National Institute for Health and Care Excellence

Final

Periodontal treatment to improve diabetic control in adults with type 1 or type 2 diabetes

Evidence review D for periodontal treatment to improve diabetic control in adults with type 1 or type 2 diabetes

NICE guideline NG17 & NG28

Evidence reviews underpinning recommendations 1.15.1 to 1.15.4 (NG17) and recommendations 1.7.1 to 1.7.4 (NG28) and research recommendations in the NICE guidelines

June 2022

Final

These evidence reviews were developed by the Guideline Development Team

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1.1 Review question

In adults with type 1 or 2 diabetes, what is the effectiveness of periodontal treatment to improve diabetic control?

1.1.1 Introduction

Diabetes and periodontitis are two chronic, highly prevalent comorbid conditions in general population that have long been considered to be bidirectionally linked. Research shows that hyperglycaemia and resultant advanced glycation end product formation, as one of several pathways that leads to the microvascular and macrovascular complications of diabetes, is also involved in the pathophysiology of periodontitis in people with diabetes. However, a growing body of scientific evidence also supports the fact that the periodontal infection adversely affects glycaemic control.

Periodontal inflammation if left untreated or inadequately controlled, could not only progress to a moderate or severe periodontitis, but could also result in increased systemic inflammatory burden, further worsening glycaemic status and perpetual promotion of associated complications of diabetes. Thus, establishing the effectiveness of periodontal treatment on glycosylated haemoglobin (HbA1c) levels is important to help to reduce the harms associated with oral diabetes complications.

This evidence review aims to assess the effectiveness of periodontal treatment for improving diabetic control in adults with type 1 or type 2 diabetes. The economic costs of periodontal treatment were also considered.

As part of a collaboration between the NICE Guideline Development Team and Cochrane, the evidence presented in this review was provided by Cochrane Oral Health (COH) and is drawn from their recently published systematic review (Simspon et al., 2022)..

We thank Cochrane Oral Health for their assistance in providing the literature searches and data for the review question relating to the Type 1 diabetes in adults: diagnosis and management guideline and the Type 2 diabetes in adults: management guideline.

1.1.2 Summary of the protocol

This review identified studies that fulfilled the conditions listed in Table 1, as specified in the protocol developed in agreement with the committee members. For full details of the review protocol, see Appendix A.

The Cochrane group did not publish a new protocol specifically for their systematic review as this work was carried out as a continuation of earlier systematic reviews (Simpson et al., 2015; Simpson et al.., 2010) with no substantive changes to the existing protocol (Simpson et al., 2004).

Table 1: Summary of the protocol

PICO Table	
Population	Adults (18+) with type 1 or type 2 diabetes and periodontitis
Interventions	A non-surgical periodontal treatment such as subgingival instrumentation also known as scaling and root planing (SRP), which may include one or more of the following: • mechanical debridement which includes scaling and root planing • subgingival curettage • antimicrobial therapy (antibacterials and antibiotics), either locally applied (including mouth rinses, gels, or dentifrices) or systemically administered • other drug therapy with a possible benefit of improving the periodontal condition of the participant • other novel interventions to manage periodontitis Studies combining periodontal treatment with usual care or with antimicrobial therapy (antibacterial and antibiotics) will be grouped for the purpose of the analysis.
Comparator	• Placebo • Usual care (defined as supragingival prophylaxis which can include scaling only or/and polish, oral hygiene instruction; education or support sessions to improve self-help or self-awareness of oral hygiene)
Outcomes	**Primary outcomes** • Change in HbA1c • Change in clinical attachment level (CAL) • Change in periodontal probing pocket depth (PPD) **Secondary outcomes** • Quality of life (QoL) (using validated tools e.g., hospital anxiety and depression scale (HADS), oral health-related quality of life (OHRQoL), health-related quality of life (HRQoL)) • Adverse events All outcomes reported at least 90 days following the intervention and grouped at 3 months, 6 months, 12 months
Study type	• Randomised controlled trials (parallel or cross-over design) • Systematic reviews

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods section in Appendix B.

As part of the collaboration, the COH performed:

- the literature search, screening of records, and study selection
- data extraction and production of evidence tables

- risk of bias of assessment of included studies against the following risk of bias criteria: random sequence generation; allocation concealment; blinding of participants; blinding of clinical operators; blinding of periodontal outcome assessors; incomplete outcome data; selective outcome reporting; other potential biases (using the Cochrane's RoB tool)
- publication bias assessment using funnel plots
- data analysis, including pairwise meta-analyses, subgroup analyses and narrative synthesis of findings.

The NICE Guideline Development Team followed the NICE Methods and further performed:

- overall quality assessment and classification of each individual RCTs into low, moderate and high risk of bias
- directness assessment of each individual study based on concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question (studies rated as direct, partially direct or indirect)
- quality assessment of the quality of the Cochrane Review using the ROBIS checklist for systematic reviews and meta-analysis of interventional studies and its applicability as the primary source of data
- alterations to the Cochrane Review meta-analyses to reflect the methodology used by the NICE Guideline Development Team
- GRADE for pairwise meta-analyses of interventional evidence to assess the quality of evidence of selected outcomes.

All alterations made by the NICE team are clearly stated in the relevant sections. In particular, the choice of random effects models presented in the Cochrane Review has been altered in the GRADE tables depending on the degree of heterogeneity of the assembled evidence to reflect NICE methodology specified in Appendix B. The GRADE analyses used to assess the quality of evidence for a specific outcome across studies using MIDs differs from the Cochrane methods which has reflected in differences in the interpretation of the quality of evidence between the COH systematic review and the ones presented in this evidence review

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The comparison of interest was periodontitis treatment versus no active treatment or usual care. The COH formed three subgroups for the intervention: subgingival instrumentation also known as scaling and root planing (SRP), non-surgical periodontal treatment or mechanical debridement SRP in combination with systemic or locally delivered antimicrobial as adjunctive treatment; and SRP combined with antimicrobial mouth rinse as adjunctive treatment. The data for these subgroups are presented at 3 follow-up time points: 3-4 months, 6 months, and 12 months.

For the primary outcome HbA1c, a subgroup analysis on provision of maintenance treatment following the initial periodontal treatment versus no maintenance treatment for studies lasting longer than three months was conducted.

Other subgroups that the NICE Committee identified as relevant to this evidence review e.g., subgrouping by diabetes type (type 1 vs type 2); diabetic control: poor (HbA1c above 8.5%)

versus fair (HbA1c from 7.5 to 8.4%) versus good (HbA1c up to 7.5%); rural/urban setting etc., could not be analysed due to insufficient and/or low quality of data.

The format of the available data did not allow pooling of secondary outcomes (adverse events and QoL) and these have been narratively synthesised.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Clinical effectiveness evidence

1.1.4.1 Included studies

In the current draft update, the COH identified 3109 records through updated database searching and 40 records identified through the previous version of the review. After deduplication, 2102 records were screened at title and abstract stage. 2030 records were discarded as they did not fulfil the review inclusion criteria. 72 records were sourced for full text screening. Of these, 15 full-text articles (11 trials) were excluded with reasons while 4 full-text articles were classified as ongoing studies. After the full text screening, 35 studies (reported in 53 publications) involving 3249 randomised participants in total fulfilled the eligibility criteria and were included for narrative synthesis; 33 of the studies (reported in 51 publications) were included in one or more meta-analyses. All studies were parallel randomised controlled trials (RCTs).

