), but for these we did not downgrade the level of certainty of evidence because the confidence intervals overlapped and there was no inconsistency in the direction of the effect estimate. |
| Indirectness  | Rate down if more than 30% of weight of pooled estimate came from studies which the populations had different characteristics (age, healthy condition) compared to the population of the PICO question (Brignardello-Petersen                                                                                                                                                                                                                                                | We assessed indirectness for each comparison. For almost all comparisons, patients had similar characteristics regarding age (late adulthood/elders), T2D and the presence of periodontitis. All patients                                                                                                                                                                                                                                              |

|                  |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                  | et al. 2018a).                                                                                                                                                                                                                                                             | met the periodontitis case-definition, according to the New Periodontal Diseases Classification (Tonetti et al., 2018). Thus, there was no problems regarding periodontitis condition.<br>The initial glycated hemoglobin (HbA1c) was similar in all populations at the beginning of the study (ranging from 7.1 to 10.4%). The included patients had moderate to unsatisfactory metabolic control. |
| Publication bias | If industry funding was associated with a positive outcome favoring the sponsored treatment (Martins et al. 2019).                                                                                                                                                         | Of the studies included in this network meta-analysis, only 1 received funded by the industry (DOXY vs NSPT – Lecio et al., 2019). However, although the results favored the treated group, there was no statistical difference for HbA1c in the study. Thus, the level was not downgraded due to publication bias.                                                                                 |
| <b>Criteria</b>  | <b>Rated down indirect estimate if:</b>                                                                                                                                                                                                                                    | <b>Analysis</b>                                                                                                                                                                                                                                                                                                                                                                                     |
| Intransitivity   | If there were differences in study characteristics that may modify treatment effect in the direct comparisons that form the basis for the indirect estimate; and if those differences were regarding population, intervention, comparison, or outcome (Puhan et al. 2014). | For intransitivity, we considered the most dominant first order loop, or, in its absence, the closest direct comparison contributing to the effect estimate. Whenever the comparisons contributing to indirect evidence showed important modifications on population or glycated hemoglobin, one point was downgraded due to intransitivity.                                                        |
| <b>Criteria</b>  | <b>Rated down NMA estimate if:</b>                                                                                                                                                                                                                                         | <b>Analysis</b>                                                                                                                                                                                                                                                                                                                                                                                     |
| Incoherence      | If node splitting test showed p-value <0.05, and direct, indirect and NMA evidence agreed with each other. (Brignardello-Petersen et al. 2018a).                                                                                                                           | Node split test was not feasible, due to the poorly connected network. In addition, it was not possible to compare the coherence between the direct and indirect estimates of the network meta-analysis.                                                                                                                                                                                            |

|             |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             |                                                                                                                                                                                                                         | Thus, the certainty of evidence was not downgraded due to incoherence.                                                                                                                                                                                                                                                                                                                                                                                |
| Imprecision | A partially contextualized approach was used, considering the large effect threshold according to Cohen's classification ( $>0.8$ SD) (Guyatt et al. 2011a; Schünemann et al. 2021; Brignardello-Petersen et al. 2021). | We downgraded in one level if the effect estimate crossed the minimum important difference (MID), considered as 0.5%; two levels if the confidence interval crossed both the MID and the null effect line. In the cases when the threshold was not crossed, the effect size was evaluated. OIS calculations were performed to large unplausible effects. Whenever OIS was not achieved, one level was downgraded (Brignardello-Petersen et al. 2021). |

**Table S1: Assessment of GRADE for direct and indirect comparisons evidence certainty for HbA1c (3 months comparisons)**

| Comparison                | Number of Studies | Risk of Bias   | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|---------------------------|-------------------|----------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| <b>DIRECT COMPARISONS</b> |                   |                |               |              |                  |                             |                                                    |                                                    |                     |                |                     |                     |                 |
| CHX_Gel vs NSPT           | 2                 | -1 (some conc) | 0             | 0            | 0                | Moderate                    | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Low             |
| Doxy vs NSPT              | 1                 | 0              | 0             | 0            | 0                | High                        | -                                                  | -                                                  | -                   | -              | -                   | -2                  | Low             |
| Mino vs                   | 2                 | -1             | 0             | 0            | 0                | Moderate                    | -                                                  | -                                                  | -                   | -              | -                   | -2                  | Very low        |

| Comparison                       | Number of Studies | Risk of Bias   | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|----------------------------------|-------------------|----------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| NSPT                             |                   | (some conc)    |               |              |                  |                             |                                                    |                                                    |                     |                |                     |                     |                 |
| Tetra_Fyber vs NSPT              | 1                 | -1 (some conc) | 0             | 0            | 0                | Moderate                    | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Low             |
| Tetra_Oint vs NSPT               | 1                 | -1 (some conc) | 0             | 0            | 0                | Moderate                    | -                                                  | -                                                  | -                   | -              | -                   | -2                  | Very low        |
| <b>INDIRECT ONLY COMPARISONS</b> |                   |                |               |              |                  |                             |                                                    |                                                    |                     |                |                     |                     |                 |
| CHX_Gel vs Doxy                  | -                 | -              | -             | -            | -                | -                           | NSPT vs CHX_Gel (moderate)                         | NSPT vs Doxy (high)                                | Moderate            | 0              | -                   | -2                  | Very low        |
| CHX_Gel vs Mino                  | -                 | -              | -             | -            | -                | -                           | NSPT vs CHX_Gel (moderate)                         | NSPT vs Mino (moderate)                            | Moderate            | 0              | -                   | -2                  | Very low        |
| CHX_Gel vs Tetra_Fyber           | -                 | -              | -             | -            | -                | -                           | NSPT vs CHX_Gel (moderate)                         | NSPT vs Tetra_Fyber (moderate)                     | Moderate            | 0              | -                   | -2                  | Very low        |
| CHX_Gel vs Tetra_Oint            | -                 | -              | -             | -            | -                | -                           | NSPT vs CHX_Gel (moderate)                         | NSPT vs Tetra_Oint (moderate)                      | Moderate            | 0              | -                   | -2                  | Very low        |

| Comparison                | Number of Studies | Risk of Bias | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|---------------------------|-------------------|--------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| Doxy vs Mino              | -                 | -            | -             | -            | -                | -                           | NSPT vs Doxy (high)                                | NSPT vs Mino (moderate)                            | Moderate            | 0              | -                   | -2                  | Very low        |
| Doxy vs Tetra_Fyber       | -                 | -            | -             | -            | -                | -                           | NSPT vs Doxy (high)                                | NSPT vs Tetra_Fyber (moderate)                     | Moderate            | 0              | -                   | -2                  | Very low        |
| Doxy vs Tetra_Oint        | -                 | -            | -             | -            | -                | -                           | NSPT vs Doxy (high)                                | NSPT vs Tetra_Oint (moderate)                      | Moderate            | 0              | -                   | -2                  | Very low        |
| Mino vs Tetra_Fyber       | -                 | -            | -             | -            | -                | -                           | NSPT vs Mino (moderate)                            | NSPT vs Tetra_Fyber (moderate)                     | Moderate            | 0              | -                   | -2                  | Very low        |
| Mino vs Tetra_Oint        | -                 | -            | -             | -            | -                | -                           | NSPT vs Mino (moderate)                            | NSPT vs Tetra_Oint (moderate)                      | Moderate            | 0              | -                   | -2                  | Very low        |
| Tetra_Fyber vs Tetra_Oint | -                 | -            | -             | -            | -                | -                           | NSPT vs Tetra_Fyber (moderate)                     | NSPT vs Tetra_Oint (moderate)                      | Moderate            | 0              | -                   | -2                  | Very low        |

### GRADE Approach result for HbA1c at 6 months:

Criteria used to assess certainty of evidence was based on the Cochrane Training - <https://training.cochrane.org/resource/grade-approach-rate-certainty-evidence-network-meta-analysis-and-summary-findings-tables> and apropos literature (listed below).

| Criteria      | Rated down direct estimate if:                                                                                                                                                                                                                                                                                                                                                                                                                                               | Analysis                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk of bias  | When at least one study on the direct comparison presented high risk or some concerns due to problems in the randomization process and lack of blinding.                                                                                                                                                                                                                                                                                                                     | We rated down the certainty in one level due to some concerns and two levels due to high risk of bias in the randomization process.<br>On the other hand, since glycate hemoglobin is assessed through an automatic laboratory process, no problems with blinding were considered and we did not rate down the certainty.                                                                        |
| Inconsistency | <ul style="list-style-type: none"> <li>• If effect estimates were similar across studies (Guyatt et al. 2011b);</li> <li>• Overlap of 95%CI (Guyatt et al. 2011b);</li> <li>• <math>I^2</math> for direct comparisons if was either moderate (30-60%), substantial (50-90%) or considerable (75%-100%) (Schunemann et al., 2021).</li> <li>• If only one study contributed to the direct effect estimate, the certainty was not rated down (Guyatt et al. 2011b).</li> </ul> | We did not rate down the certainty for single studies forming the effect estimate.<br>One comparison had 2 studies included (CHX_Gel vs NSPT – Faramarzi et al., 2017 and Santos et al., 2013) and we downgraded one level of certainty of evidence because the confidence intervals overlapped, but the effect estimates were opposite.                                                         |
| Indirectness  | Rate down if more than 30% of weight of pooled estimate came from studies which the populations had different characteristics (age, healthy condition) compared to the population of the PICO question (Brignardello-Petersen et al. 2018a).                                                                                                                                                                                                                                 | We assessed indirectness for each comparison. For almost all comparisons, patients had similar characteristics regarding age (late adulthood/elders), T2D and the presence of periodontitis. All patients met the periodontitis case-definition, according to the New Periodontal Diseases Classification (Tonetti et al., 2018). Thus, there was no problems regarding periodontitis condition. |