The last search was conducted on the 7th of September 2021 and the search strategy is presented in Appendix C. The PRISMA diagram for the study selection process is included in Appendix D. The evidence tables of the included studies are presented in Appendix E. Additional searches by the NICE Guideline Development Team were not performed.

1.1.4.2 Excluded studies

All excluded references with reasons for exclusion are given in Appendix K. This appendix also includes the references of ongoing studies.

1.1.5 Summary of clinical studies included in the effectiveness evidence

As a result of these exclusions, the Cochrane review included 35 parallel RCTs in its narrative synthesis and 33 studies in the quantitative synthesis 33 studies included participants with confirmed diagnosis of type 2 diabetes; 1 study assumed participants to all be type 2 diabetes without confirmed diagnosis (Jones 2007). 1 study included participants with either type 1 or type 2 diabetes (Vergnes 2018).

There was substantial variation in both the level and range of HbA1c of participants at baseline, with consequent variation in the potential for improvement in glycaemic control as a result of the intervention. Most studies were mixed and involved participants with good (HbA1c up to 7.5%), fair (HbA1c from 7.5 to 8.4%) and/or poor (HbA1c over 8.5%) metabolic control. The use of antidiabetic therapy and whether this was changed during the study conduct period varied across the trials. The severity of periodontitis also varied across studies, with some including people with mild to moderate periodontitis, some with moderate to severe periodontitis and some including the full range.

21 studies assessed the effects of SRP versus no treatment/ usual care, 11 studies assessed SRP plus systemic or locally delivered antimicrobial versus no treatment/usual care and 3 studies assessed SRP plus antimicrobial mouth rinse (chlorhexidine) vs no treatment/ usual care

4 studies included supragingival scaling as part of usual care (Koromantzos 2011; Mauri-Obradors 2018; Mizuno 2017; Rodrigues 2015).

Most of the studies (30) measured the outcomes at 3-4 months. For the 11 studies that reported data at 6 months, maintenance was provided following the initial periodontal treatment in 8 studies, with 3 studies not providing maintenance. Only one study reported outcomes at 12 months (D'Aiuto 2018

All 35 studies reported data on HbA1c. However, 2 included studies did not present results for HbA1c in a way that allowed them to be used in meta-analysis (Artese 2015; Rapone 2021) and thus were excluded from the quantitative synthesis. Clinical attachment loss was reported in 19 studies and probing pocket depth in 24 studies.

7 studies reported some adverse events (D'Aiuto 2018; Jones 2007; Koromantzos 2011; Mauri-Obradors 2018; Qureshi 2021; Tsobgny-Tsague 2018; Vergnes 2018) and 6 studies reported that there were no adverse effects (Chen 2012; Das 2019; El-Makaky 2020; Engebretson 2013; Mizuno 2017; Singh 2008). The remainder (22 studies) did not report whether there were any adverse events or not.

3 included studies reported data relating to QoL (D'Aiuto 2018; Mizuno 2017; Vergnes 2018) using different validated questionnaires.

All studies were at high risk of bias for blinding of participants and clinical operators as this could not be avoided in the trials due to the nature of interventions. A funnel plot of the 30 included studies that assessed HbA1c at 3-4 months failed to indicate any relationship between mean percentage reduction in HbA1c and precision (related to sample size) and no presence of publication bias was observed.

The NICE technical team judged the Cochrane systematic review as being fully applicable and of a high quality and it was used as the primary source of data (for details see the methods section in Appendix B).

The detailed evidence tables, the resulting summaries of risks of bias and publication bias, and assessment of the Cochrane systematic review and study applicability to this evidence review are all presented in Appendix E. Included studies are referenced in full in section 1.1.13 References **.** The NICE's assessment of study applicability to the review protocol and the ROBIS summary are presented in Appendix D, following the funnel plot of publication bias assessment.

1.1.6 Summary of the clinical effectiveness evidence

1.1.6.1 Primary outcomes:

The forest plots of the analyses of primary outcomes included in the GRADE tables are presented in Appendix F, with the GRADE tables in Appendix G. Studies were grouped based on the outcome, follow-up time and type of periodontal intervention, and the provision of maintenance treatment following initial intervention. Situations where the data are consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant') it is stated that the evidence showed **an effect**. Where the 95% CI crosses the line of no effect, the evidence **could not differentiate** between the comparators.

Results for the individual subgroups are reported when there was evidence of between group heterogeneity (for details see the methods section in Appendix B). The summaries of GRADE tables are presented below:

Table 2: Effects of periodontal treatment versus usual care/no active intervention on HbA1c

Outcome: HbA1c (%)	No. of studies	Sample size	Effect estimate MD [95% CI]	MID	Quality	Interpretation of effect
Periodontal treatment vs usual care/no active intervention at 3-4 months	30	2443	-0.43 [-0.59, -0.28]	+/- 0.50	Very low	Effect (favouring periodontal treatment)
Periodontal treatment vs usual care/no active intervention at 6 months	12	1457	-0.30 [-0.52, -0.08]	+/- 0.50	Very low	Effect (favouring periodontal treatment)
Periodontal treatment vs usual care/no active intervention at 12 months	1	264	-0.50 [-0.55, -0.45] *	+/- 0.50	Moderate	Effect (favouring periodontal treatment)

* Subgroups reported using fixed effect model due to I^2<50% (as per NICE methods, Appendix B)

Table 3: Effects of periodontal treatment versus usual care/no active intervention on clinical attachment loss (CAL)

Outcome: CAL (mm)	No. of studies	Sample size	Effect estimate MD [95% CI]	MIDs	Quality	Interpretation of effect
Periodontal treatment vs usual care/no active intervention at 3-4 months	18	1606	-0.48 [-0.65, -0.31]	+/- 0.41	Very low	Effect (favouring periodontal treatment)
Periodontal treatment vs usual care/no active intervention at 6 months	5	789	-0.52 [-0.77, -0.26]	+/- 0.32	Very low	Effect (favouring periodontal treatment)
SRP vs usual care/no active intervention at 6 months	4	329	-0.66 [-0.80, -0.53] *	+/- 0.41	Moderate	Effect (favouring periodontal treatment)
SPR + mouth rinse vs usual care/no active intervention at 6 months	1	460	-0.25 [-0.36, -0.14] *	+/- 0.15	Moderate	Effect (favouring periodontal treatment)

* Subgroups reported using fixed effect model due to I^2<50% (as per NICE methods, Appendix B)

Table 4: Effects of periodontal treatment versus usual care/no active intervention on probing pocket depth (PPD)

Outcome PPD (mm)	No. of studies	Sample size	Effect estimate MD [95% CI]	MIDs	Quality	Interpretation of effect
Periodontal treatment vs usual care/no active intervention at 3-4 months	21	1775	-0.56 [-0.72, -0.40]	+/- 0.31	Very low	Effect (favouring periodontal treatment)
SRP vs usual care/no active intervention 3-4 months	12	691	-0.48 [-0.70, -0.26]	+/- 0.28	Very low	Effect (favouring periodontal treatment)
SPR + local/ systemic antimicrobials vs usual care/no active intervention at 3-4 months	9	532	-0.76 [-1.09, -0.43]	+/- 0.30	Very low	Effect (favouring periodontal treatment)
SPR + mouth rinse vs usual care/no active intervention at 3-4 months	3	532	-0.30 [-0.41, -0.20] *	+/- 0.35	Moderate	Effect (favouring periodontal treatment)
Periodontal treatment vs usual care/no active intervention at 6 months	8	1181	-0.50 [-0.70, -0.29]	+/- 0.32	Very low	Effect (favouring periodontal treatment)
Periodontal treatment vs usual care/no active intervention at 12 months	1	264	-0.90 [-1.18, -0.62] *	+/- 0.57	Moderate	Effect (favouring periodontal treatment)

* Subgroups reported using fixed effect model due to I^2<50% (as per NICE methods, Appendix B)

For studies reporting data at 6 months, a subgroup analysis for HbA1c was conducted based on the provision of maintenance treatment following the initial periodontal treatment. The results of the subgroup analysis are presented in Table 5. There was no evidence of a difference between the subgroups (P = 0.58) and differences in the provision of maintenance did not explain the heterogeneity.

Table 5: Effects of maintenance treatment versus no maintenance treatment on HbA1c at 6 months

HbA1c measured at 6 months				
Maintenance	**Number of studies**	**Effect size MD [95% CI]**	**Heterogeneity P-value; I^2**	**P-value for subgroup comparison**
Maintenance	8	-0.23 [-0.45, -0.01]	$<1x10^{-5}$; 82%	
No maintenance	3	-0.06 [-0.60, 0.47]	0.30; 16%	
Overall	10*		$<1x10^{-5}$; 76%	0.58

* Two arms from one study (Chen 2012) included in both subgroups

1.1.6.2 Secondary outcomes

Due to insufficient data and the format presented, secondary outcomes were not meta-analysed and were narratively synthesised.

Adverse effects

7 studies reported adverse events (D'Aiuto 2018; Jones 2007; Mauri-Obradors 2018; Vergnes 2018; Koromantzos 2011; Qureshi 2021; Tsobgny-Tsague 2018). These studies suggested their participants in the intervention group experienced minor side effects such as more soreness, tenderness, pain and thermal sensitivity than the control group; these are common sequelae of SRP. The most reported symptoms among those taking systemic or locally delivered antimicrobials were diarrhoea, abdominal pain, and nausea. For participants using antibacterial mouth rinse, the most common complaints were oral disorders: changes in taste, tooth staining, and sore mouth or tongue tip irritation. Swelling of the face, lips, and throat and shortness of breath were also reported.

6 studies reported that there were no adverse effects: Chen 2012; Das 2019 (reported no adverse effects from use of doxycycline but did not mention other aspects of interventions), El-Makaky 2020 ("no significant side effects"), Engebretson 2013, Mizuno 2017 ("no serious study-related adverse events"), and Singh 2008 (reported no adverse effects from use of doxycycline but did not mention other aspects of interventions).

Quality of life (QoL)

The available evidence from the three studies that measured QoL as an outcome is sparse and mixed as studies have used different standardised questionnaires to measure it. However, there is some limited evidence of a possible benefit from periodontal treatment in terms of QoL related to some aspects of living with diabetes and periodontitis.

1.1.7 Economic evidence

1.1.7.1 Included studies

A systematic literature search was undertaken to identify published health economic evidence relevant to the review questions. Studies were identified by searching EconLit, Embase, CRD NHS EED, International HTA database, MEDLINE, PsycINFO and NHS EED. All searches

were updated on 4th November 2021, and no papers published after this date were considered. This returned 1,542 references (see Appendix C for the literature search strategy). After deduplication and title and abstract screening against the review protocol, 1,540 references were excluded, and 3 references were ordered for screening based on their full texts.

Of the 3 references screened as full texts, one study was a systematic review which was investigated as a source of references; however, no cost-utility studies were included. In total there were two studies that contained cost-utility analyses evaluating non-surgical periodontal treatment. One UK study was included in this evidence review in full as the most relevant evidence, with the other being excluded as not sufficiently applicable to the UK context. The health economic evidence study selection is presented as a flowchart in Appendix H. Full economic evidence tables along with the checklists for study applicability and study limitations are shown in Appendix I.

1.1.7.2 Excluded studies

Studies excluded in the full text review, together with reasons for exclusion, are listed in Appendix K.

1.1.8 Summary of included economic evidence

The only relevant study identified assessed the cost-effectiveness of non-surgical periodontal treatment for people with periodontitis with newly diagnosed type 2 diabetes. Solowiej-Wedderburn et al (2017) found non-surgical periodontal treatment to be cost-effective at the £30,000 cost-effectiveness threshold.

Table 6: Summary of economic evidence

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
Solowiej-Wedderburn et al 2017	Cost utility analysis using simulation model DiabForecaster McEwan et al 2006 to estimate the impact of reductions in HbA1c on lifetime costs of diabetes management	UK Setting. Provider perspective: includes costs to health care and dental care providers	Non-surgical periodontal therapy: Scaling and root planning provided by the dentist and lifetime maintenance therapy is commenced by the patient, with dental retreatment as necessary. Periodontal therapy: Two 60-minute sessions delivered by a practitioner with experience of periodontal treatment Followed by maintenance of:	People with periodontitis newly diagnosed with T2DM not previously receiving regular periodontal maintenance. The base case analysis assumes a 58-year-old man with a baseline HbA1c level of 7-7.9%.	Change in HbA1c sourced from previous Cochrane review by Simpson et al., 2015. Effectiveness separated by patient compliance, model assumed 30% patients compliant with maintenance treatment based on rates reported in the literature of 11-70% (Fardal, Johannessen, & Linden, 2003; Pretzl et al., 2009; Ramseier et al., 2014). 87% of compliant patients assumed to	£28,000 per QALY for a man aged 58 with glycated haemoglobin of 7-7.9%	**Deterministic**: impact of periodontal therapy on HbA1c, percentage of compliance and response were the main drivers of cost - effectiveness results **Probabilistic:** not completed	**Source of funding:** Unfunded **Limitations identified by the authors:** 1) Large uncertainty around the decrease in HbA1c attributable to periodontal treatment; 2) Results dependent on short term gains in HbA1c if treatment are maintained; 3) insufficient long-term data. **Authors' conclusions:** Periodontal therapy may be

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
			30-minute hygienist sessions every 3 months and follow-up of periodontal therapy of one 60-minute session every 3 years No treatment: Regular dental care only which comprises of routine scale and polish		respond to treatment (Lorentz, Miranda Cota, Cortelli, Vargas, & Costa, 2009) Remaining 13% assumed to incur full cost of treatment and maintenance without benefit Non-compliant patients assumed to only incur the costs of the initial treatment and tooth loss repair and assumed to have no benefit of treatment **Time horizon**: Lifetime **Discount rate:** 3.5%			cost-effective for patients with type 2 diabetes assuming improvements in HbA1c are maintained

1.1.9 Economic model

An original cost-effectiveness analysis was undertaken for this review question. A summary is included here, with the full analysis available in the economic model report.