|                  |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                              |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                  |                                                                                                                                                                                                                                                                            | The initial glycated hemoglobin (HbA1c) was similar in all populations at the beginning of the study (ranging from 7.1 to 10.4%). The included patients had moderate to unsatisfactory metabolic control.                                                                                                                                    |
| Publication bias | If industry funding was associated with a positive outcome favoring the sponsored treatment (Martins et al. 2019).                                                                                                                                                         | Of the studies included in this network meta-analysis, only 1 received funded by the industry (DOXY vs NSPT – Lecio et al., 2019). However, although the results favored the treated group, there was no statistical difference for HbA1c in the study. Thus, the level was not downgraded due to publication bias.                          |
| <b>Criteria</b>  | <b>Rated down indirect estimate if:</b>                                                                                                                                                                                                                                    | <b>Analysis</b>                                                                                                                                                                                                                                                                                                                              |
| Intransitivity   | If there were differences in study characteristics that may modify treatment effect in the direct comparisons that form the basis for the indirect estimate; and if those differences were regarding population, intervention, comparison, or outcome (Puhan et al. 2014). | For intransitivity, we considered the most dominant first order loop, or, in its absence, the closest direct comparison contributing to the effect estimate. Whenever the comparisons contributing to indirect evidence showed important modifications on population or glycated hemoglobin, one point was downgraded due to intransitivity. |
| <b>Criteria</b>  | <b>Rated down NMA estimate if:</b>                                                                                                                                                                                                                                         | <b>Analysis</b>                                                                                                                                                                                                                                                                                                                              |
| Incoherence      | If node splitting test showed p-value <0.05, and direct, indirect and NMA evidence agreed with each other. (Brignardello-Petersen et al. 2018a).                                                                                                                           | Node split test was not feasible, due to the poorly connected network. In addition, it was not possible to compare the coherence between the direct and indirect estimates of the network meta-analysis. Thus, the certainty of evidence was not downgraded due to incoherence.                                                              |
| Imprecision      | A partially contextualized approach was used, considering the large effect threshold according to Cohen's classification (>0.8 SD) (Guyatt et al. 2011a;                                                                                                                   | We downgraded in one level if the effect estimate crossed the minimum important difference (MID), considered as 0.5%; two levels if the confidence                                                                                                                                                                                           |

|  |                                                             |                                                                                                                                                                                                                                                                                               |
|--|-------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | Schünemann et al. 2021; Brignardello-Petersen et al. 2021). | interval crossed the MID and the null effect line. In the cases when the threshold was not crossed, the effect size was evaluated. OIS calculations were performed to large unplausible effects. Whenever OIS was not achieved, one level was downgraded (Brignardello-Petersen et al. 2021). |
|--|-------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**Table S2: Assessment of GRADE for direct and indirect comparisons evidence certainty for HbA1c (6 months comparisons)**

| Comparison                       | Number of Studies | Risk of Bias   | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|----------------------------------|-------------------|----------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| <b>DIRECT COMPARISONS</b>        |                   |                |               |              |                  |                             |                                                    |                                                    |                     |                |                     |                     |                 |
| CHX_Gel vs NSPT                  | 2                 | -1 (some conc) | -1            | 0            | 0                | Low                         | -                                                  | -                                                  | -                   | -              | -                   | -2                  | Very low        |
| Doxy vs NSPT                     | 1                 | 0              | 0             | 0            | 0                | High                        | -                                                  | -                                                  | -                   | -              | -                   | -2                  | Low             |
| Mino vs NSPT                     | 1                 | 0              | 0             | 0            | 0                | High                        | -                                                  | -                                                  | -                   | -              | -                   | -2                  | Low             |
| <b>INDIRECT ONLY COMPARISONS</b> |                   |                |               |              |                  |                             |                                                    |                                                    |                     |                |                     |                     |                 |
| CHX_Gel                          | -                 | -              | -             | -            | -                | -                           | NSPT vs                                            | NSPT vs                                            | Low                 | 0              | -                   | -2                  | Very low        |

| Comparison      | Number of Studies | Risk of Bias | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|-----------------|-------------------|--------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| vs Doxy         |                   |              |               |              |                  |                             | CHX_Gel (low)                                      | Doxy (high)                                        |                     |                |                     |                     |                 |
| CHX_Gel vs Mino | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel (low)                              | NSPT vs Mino (high)                                | Low                 | 0              | -                   | -2                  | Very low        |
| Doxy vs Mino    | -                 | -            | -             | -            | -                | -                           | NSPT vs Doxy (high)                                | NSPT vs Mino (high)                                | High                | 0              | -                   | -2                  | Low             |

### GRADE Approach result for PPD at 3 months:

Criteria used to assess certainty of evidence was based on the Cochrane Training - <https://training.cochrane.org/resource/grade-approach-rate-certainty-evidence-network-meta-analysis-and-summary-findings-tables> and apropos literature (listed below).