Model structure

The economic analysis was done using the IQVIA CORE Diabetes model (CDM) version 9.5. IQVIA CDM is a Markov simulation model predicting the progression of diabetes over time using a series of interlinked and interdependent Markov sub models for diabetes related complications. The model can be run over different time horizons including the lifetime of a patient. The model has been previously validated against epidemiological and clinical studies of type 1 and type 2 diabetes. A more detailed description of IQVIA CDM has been published by Palmer et al (2004). The model allows for transition probabilities and management strategies to be differentiated by type of diabetes. Due to the model structure our analysis for type 1 diabetes and type 2 diabetes were conducted separately. Diabetes type specific data were used for baseline characteristics, diabetes progression and complications.

Diabetes progression with the IQVIA CDM is simulated using a series of interlinked, inter-dependent sub-models which simulate the following complications:

- angina
- myocardial infarction
- congestive heart failure
- stroke
- peripheral vascular disease
- diabetic retinopathy
- macular oedema
- cataract
- hypoglycaemia
- ketoacidosis
- lactic acidosis
- nephropathy and end-stage renal disease
- neuropathy
- foot ulcer
- amputation
- non-specific mortality

The Markov sub models listed above use time, state, and diabetes type-dependent probabilities from published sources. Interactions between these sub models are moderated by employing Monte Carlo simulations using tracker variables.

The analysis simulates the use of non-surgical periodontal treatment compared to no treatment. The analysis is separated by type 1 and type 2 diabetes, although treatment is assumed to have the same efficacy between the two populations.

Analysis

A cohort of people with type 1 and type 2 diabetes were defined using patient demographics, racial characteristics, baseline risk factors, and baseline complications to reflect an adult type 1 diabetes and type 2 diabetes population in the UK. The analysis was performed across a lifetime horizon. Costs and quality-adjusted life years (QALYs) were considered from a UK NHS perspective. The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects.

Treatment effectiveness was characterised by a reduction in HbA1c levels. Effectiveness evidence was pooled across both type 1 and type 2 studies. This value was then used to adjust the HbA1c level for usual care value which was different in type 1 and type 2 diabetes. All periodontal treatments have been pooled because there is limited clinical evidence for this comparison.

UK specific sources were identified model inputs relating to costs, utilities, and other management parameters. In cases where UK specific sources were not available, default IQVIA CDM parameters were used. Treatment specific costs were calculated using published national sources.

Results

The base case results for people with type 1 diabetes (Table 7) showed that periodontal treatment compared with usual care was cost-effective. Periodontal treatment results in both an increase in QALYs and a decrease in costs meaning treatment dominates compared with usual care.

Table 7: Type 1 base-case deterministic cost-utility results

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (vs usual care)
Usual care	£44,048	12.741			
Periodontal treatment	£42,977	12.796	-£1,070	0.055	Dominates

The base case results for people with type 2 diabetes (Table 8) showed that treatment compared with usual care was cost-effective at a threshold of £20,000 per QALY.

Table 8: Type 2 base-case deterministic cost-utility results

Treatments	Absolute		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (vs usual care)
Usual care	£10,840	7.895			
Periodontal treatment	£11,087	7.917	£247	0.022	£11,375*

* The costs and QALYs in the table are rounded and the ICER is calculated using the exact values, therefore the ICER in the table is slightly different

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee agreed that HbA1c, Clinical Attachment Level (CAL) and Probing Pocket Depth (PPD) are important outcomes to assess the link between diabetes and periodontitis. Successful periodontal treatment leads to reduction in HbA1c, CAL and PPD and consequently improved Quality of Life (QoL) which was considered a secondary outcome.

Adverse effects were thought to be less important due to the nature of conventional non-surgical periodontal treatment which generally causes only minor discomfort and tooth sensitivity that normally resolves after a few days.

1.1.11.2 The quality of the evidence

The certainty of the body of evidence for the effect of periodontal treatment on diabetic control ranged from very low to moderate, however, several factors were considered when linking the evidence to recommendations.

There was substantial variation in inclusion criteria at baseline, with consequent variation in the potential for improvement in glycaemic control as a result of the intervention. All studies included participants with type 2 diabetes with only one study including participants with either type 1 or type 2 diabetes and lack of studies on type 1 diabetes was acknowledged. Most studies involved mixed participants with HbA1c ranging from 6%-14%, diabetic control classified as poor (HbA1c above 8.5%), fair (HbA1c from 7.5 to 8.4%) and good (HbA1c up to 7.5%) and severity of periodontitis ranging from mild-to-moderate, moderate, moderate-to-severe and severe.

The committee agreed to not downgrade the quality of the studies for lack of blinding of participants and clinical operators, as this was not thought to be feasible when knowledge of the intervention is inherent to its use. Also, the committee agreed that for the primary outcome HbA1c, performance and detection bias (blinding of periodontal assessors) was not relevant, as HbA1c tests were carried out remotely.

The subgroup analyses (based on intervention type and provision of a maintenance periodontal treatment for studies longer than 3 months) could not explain the substantial heterogeneity among studies, and it was agreed that the possible cause is the substantial variation in both the level and range of HbA1c, and severity of periodontitis at baseline. The committee also acknowledged that subgrouping based on metabolic control at baseline could not be meaningfully done with the available data.

Only three studies provided evidence on QoL. As all used different standardised tools e.g., assessing either diabetes or oral health QoL measures, no clear conclusions on QoL could be drawn. Adverse events were rarely assessed but the studies that measured adverse effects generally reported no or mild adverse effects, and any serious adverse events were similar in intervention and control arms. The dental healthcare professionals co-opted to the committee noted that these findings reflected their own clinical experience.

Combined with the positive health economic results, the committee concluded that the clinical evidence base had a consistent and adequate volume of effectiveness to justify the recommendation of periodontal treatment in people diagnosed with diabetes and periodontitis.

Despite of the lack of evidence especially on type 1 diabetes and QoL, the committee did not make any recommendations for future research. It was thought the findings based on type 2

diabetes were applicable to people with type 1 diabetes and future research was unlikely to change these conclusions.

1.1.11.3 Benefits and harms

The committee acknowledged the benefits of periodontal treatment in improving diabetes control in adults with type 1 and type 2 diabetes. Although most of the research has focused on type 2 diabetes mellitus, the committee thought that that the evidence on the link between increased HbA1c and periodontitis is applicable to people with type 1 diabetes mellitus as well. The committee members agreed that all people with diabetes are at increased risk of developing periodontitis and stated that this should be routinely discussed as a potential complication of diabetes alongside eye disease and diabetes related foot problems.

The pooled effect of periodontal treatment when compared to no active intervention or usual care demonstrated that the treatment of periodontitis using subgingival instrumentation/ scaling and root planing improved all primary outcomes (HbA1c, Clinical Attachment Level and Probing Pocket Depth).

The few studies that measured adverse effects generally reported no or mild adverse effects. However, the committee members, based on their own clinical experience, agreed that most reported adverse effects resulting from periodontal treatment are not serious and increased soreness, tenderness, pain, and thermal sensitivity are common sequelae of subgingival instrumentation/ scaling and root planing. The committee acknowledged that the evidence of the possible benefit of periodontal treatment in terms of health-related quality of life was limited.

Overall, it was agreed that the benefits outweigh the minor side effects and the treatment of periodontitis using conventional non-surgical techniques should be recommended to improve diabetic control. The decision about which periodontal treatment to perform would be made by the dental healthcare professional during oral health reviews in line with the NICE clinical guideline CG19. To prevent and manage periodontitis, advice on regular oral health reviews, and maintaining good oral health hygiene was suggested in the long term. The frequency of the oral health reviews should be advised by a dental practitioner and be personalised to the individual's oral health needs as outlined in the NICE guideline on dental checks: intervals between oral health reviews. Lastly, for prevention of periodontitis and oral health advice, a reference to the NICE's guidance on oral health promotion was made. In support of the proposed recommendations, the committee also referred to the NHS England commissioning standard: Dental Care for People with Diabetes which should ensure that people with diabetes can access effective oral healthcare services with the aim of improving their oral health.

1.1.11.4 Cost-effectiveness and resource use

The committee noted there was only one published economic study in the UK context, which found non-surgical periodontal treatment might be cost-effective among people with type 2 diabetes. The results were sensitive to changes in the baseline HbA1c level, age, rates of adherence response to the treatments. The key limitation is that the study only focused on type 2 diabetes and did not carry out probabilistic sensitivity analysis to account for the joint uncertainty in model inputs. Therefore, we adopted a more comprehensive modelling structure (IQVIA Core Diabetes Model) based on the most updated clinical evidence to assess the cost-effectiveness of non-surgical periodontal treatments for improving HbA1c control in people with either type 1 or type 2 diabetes.

The committee generally agreed with the underlying assumptions for the cost and utility inputs. They raised some concerns over removing patient co-payments from the overall cost, since it did not take into account affordability of the treatment and inequality in the access to dental care. However, the committee also noted that the cost-effectiveness analysis was undertaken from an NHS perspective, and only costs incurred by health care sector and public sectors should be included in the analysis. To address the concerns about affordability among people from lower socio-economic backgrounds, we added an additional scenario in the sensitivity analyses to include the full cost of the treatment (no co-payment was deducted). The results remained cost-effective at the £30,000 per QALY threshold. Therefore, even with the increasing proportion of people who are exempt from dental charges, periodontal treatments could still be cost-effective for the NHS.

The committee acknowledged the fact that the model only considered diabetes-related outcomes (reduction in HbA1c) and did not take dental outcomes into account. Our model structure did not contain a dental module that can be used to model the costs and consequences along the periodontal pathway of intervening with treatment in a cohort of people with diabetes. In addition, the commonly adopted utility measure, EQ-5D, is not sufficient to capture the processes and outcomes of dental care due to its insensitivity and short health state durations. There are also no good mapping algorithms to translate disease specific measures (e.g. Oral Health Impact Profile) onto utility values. Given that periodontal treatment appears highly cost-effective in our base case analysis, the inclusion of any potential oral health benefit will further increase its cost-effectiveness and will not influence our conclusions.

The committee recognised that periodontal treatment is cost-effective for people with type 1 and type 2 diabetes in the base case analysis, and the results remain robust across most scenarios in the sensitivity test. Although the treatment appears not cost-effective under some scenarios (e.g. shorter time horizon, lower compliance/response rate, reduced treatment benefit over time), the committee felt that these were extreme cases and unlikely to reflect the real-world practice. In addition, the committee discussed about the potential resource impact and agreed that the new recommendations will increase health professionals' awareness of periodontitis among people with diabetes. This might lead to a short-term increase in the number of dental appointments, but the associated cost increase is likely to be overweighed by the long-term benefits in the improvement of dental and diabetic outcomes.

1.1.11.5 Other factors the committee took into account

The committee agreed that to help prevent or manage periodontitis among people with diabetes enhanced advice and continuing educational support is necessary. The multidisciplinary approach would be a step forward towards achieving comprehensive care and has the potential to improve consistency in service delivery and consequently diabetes control and oral health outcomes.

The committee acknowledged that the terms used to refer to the non-surgical periodontal treatment such as scaling, polishing etc. are now historic terms and no longer in use as per the new periodontal disease nomenclature. However, to increase acceptance among the target population, these terms have not been replaced to reflect the new terminology, as these are still widely recognised by the public.

The committee wished to stress that NHS dental services are free only for pregnant women or women who have had a baby in the last 12 months and those receiving low-income benefits and thus wished to highlight the increased risk of periodontitis and the needs of certain groups

with diabetes. The committee noted that people from lower socio-economic and disadvantaged groups (e.g., e.g., homeless people and Gypsy, Roma and Traveller communities)) may experience difficulties in accessing higher-cost periodontal treatment. In this case, to reduce inequality the provision of fee-free periodontal treatment was suggested. The committee also considered the needs of certain groups such as people with frailty, people with physical disability, mental health related or learning disability. These groups may also have limitations with their dexterity and compliance which can cause difficulties in using toothbrushes or interdental and interproximal brushes to maintain good oral hygiene and this may diminish the effect of periodontal treatment over time. The committee highlighted that these groups may not tolerate dental care and general anaesthetics might be needed to perform periodontal treatment. This would potentially require palliative periodontal care to avoid repeated general anaesthetics. Consideration for prisoners/ detainees was also stressed, as access to interdental and/or interproximal brushes and other dental health care products is limited in these settings for security reasons. The committee highlighted racial or ethnic disparities, e.g., higher prevalence and increased risk of severe periodontitis among the Black, African and Asian community.. Overall, access to adequate dental treatment/ oral health reviews and personal oral hygiene products in combination with proactive engagement and enhanced educational support have the potential to reduce inequalities among disadvantaged groups.