| Criteria      | Rated down direct estimate if:                                                                                                                                                                                                                                                                                                                                                                                                                                               | Analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk of bias  | When at least one study on the direct comparison presented high risk or some concerns due to problems in the randomization process and lack of blinding.                                                                                                                                                                                                                                                                                                                     | We rated down the certainty in one level due to some concerns and two levels due to high risk of bias in the randomization process. One additional level was downgraded due to lack of outcome assessor blinding.                                                                                                                                                                                                                                                                                        |
| Inconsistency | <ul style="list-style-type: none"> <li>• If effect estimates were similar across studies (Guyatt et al. 2011b);</li> <li>• Overlap of 95%CI (Guyatt et al. 2011b);</li> <li>• <math>I^2</math> for direct comparisons if was either moderate (30-60%), substantial (50-90%) or considerable (75%-100%) (Schunemann et al., 2021).</li> <li>• If only one study contributed to the direct effect estimate, the certainty was not rated down (Guyatt et al. 2011b).</li> </ul> | We did not rate down the certainty for single studies forming the effect estimate. One pair wise meta-analysis included two studies (CHX_Gel vs NSPT - Faramarzi et al., 2017 and Santos et al., 2013). Since the effect estimates were opposite and the confidence intervals did not completely overlap, one level was downgraded.                                                                                                                                                                      |
| Indirectness  | Rate down if more than 30% of weight of pooled estimate came from studies which the populations had different characteristics (age, healthy condition) compared to the population of the PICO question (Brignardello-Petersen et al. 2018a).                                                                                                                                                                                                                                 | We assessed indirectness for each comparison. For almost all comparisons, patients had similar characteristics regarding age (late adulthood/elders), T2D and the presence of periodontitis. All patients met the periodontitis case-definition, according to the New Periodontal Diseases Classification (Tonetti et al., 2018). Thus, there was no problems regarding periodontitis condition.<br>The initial glycated hemoglobin (HbA1c) was similar in all populations at the beginning of the study |

|                  |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                  |                                                                                                                                                                                                                                                                            | (ranging from 7.1 to 10.4%). The included patients had moderate to unsatisfactory metabolic control.                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Publication bias | If industry funding was associated with a positive outcome favoring the sponsored treatment (Martins et al. 2019).                                                                                                                                                         | Of the studies included in this network meta-analysis, 4 were funded by the industry. Of these, 2 showed clear favoring for the substance tested (CLM vs NSPT – Bajaj et al., 2012 and STZ vs NSPT – Priyanka et al., 2015). For these, the level of certainty of evidence was one level downgraded. For comparisons AZT vs NSPT – Agarwal et al., 2012 and DOXY vs NSPT – Lecio et al., 2019, although the results was favorable for the test groups, there was no statistical difference between the groups. So, the level of certainty of evidence was not downgraded. |
| <b>Criteria</b>  | <b>Rated down indirect estimate if:</b>                                                                                                                                                                                                                                    | <b>Analysis</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Intransitivity   | If there were differences in study characteristics that may modify treatment effect in the direct comparisons that form the basis for the indirect estimate; and if those differences were regarding population, intervention, comparison, or outcome (Puhan et al. 2014). | For intransitivity, we considered the most dominant first order loop, or, in its absence, the closest direct comparison contributing to the effect estimate. Whenever the comparisons contributing to indirect evidence showed important modifications on population or glycated hemoglobin, one point was downgraded due to intransitivity.                                                                                                                                                                                                                              |
| <b>Criteria</b>  | <b>Rated down NMA estimate if:</b>                                                                                                                                                                                                                                         | <b>Analysis</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Incoherence      | If node splitting test showed p-value <0.05, and direct, indirect and NMA evidence agreed with each other. (Brignardello-Petersen et al. 2018a).                                                                                                                           | Node split test was not feasible, due to the poorly connected network. In addition, it was not possible to compare the coherence between the direct and indirect estimates of the network meta-analysis. Thus, the certainty of evidence was not downgraded due to incoherence.                                                                                                                                                                                                                                                                                           |

|             |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Imprecision | A partially contextualized approach was used, considering the large effect threshold according to Cohen's classification ( $>0.8$ SD) (Guyatt et al. 2011a; Schünemann et al. 2021; Brignardello-Petersen et al. 2021). | We downgraded in one level if the effect estimate crossed the minimum important difference (MID), considered as 1mm; two levels if the confidence interval crossed the MID and the null effect line. In the cases when the threshold was not crossed, the effect size was evaluated. OIS calculations were performed to large un plausible effects. Whenever OIS was not achieved, one level was downgraded (Brignardello-Petersen et al. 2021). |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**Table S3: Assessment of GRADE for direct and indirect comparisons evidence certainty for PPD (3 months comparisons)**

| Comparison                | Number of Studies | Risk of Bias   | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|---------------------------|-------------------|----------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| <b>DIRECT COMPARISONS</b> |                   |                |               |              |                  |                             |                                                    |                                                    |                     |                |                     |                     |                 |
| AZT vs NSPT               | 1                 | 0              | 0             | 0            | 0                | High                        | -                                                  | -                                                  | -                   | -              | -                   | -2                  | Low             |
| CHX_Gel vs NSPT           | 2                 | -1 (some conc) | -1            | 0            | 0                | Low                         | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Very low        |
| CLM vs NSPT               | 1                 | 0              | 0             | 0            | -1               | Moderate                    | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Low             |

| Comparison                       | Number of Studies | Risk of Bias | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|----------------------------------|-------------------|--------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| Doxy vs NSPT                     | 1                 | 0            | 0             | 0            | 0                | High                        | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Moderate        |
| Mino vs NSPT                     | 1                 | -2 (high*)   | 0             | 0            | 0                | Low                         | -                                                  | -                                                  | -                   | -              | -                   | -2                  | Very low        |
| STZ vs NSPT                      | 1                 | 0            | 0             | 0            | -1               | Moderate                    | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Low             |
| Tetra_Fiber vs NSPT              | 1                 | -2 (high*)   | 0             | 0            | 0                | Low                         | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Very low        |
| <b>INDIRECT ONLY COMPARISONS</b> |                   |              |               |              |                  |                             |                                                    |                                                    |                     |                |                     |                     |                 |
| AZT vs CHX_Gel                   | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs CHX_Gel (low)                              | Low                 | 0              | -                   | -2                  | Very low        |
| AZT vs CLM                       | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs CLM (moderate)                             | Moderate            | 0              | -                   | -2                  | Very low        |
| AZT vs Doxy                      | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs Doxy (high)                                | High                | 0              | -                   | -2                  | Low             |

| Comparison         | Number of Studies | Risk of Bias | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|--------------------|-------------------|--------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| AZT vs Mino        | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs Mino (low)                                 | Low                 | 0              | -                   | -2                  | Very low        |
| AZT vs STZ         | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs STZ (moderate)                             | Moderate            | 0              | -                   | -2                  | Very low        |
| AZT vs Tetra_Fiber | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs Tetra_Fiber (low)                          | Low                 | 0              | -                   | -2                  | Very low        |
| CHX_Gel vs CLM     | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel (low)                              | NSPT vs CLM (moderate)                             | Low                 | 0              | -                   | -1                  | Very low        |
| CHX_Gel vs Doxy    | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel (low)                              | NSPT vs Doxy (high)                                | Low                 | 0              | -                   | -1                  | Very low        |
| CHX_Gel vs Mino    | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel (low)                              | NSPT vs Mino (low)                                 | Low                 | 0              | -                   | -2                  | Very low        |
| CHX_Gel vs STZ     | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel                                    | NSPT vs STZ                                        | Low                 | 0              | -                   | -1                  | Very low        |

| Comparison             | Number of Studies | Risk of Bias | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|------------------------|-------------------|--------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
|                        |                   |              |               |              |                  |                             | (low)                                              | (moderate)                                         |                     |                |                     |                     |                 |
| CHX_Gel vs Tetra_Fiber | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel (low)                              | NSPT vs Tetra_Fiber (low)                          | Low                 | 0              | -                   | -1                  | Very low        |
| CLM vs Doxy            | -                 | -            | -             | -            | -                | -                           | NSPT vs CLM (moderate)                             | NSPT vs Doxy (high)                                | Moderate            | 0              | -                   | -1                  | Low             |
| CLM vs Mino            | -                 | -            | -             | -            | -                | -                           | NSPT vs CLM (moderate)                             | NSPT vs Mino (low)                                 | Low                 | 0              | -                   | -1                  | Very low        |
| CLM vs STZ             | -                 | -            | -             | -            | -                | -                           | NSPT vs CLM (moderate)                             | NSPT vs STZ (moderate)                             | Moderate            | 0              | -                   | -2                  | Very low        |
| CLM vs Tetra_Fiber     | -                 | -            | -             | -            | -                | -                           | NSPT vs CLM (moderate)                             | NSPT vs Tetra_Fiber (low)                          | Low                 | 0              | -                   | -2                  | Very low        |
| Doxy vs Mino           | -                 | -            | -             | -            | -                | -                           | NSPT vs Doxy (high)                                | NSPT vs Mino (low)                                 | Low                 | 0              | -                   | -2                  | Very low        |

| Comparison          | Number of Studies | Risk of Bias | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|---------------------|-------------------|--------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| Doxy vs STZ         | -                 | -            | -             | -            | -                | -                           | NSPT vs Doxy (high)                                | NSPT vs STZ (moderate)                             | Moderate            | 0              | -                   | -1                  | Low             |
| Doxy vs Tetra_Fiber | -                 | -            | -             | -            | -                | -                           | NSPT vs Doxy (high)                                | NSPT vs Tetra_Fiber (low)                          | Low                 | 0              | -                   | -1                  | Very low        |
| Mino vs STZ         | -                 | -            | -             | -            | -                | -                           | NSPT vs Mino (low)                                 | NSPT vs STZ (moderate)                             | Low                 | 0              | -                   | -1                  | Very low        |
| Mino vs Tetra_Fiber | -                 | -            | -             | -            | -                | -                           | NSPT vs Mino (low)                                 | NSPT vs Tetra_Fiber (low)                          | Low                 | 0              | -                   | -2                  | Very low        |
| STZ vs Tetra_Fiber  | -                 | -            | -             | -            | -                | -                           | NSPT vs STZ (moderate)                             | NSPT vs Tetra_Fiber (low)                          | Low                 | 0              | -                   | -2                  | Very low        |

\*This comparison presented some concerns regarding randomization process and outcome assessment.