Lastly, how the delivery of care for people with diabetes is best integrated across healthcare settings was considered. Following the publication of this guideline, the committee members discussed the uncertainty regarding the initial increase in referrals of people with diabetes for dental checks and oral health reviews as this will potentially impact on the scarce NHS dental service. Clear advice from the oral healthcare/ dental teams, of what is expected of them regarding diabetes dental care and clear care pathways are necessary to enhance the quality of care across the continuum and improve service delivery. In line with the NHS England commissioning standard: Dental Care for People with Diabetes, the committee agreed it is expected that the majority of general dental providers will be able to deliver level 1 services to diagnose and manage patients with uncomplicated periodontitis but access to level 2 dental services was uncertain. The committee members were also uncertain how this would impact on dental and oral health services in the long term, as this would depend on the frequency of oral health reviews as advised by the oral healthcare/ dental team and personalised to the individual's oral health risk, individual's compliance and the capacity of dental services. The long-term impact becomes even more complicated considering population demographics and increasing prevalence of the two chronic conditions (diabetes and periodontitis). Overall, current lack of access to NHS dentistry and gaps in periodontal services, especially treatment of severe periodontal cases (e.g., lack of access to dental hospitals across the country) and future provision of periodontal treatment was of major concern, warranting a broader and more flexible dental care access and services.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.15.1 to 1.15.4 of the Type 1 diabetes in adults: diagnosis and management guideline and recommendations 1.7.1 to 1.7.4 of the Type 2 diabetes in adults: management guideline.

1.1.13 References

1.1.13.1 Effectiveness

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Note: * Indicates the major publication for the study

1.1.13.2 Economic

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Appendices

Appendix A – Review protocols

Review protocol for effectiveness of periodontal treatment in improving diabetic control in adults with type 1 or type 2 diabetes.

Review carried out in collaboration with the Cochrane Oral Health Group as an update on an earlier review (Simpson et al 2015).

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Periodontal treatment to improve diabetic control in adults with type 1 or type 2 diabetes.
2.	Review question	In adults with type 1 or 2 diabetes, what is the effectiveness of periodontal treatment to improve diabetic control?
3.	Objective	Determine the effectiveness of periodontal treatment to improve diabetic control.
4.	Searches	See Cochrane review
5.	Condition or domain being studied	Type 1 diabetes, type 2 diabetes and periodontitis.
6.	Population	**Inclusion:** Adults with type 1 diabetes, type 2 diabetes and periodontitis Adults defined as ages 18 years and above. **Exclusion:** Gestational diabetes and children and young people with diabetes.

7.	Intervention	A non-surgical periodontal treatment such as subgingival instrumentation also known as scaling and root planing (SRP), which may include one or more of the following: • mechanical debridement which includes scaling and root planing • subgingival curettage • antimicrobial therapy (encompassing antibacterials and antibiotics), either locally applied (including mouth rinses, gels or dentifrices) or systemically administered • other drug therapy with a possible benefit of improving the periodontal condition of the participant • other novel interventions to manage periodontitis **Note:** Studies combining periodontal treatment with usual care will be included. Usual care can include scale and polish, oral hygiene instruction; education or support sessions to improve self-help or self-awareness of oral hygiene. **Note:** studies combining periodontal treatment with antimicrobial therapy (antibacterial and antibiotics) will be included. Each arm of the trial should be given identical antimicrobial therapy.
8.	Comparator	• Placebo • Usual care (which we defined as supragingival prophylaxis and/or oral hygiene instruction) **Note:** Usual care can include scaling only or/and polish, oral hygiene instruction; education or support sessions to improve self-help or self-awareness of oral hygiene.
9.	Types of study to be included	• Randomised controlled trials (RCTs) • Systematic reviews of RCTs
10.	Other exclusion criteria	• Trials which followed up participants for less than 90 days after completion of treatment course • RCTs with more than 10% of the study sample diagnosed with gestational diabetes • Split mouth and cross-over studies **Definition:** Split mouth is a research design in which instead of randomising individuals, a mouth is divided into two or more experimental segments that are randomly assigned to different treatments.

11.	Context	This review is part of an update of the NICE guideline on Type 1 diabetes in adults: diagnosis and management (NG17) and NICE guideline on Type 2 diabetes in adults: diagnosis and management (NG28). https://www.nice.org.uk/guidance/ng28 https://www.nice.org.uk/guidance/ng17 This guideline will also cover all settings where NHS healthcare is provided or commissioned.
12.	Primary outcomes (critical outcomes)	All outcomes will have to be reported at least 3 months following the intervention. Outcomes will be reported based on duration of follow up e.g., 3 months, 6 months, 12 months etc. from the periodontal intervention The outcomes will include: • Change in HbA1c • Change in periodontal attachment level • Periodontal pocket reduction
13.	Secondary outcomes (important outcomes)	• Quality of life (using validated tools e.g., hospital anxiety and depression scale (HADS), oral health-related quality of life (OHRQoL), health-related quality of life (HRQoL)) • Adverse events
14.	Data extraction (selection and coding)	The update of Simpson et al 2015 Cochrane review (ongoing at the time of protocol development) on the treatment of periodontitis for glycaemic control in people with diabetes mellitus will be used as the evidence base for periodontal interventions in accordance with section 3 Developing or updating Cochrane reviews for use in NICE guidelines of the Guideline support document: Cochrane reviews and NICE guideline development The use of existing systematic reviews in the process of developing guideline is in line with section 4 of Developing Guidelines: the manual
15.	Risk of bias (quality) assessment	The update of Simpson et al 2015 Cochrane review (ongoing at the time of protocol development) on the treatment of periodontitis for glycaemic control in people with diabetes mellitus will be used as the

		evidence base for periodontal interventions as described in section 4.4.of Developing NICE guidelines: the manual The ROBIS checklist for systematic reviews and meta-analysis of interventional studies will be used to assess the Risk of Bias of the Simspon et al. 2015 Cochrane review update.https://www.nice.org.uk/process/pmg20/chapter/reviewing-research-evidence - assessing-the-quality-of-the-evidence
16.	Strategy for data synthesis	For details, please see section 4 of Developing NICE guidelines: the manual. – existing systematic reviews. In addition to the Cochrane Simpson 2015 review update, the cost-effectiveness of periodontal treatments to improve glucose control in people with diabetes will also be considered. Network meta-analysis is not planned for this review.
17.	Analysis of sub-groups	We plan to carry out the following subgroup analyses: • Type of intervention and comparison (e.g., SRP, SRP plus systemic/locally delivered antimicrobials or SRP plus antimicrobial mouth rinse vs supragingival scaling or hygiene instructions) • Length of follow up since completion of treatment (e.g., 3,6,12 months) Should we find sufficient data, we will also consider the following groups for subgroup analyses: • Periodontitis severity at baseline (e.g., chronic or aggressive periodontitis, necrotising ulcerative gingivitis, periodontal abscess) • Intensiveness of periodontal treatment (e.g., single intervention or a supportive care programme on 3-monthly basis)

		• Diabetes control-through categorisation of participants into good, fair and poor (mean HbA1c 7%, between 7% and 8.5% or >8.5% on the DCCT or equivalent scale) • Diabetes type (Type1 or Type 2) • Diabetes duration (since diagnosis) • Age (younger adults 18-29), adults (30-59) and older adults (60+)) • Sex • Smoking habits (never, former, current) • Alcohol consumption (drinks per day) - never, 0.5 drinks/day, 0.5–0.99 drinks/day, 1.0–2.99 drinks/day, and 3 drinks/day; assuming an average of 12 g/drink • General health status (presence of other diabetes complications) • Other medical conditions • Plaque control • Socioeconomic status/ health inequalities (ethnicity and social class) • Drug therapy • Bariatric patients • People with learning difficulties • People with disabilities • Location (urban or rural) • Prison units • Eating disorders and disordered eating Statistical heterogeneity will be calculated using the 'Q' statistic with P value set at $P < 0.10$ and will be quantified by the calculation of the I^2 statistic for heterogeneity. If there are sufficient studies, sensitivity analyses will be used to explore, quantify, and control for sources of heterogeneity between studies by excluding studies at high and unclear risk of bias to ensure our conclusions are robust.
18.	Type and method of review	☒ Intervention ☐ Diagnostic

		☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	November 2021		
22.	Anticipated completion date	June 2022		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** Diabetesupdate@nice.org.uk **5c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: • Caroline Mulvihill • Teuta Gjuladin-Hellon • Miaoqing Yang • Steph Armstrong • Kirsty Hounsell • David Nicholls		

26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	NICE will collaborate with the Cochrane Oral Health group in using the findings from their updated review. Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10158
29.	Other registration details	None
30.	Reference/URL for published protocol	None

31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Periodontitis, periodontal treatment, type 1 diabetes, type 2 diabetes
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☐ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Methods

The evidence presented in this review is based on the systematic review update conducted by Cochrane Oral Health (COH) as part of a collaboration between the NICE Guideline Development Team and Cochrane..

This review entitled “Treatment of periodontitis for glycaemic control in people with diabetes mellitus” (Simpson et al, 2015) was identified as a priority title during the Cochrane Oral Health 2020 prioritisation project. It was conducted using the methods described in detail in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Literature search, screening, and study selection

The literature search, eligibility screening and selection of studies were performed by the COH. Details of the search strategy are reported in Appendix C, included studies are presented in 1.1.4.1 Included studies, the PRISMA diagram in Appendix D and the evidence tables in Appendix E.

Evidence of effectiveness of interventions

Quality assessment

The COH assessed the risk of bias of individual RCTs in accordance with the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (Higgins 2011) against the following risk of bias criteria: random sequence generation; allocation concealment; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; other potential biases. They also included the domains 'blinding of participants' and 'blinding of clinical operators' even though it is not possible to blind participants and personnel due to subgingival instrumentation / scaling and root planing being provided in one arm and not in the other. Each domain was assessed as being at low, high or unclear risk of bias. 'Unclear' indicates either lack of information or uncertainty over the potential for bias and this is presented in Appendix E.

The NICE Guideline Development Team further assessed and classified each individual study into one of three groups for directness, based on whether there were concerns about the relevance of the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Individual RCTs were also quality assessed based on the COH’s judgement for Risk of Bias. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.

- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.

- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

The NICE Guideline Development Team performed quality assessment of the Cochrane's systematic review using the ROBIS tool, which classifies systematic reviews into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.

- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.

- Low quality – It is possible that relevant and important studies have been missed by the review.

In addition, the Cochrane systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matched the specified review protocol in the guideline. The following applicability ratings were used:

- Fully applicable – The identified review fully covers the review protocol in the guideline.

- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.

- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

These assessments are presented in Appendix E.

Using the Cochrane systematic review as a source of data

The use of the Cochrane systematic review as a source of data was based on the criteria of its applicability and quality, as presented in the Table 9:

Table 9: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Quality	Applicability	Use of systematic review
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Data from this systematic review are presented in GRADE tables in the same way as if data had been extracted from primary studies.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). All the outcomes analysed were continuous. Pooled outcomes were expressed as mean differences with their associated 95% confidence intervals.

Fixed-effects models were the preferred choice to report the outcome data from the Cochrane review, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention, or comparator was identified by the reviewer.

- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses are less heterogeneous (with $I^2 < 50\%$) the results from these subgroups were reported using fixed effects models. This may lead to situations where pooled results are reported from random-effects models and subgroup results are reported from fixed-effects models.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence was identified, only pooled results are presented.

In any meta-analyses where some (but not all) of the data came from studies at critical or high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3. Forest plots are presented in Appendix F.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 10. For other continuous outcomes not specified in the table below, no MID was defined.

Table 10: Identified MIDs

Outcome	MID	Source *
HbA1c (presented as a percentage or mmol/l)	0.5 percentage points (5.5 mmol/ mol)	Little 2013
Time in range (%)	5% change in time in range	Battelino 2019
*Full reference provided in reference section.		

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003).

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review makes explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2018)'. As this review is based on Cochrane data from randomised controlled trials, the studies were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 11 below:

Table 11: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.

GRADE criteria	Reasons for downgrading quality
	Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e., the outcome was not statistically significant).

GRADE criteria	Reasons for downgrading quality
	If relative risk could not be estimated (due to zero events in both arms), outcome was downgraded for very serious imprecision as effect size could not be calculated. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Summary of evidence is presented in section 1.1.6. This summarises the effect size, quality of evidence and interpretation of the evidence in relation to the significance of the data.

Evidence was also identified for which GRADE could not be applied due to the lack of data and/or its poor quality. This evidence has been summarised narratively in section 1.1.6. under the subheading Secondary outcomes.

The full GRADE tables can be found in Appendix G.

Publication bias

Publication bias was assessed for the diabetes outcome at 3-4 months by generating a funnel plot (Appendix E), which would indicate potential presence of reporting biases by testing for asymmetry, and via the Egger et al regression asymmetry test (Egger 1997).

Appendix C Literature search strategies

Evidence review on effectiveness of periodontal treatment in improving diabetic control in adults with type 1 or type 2 diabetes.

Clinical search literature search strategy

The search was conducted on 7th September 2021.

The COH searched the following databases, intervention and population terms :

The Cochrane Oral Health Group Trials Register search strategy
#1 (diabet* or IDDM OR DMI OR MODY OR DM2 OR NIDDM OR IIDM):ti,ab
#2 periodont*:ti,ab
#3 (#1 and #2) AND (INREGISTER)
Previous searches of the Cochrane Oral Health Trials Register were carried out using the Procite soMware and the search strategy below:
((diabet* or IDDM OR DMI OR MODY OR DM2 OR NIDDM OR IIDM) and periodont*)
The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy
#1 MeSH descriptor DIABETES MELLITUS explode all trees
#2 (diabet* in Abstract or diabet* in Record Title)
#3 (dka in All Text or iddm in All Text)
(dmi in Record Title or dmi in Abstract)
#5 (mody in All Text or dm2 in All Text or niddm in All Text)
#6 (iidm in Record Title or iidm in Abstract)
#7 insulin* next secret* next dysfunc* in All Text
#8 (insulin* next resist* in Record Title or insulin* next resist* in Abstract)
#9 ((impaired next glucose next tolerance in All Text or glucose next intoleran* in All Text or insulin* next resist* in Record Title) and (DM
in Record Title or DM in Abstract or DM2 in Record Title or DM2 in Abstract))
#10 ((juvenile* in All Text or child* in All Text or keto* in All Text or labil* in All Text or brittl* in All Text or "early onset" in All Text) and
(diabetes in All Text or DM in All Text or DM1 in All Text))
#11 (("keto* prone" in All Text near/6 diabet* in All Text) or (autoimmun* in All Text near/6 diabet* in All Text) or ("auto immun*" in All Text

near/6 diabet* in All Text) or ("sudden onset" in All Text near/6 diabet* in All Text))