### GRADE Approach result for PPD at 6 months:

Criteria used to assess certainty of evidence was based on the Cochrane Training - <https://training.cochrane.org/resource/grade-approach-rate-certainty-evidence-network-meta-analysis-and-summary-findings-tables> and apropos literature (listed below).

| Criteria      | Rated down direct estimate if:                                                                                                                                                                                                                                                                                                                                                                                                                                               | Analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk of bias  | When at least one study on the direct comparison presented high risk or some concerns due to problems in the randomization process and lack of blinding.                                                                                                                                                                                                                                                                                                                     | We rated down the certainty in one level due to some concerns and two levels due to high risk of bias in the randomization process. One additional level was downgraded due to lack of outcome assessor blinding.                                                                                                                                                                                                                                                                                        |
| Inconsistency | <ul style="list-style-type: none"> <li>• If effect estimates were similar across studies (Guyatt et al. 2011b);</li> <li>• Overlap of 95%CI (Guyatt et al. 2011b);</li> <li>• <math>I^2</math> for direct comparisons if was either moderate (30-60%), substantial (50-90%) or considerable (75%-100%) (Schunemann et al., 2021).</li> <li>• If only one study contributed to the direct effect estimate, the certainty was not rated down (Guyatt et al. 2011b).</li> </ul> | We did not rate down the certainty for single studies forming the effect estimate. One pair wise meta-analysis included two studies (CHX_Gel vs NSPT - Faramarzi et al., 2017 and Santos et al., 2013). Since the effect estimates were opposite and the confidence intervals did not completely overlap, one level was downgraded.                                                                                                                                                                      |
| Indirectness  | Rate down if more than 30% of weight of pooled estimate came from studies which the populations had different characteristics (age, healthy condition) compared to the population of the PICO question (Brignardello-Petersen et al. 2018a).                                                                                                                                                                                                                                 | We assessed indirectness for each comparison. For almost all comparisons, patients had similar characteristics regarding age (late adulthood/elders), T2D and the presence of periodontitis. All patients met the periodontitis case-definition, according to the New Periodontal Diseases Classification (Tonetti et al., 2018). Thus, there was no problems regarding periodontitis condition.<br>The initial glycated hemoglobin (HbA1c) was similar in all populations at the beginning of the study |

|                  |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                  |                                                                                                                                                                                                                                                                            | (ranging from 7.1 to 10.4%). The included patients had moderate to unsatisfactory metabolic control.                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Publication bias | If industry funding was associated with a positive outcome favoring the sponsored treatment (Martins et al. 2019).                                                                                                                                                         | Of the studies included in this network meta-analysis, 4 were funded by the industry. Of these, 2 showed clear favoring for the substance tested (CLM vs NSPT – Bajaj et al., 2012 and STZ vs NSPT – Priyanka et al., 2015). For these, the level of certainty of evidence was one level downgraded. For comparisons AZT vs NSPT – Agarwal et al., 2012 and DOXY vs NSPT – Lecio et al., 2019, although the results was favorable for the test groups, there was no statistical difference between the groups. So, the level of certainty of evidence was not downgraded. |
| <b>Criteria</b>  | <b>Rated down indirect estimate if:</b>                                                                                                                                                                                                                                    | <b>Analysis</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Intransitivity   | If there were differences in study characteristics that may modify treatment effect in the direct comparisons that form the basis for the indirect estimate; and if those differences were regarding population, intervention, comparison, or outcome (Puhan et al. 2014). | For intransitivity, we considered the most dominant first order loop, or, in its absence, the closest direct comparison contributing to the effect estimate. Whenever the comparisons contributing to indirect evidence showed important modifications on population or glycated hemoglobin, one point was downgraded due to intransitivity.                                                                                                                                                                                                                              |
| <b>Criteria</b>  | <b>Rated down NMA estimate if:</b>                                                                                                                                                                                                                                         | <b>Analysis</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Incoherence      | If node splitting test showed p-value <0.05, and direct, indirect and NMA evidence agreed with each other. (Brignardello-Petersen et al. 2018a).                                                                                                                           | Node split test was not feasible, due to the poorly connected network. In addition, it was not possible to compare the coherence between the direct and indirect estimates of the network meta-analysis. Thus, the certainty of evidence was not downgraded due to incoherence.                                                                                                                                                                                                                                                                                           |

|             |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Imprecision | A partially contextualized approach was used, considering the large effect threshold according to Cohen's classification ( $>0.8$ SD) (Guyatt et al. 2011a; Schünemann et al. 2021; Brignardello-Petersen et al. 2021). | We downgraded in one level if the effect estimate crossed the minimum important difference (MID), considered as 1mm; two levels if the confidence interval crossed the MID and the null effect line. In the cases when the threshold was not crossed, the effect size was evaluated. OIS calculations were performed to large un plausible effects. Whenever OIS was not achieved, one level was downgraded (Brignardello-Petersen et al. 2021). |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**Table S4: Assessment of GRADE for direct and indirect comparisons evidence certainty for PPD (6 months comparisons)**

| Comparison                | Number of Studies | Risk of Bias      | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|---------------------------|-------------------|-------------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| <b>DIRECT COMPARISONS</b> |                   |                   |               |              |                  |                             |                                                    |                                                    |                     |                |                     |                     |                 |
| AZT vs NSPT               | 1                 | 0                 | 0             | 0            | 0                | High                        | -                                                  | -                                                  | -                   | -              | -                   | -2                  | Low             |
| CHX_Gel vs NSPT           | 2                 | -1<br>(some conc) | -1            | 0            | 0                | Low                         | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Very low        |
| CLM vs NSPT               | 1                 | 0                 | 0             | 0            | -1               | Moderate                    | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Low             |

| Comparison                       | Number of Studies | Risk of Bias | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|----------------------------------|-------------------|--------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| Doxy vs NSPT                     | 1                 | 0            | 0             | 0            | 0                | High                        | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Moderate        |
| Mino vs NSPT                     | 1                 | -2 (high*)   | 0             | 0            | 0                | Low                         | -                                                  | -                                                  | -                   | -              | -                   | -1                  | Very low        |
| STZ vs NSPT                      | 1                 | 0            | 0             | 0            | -1               | Moderate                    | -                                                  | -                                                  | -                   | -              | -                   | 0                   | Moderate        |
| <b>INDIRECT ONLY COMPARISONS</b> |                   |              |               |              |                  |                             |                                                    |                                                    |                     |                |                     |                     |                 |
| AZT vs CHX_Gel                   | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs CHX_Gel (low)                              | Low                 | -              | -                   | -1                  | Very low        |
| AZT vs CLM                       | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs CLM (moderate)                             | Moderate            | -              | -                   | -2                  | Very low        |
| AZT vs Doxy                      | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs Doxy (high)                                | High                | -              | -                   | -2                  | Low             |
| AZT vs Mino                      | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs Mino (low)                                 | Low                 | -              | -                   | -2                  | Very low        |

| Comparison      | Number of Studies | Risk of Bias | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|-----------------|-------------------|--------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
| AZT vs STZ      | -                 | -            | -             | -            | -                | -                           | NSPT vs AZT (high)                                 | NSPT vs STZ (moderate)                             | Moderate            | -              | -                   | 0                   | Moderate        |
| CHX_Gel vs CLM  | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel (low)                              | NSPT vs CLM (moderate)                             | Low                 | -              | -                   | -1                  | Very low        |
| CHX_Gel vs Doxy | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel (low)                              | NSPT vs Doxy (high)                                | Low                 | -              | -                   | -1                  | Very low        |
| CHX_Gel vs Mino | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel (low)                              | NSPT vs Mino (low)                                 | Low                 | -              | -                   | -2                  | Very low        |
| CHX_Gel vs STZ  | -                 | -            | -             | -            | -                | -                           | NSPT vs CHX_Gel (low)                              | NSPT vs STZ (moderate)                             | Low                 | -              | -                   | 0                   | Low             |
| CLM vs Doxy     | -                 | -            | -             | -            | -                | -                           | NSPT vs CLM (moderate)                             | NSPT vs Doxy (high)                                | Moderate            | -              | -                   | -1                  | Low             |
| CLM vs Mino     | -                 | -            | -             | -            | -                | -                           | NSPT vs CLM                                        | NSPT vs Mino (low)                                 | Low                 | -              | -                   | -2                  | Very low        |

| Comparison   | Number of Studies | Risk of Bias | Inconsistency | Indirectness | Publication Bias | Direct comparison Certainty | Indirect evidence comparison from the closest loop | Indirect evidence comparison from the closest loop | Lowest between both | Intransitivity | Incoherence for NMA | Imprecision for NMA | Final Certainty |
|--------------|-------------------|--------------|---------------|--------------|------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------|---------------------|----------------|---------------------|---------------------|-----------------|
|              |                   |              |               |              |                  |                             | (moderate)                                         |                                                    |                     |                |                     |                     |                 |
| CLM vs STZ   | -                 | -            | -             | -            | -                | -                           | NSPT vs CLM (moderate)                             | NSPT vs STZ (moderate)                             | Moderate            | -              | -                   | -1                  | Low             |
| Doxy vs Mino | -                 | -            | -             | -            | -                | -                           | NSPT vs Doxy (high)                                | NSPT vs Mino (low)                                 | Low                 | -              | -                   | -2                  | Very low        |
| Doxy vs STZ  | -                 | -            | -             | -            | -                | -                           | NSPT vs Doxy (high)                                | NSPT vs STZ (moderate)                             | Moderate            | -              | -                   | 0                   | Moderate        |
| Mino vs STZ  | -                 | -            | -             | -            | -                | -                           | NSPT vs Mino (low)                                 | NSPT vs STZ (moderate)                             | Low                 | -              | -                   | 0                   | Low             |

\*This comparison presented some concerns regarding outcome assessment.

## Supplement References

Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerf B, Hazlewood GS, Alhazzani W, Mustafa RA, Murad MH, Puhan MA, Schünemann HJ, Guyatt GH; GRADE Working Group. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol. 2018 Jan;93:36-44. doi: 10.1016/j.jclinepi.2017.10.005. (a)

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Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, Kessels AG, Guyatt GH; GRADE Working Group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ*. 2014 Sep 24;349:g5630. doi: 10.1136/bmj.g5630.

Schünemann HJ, Vist GE, Higgins JPT, Santesso N, Deeks JJ, Glasziou P, Akl EA, Guyatt GH. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).

Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Periodontol*. 2018;89(Suppl 1):S159-S172. doi:10.1002/JPER.18-0006

## SUPPLEMENTARY FILE 6 – PRISMA NMA CHECKLIST

| Section/Topic             | Item # | Checklist Item                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Reported on Page # |
|---------------------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| <b>TITLE</b>              |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |
| Title                     | 1      | Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | #1                 |
| <b>ABSTRACT</b>           |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |
| Structured summary        | 2      | Provide a structured summary including, as applicable:<br><b>Background:</b> main objectives<br><b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> .<br><b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i><br><b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings.<br><b>Other:</b> primary source of funding; systematic review registration number with registry name. | #8                 |
| <b>INTRODUCTION</b>       |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |
| Rationale                 | 3      | Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | #12                |
| Objectives                | 4      | Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | #13                |
| <b>METHODS</b>            |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                    |
| Protocol and registration | 5      | Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | #14                |
| Eligibility criteria      | 6      | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | #14                |

|                                        |           |                                                                                                                                                                                                                                                                                                                                   |                |
|----------------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                                        |           | criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).</i>                                                                                                            |                |
| Information sources                    | 7         | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                                        | #15            |
| Search                                 | 8         | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                                                     | #suppl. file 1 |
| Study selection                        | 9         | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                                         | #15            |
| Data collection process                | 10        | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                                        | #15            |
| Data items                             | 11        | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                                                                             | #14            |
| <b>Geometry of the network</b>         | <b>S1</b> | Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.                      | #16            |
| Risk of bias within individual studies | 12        | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                                            | #16            |
| Summary measures                       | 13        | State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i> | #16            |

|                                          |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                |
|------------------------------------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Planned methods of analysis              | 14        | Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>                            | #17            |
| <b>Assessment of Inconsistency</b>       | <b>S2</b> | Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.                                                                                                                                                                                                                                                   | #suppl. file 5 |
| Risk of bias across studies              | 15        | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                                                                                                                                                                                                                                                      | #suppl. file 5 |
| Additional analyses                      | 16        | Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul> | Not applicable |
| <b>RESULTS</b>                           |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                |
| Study selection                          | 17        | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                                                                                                                                                                                                                                                   | #18            |
| <b>Presentation of network structure</b> | <b>S3</b> | Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.                                                                                                                                                                                                                                                                                                                                 | #29            |
| <b>Summary of network geometry</b>       | <b>S4</b> | Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.                                                                                                                 | #28            |
| Study characteristics                    | 18        | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                                                                                                                                                                                                                                                      | #20            |

|                                      |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                       |
|--------------------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Risk of bias within studies          | 19        | Present data on risk of bias of each study and, if available, any outcome level assessment.                                                                                                                                                                                                                                                                                                                                                                  | #26                   |
| Results of individual studies        | 20        | For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>                                                                                                                                                                                      | #31                   |
| Synthesis of results                 | 21        | Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented. | #30<br>#suppl. file 3 |
| <b>Exploration for inconsistency</b> | <b>S5</b> | Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.                                                                                                                                                              | #suppl. file 4        |
| Risk of bias across studies          | 22        | Present results of any assessment of risk of bias across studies for the evidence base being studied.                                                                                                                                                                                                                                                                                                                                                        | #26<br>#suppl. file 5 |
| Results of additional analyses       | 23        | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).                                                                                                                                                                                                              | Not applicable        |
| <b>DISCUSSION</b>                    |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                       |
| Summary of evidence                  | 24        | Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).                                                                                                                                                                                                                                                                        | #32                   |
| Limitations                          | 25        | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on</i>                                                                                                                                                                                            | #35                   |

|                |    |                                                                                                                                                                                                                                                                                                                                                                                                                                |     |
|----------------|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|                |    | <i>any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>                                                                                                                                                                                                                                                                                                                                       |     |
| Conclusions    | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                                                                                                                                                                                                                                        | #36 |
| <b>FUNDING</b> |    |                                                                                                                                                                                                                                                                                                                                                                                                                                |     |
| Funding        | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network. | #36 |

### Supplement Reference

Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann Intern Med.* 2015;162(11):777-784. doi:10.7326/M14-2385