#12 ((keto* in All Text and (resist* in All Text near/6 diabet* in All Text)) or (nonketo* in All Text near/6 diabet* in All Text) or (non in All Text

and (keto* in All Text near/6 diabet* in All Text)) or (adult* in All Text and (onset in All Text near/6 diabet* in All Text)) or (matur* in All Text

and (onset in All Text near/6 diabet* in All Text)) or (late* in All Text and (onset in All Text near/6 diabet* in All Text)) or (slow* in All Text and

(onset in All Text near/6 diabet* in All Text)) or (stabl* in All Text near/6 diabet* in All Text))

#13 MeSH descriptor INSULIN RESISTANCE explode all trees

#14 ("insulin* depend*" in All Text or "noninsulin* depend*" in All Text or "non insulin-depend*" in All Text or (typ* in All Text and (I in All

Text near/6 diabet* in All Text)) or (typ* in All Text and (II in All Text near/6 diabet* in All Text)))

#15 ((insulin* in All Text and (defic* in All Text near/6 absolut in All Text)) or (insulin* in All Text and (defic* in All Text near/6 relativ* in All Text)))

#16 ((metabolic* in All Text and syndrom* in Record Title) or (metabolic* in All Text and syndrom* in Abstract) or (plurimetabolic* in All Text and syndrom* in Record Title) or (plurimetabolic* in All Text and syndrom* in Abstract) or (pluri in All Text and metabolic* in All Text and syndrom* in Record Title) or (pluri in All Text and metabolic* in All Text and syndrom* in Abstract))

#17 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)

#18 MeSH descriptor PERIODONTICS explode all trees

#19 MeSH descriptor PERIODONTITISS explode all trees

#20 MeSH descriptor PREVENTIVE DENTISTRY explode all trees

#21 MeSH descriptor Dental Care for Chronically Ill explode all trees

#22 (periodont* in All Text or gingivitis in All Text or gingiva* in All Text)

#23 MeSH descriptor DENTAL PROPHYLAXIS explode all trees

#24 ((scale* in All Text near/6 polish* in All Text) or (scaling in All Text near/6 polish* in All Text) or (root in All Text near/6 plane in All Text)

or (root in All Text near/6 planed in All Text) or (root in All Text near/6 planing in All Text))

#25 MeSH descriptor SURGICAL FLAPS explode all trees

#26 ((#25 or (surgical in All Text and flap* in All Text)) and periodont* in All Text)

#27 ((tooth in All Text near/6 scaling in All Text) or (teeth in All Text near/6 scaling in All Text) or (dental in All Text near/6 scaling in All Text))

#28 ((tooth in All Text near/6 scale* in All Text) or (teeth in All Text near/6 scale* in All Text) or (dental in All Text near/6 scale* in All Text))

#29 ((oral in All Text near/6 prophylaxis in All Text) or (dental in All Text near/6 prophylaxis in All Text))

#30 MeSH descriptor ORAL HYGIENE this term only

#31 MeSH descriptor ORAL HEALTH this term only

#32 (oral next hygien* in All Text or oral next health* in All Text)

#33 (#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32)

#34 (#17 and #33)

MEDLINE via OVID search strategy

1. exp Diabetes Mellitus/

2. diabet$.ab,ti.

3. (DKA or IDDM).mp. or DMI.ab,ti. [mp=title, original title, abstract, name of substance word, subject heading word]

4. (MODY or DM2 or NIDDM).mp. or IIDM.ti,ab. [mp=title, original title, abstract, name of substance word, subject heading word]

5. insulin$ secret$ dysfunc$.ti,ab.

6. insulin$ resist$.ti,ab.

7. ((impaired glucose tolerance or glucose intoleran$ or insulin$ resist$) and (DM or DM2)).ti,ab.

8. insulin$ depend$.mp. or insulin?depend$.ti,ab. [mp=title, original title, abstract, name of substance word, subject heading word]

9. (non insulin$ depend$ or nonisulin$ depend$ or nonisulin?depend).mp. or non insulin?depend$.ti,ab. [mp=title, originaltitle, abstract,

name of substance word, subject heading word]

10.(("typ$ 1" or typ$ I) adj6 DM).ti,ab.

11.(("typ$ 2" or typ$ II) adj6 DM).ti,ab.

12.((juvenil$ or child$ or keto$ or labil$ or brittl$ or earl$ onset) adj6 (DM or DM1)).ti,ab.

13.((keto$ prone or autoimmun$ or auto immun$ or sudden onset) adj6 (DM or DM1)).ti,ab.

14.((keto$ resist$ or nonketo$ or non keto$ or adult$ onset or matur$ onset or late$ onset or slow onset or stabl$) adj6 (DM or DM2)).ti,ab.
5.exp Insulin Resistance/

16.(insulin$ defic$ adj6 (absolut$ or relativ$)).ti,ab.

17.metabolic$ syndrom$.ti,ab.

18.(syndrom$ X not (fragil$ X or X linked)).ti,ab.

19.(plurimetabolic$ syndrom$ or pluri metabolic$ syndrom$).ti,ab.

20.or/1-19

21.exp Periodontics/

22.exp Periodontitiss/

23.exp Preventive Dentistry/

24.exp Dental Care for Chronically Ill/

25.periodont$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

26.Surgical Flaps/

27.surgical flap$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

28.(26 or 27) and periodont$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]

29.exp Dental Prophylaxis/

30.(scale$ adj4 polish$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

31.(scaling adj4 polish$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

32.((root$ adj4 planing) or (root$ adj4 plan$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

33.(gingivitis or gingiva$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

34.((tooth adj6 scaling) or (teeth adj6 scaling) or (dental adj6 scaling)).mp. [mp=title, original title, abstract, name of substance word,

subject heading word]

35.(((tooth adj6 scale$) or teeth) adj6 scale$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

36.(((oral adj3 prophylaxis) or dental) adj3 prophylaxis).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

37.Oral Hygiene/

38.Oral Health/

39.(oral hygien$ or oral health$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

40.or/21-25

41.or/28-40

42.or/40-41

43.20 and 42

The above subject searchwas linkedtotheCochraneHighly Sensitive SearchStrategy (CHSSS)foridentifying randomisedtrials inMEDLINE:

sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011).

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. drug therapy.fs.

6. randomly.ab.

7. trial.ab.

8. groups.ab.

9. or/1-8

10. exp animals/ not humans.sh.

11. 9 not 10

EMBASE via OVID search strategy
1. exp Diabetes Mellitus/

2. diabet$.ab,ti.

3. (DKA or IDDM).mp. or DMI.ab,ti. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug

manufacturer name]

4. (MODY or DM2 or NIDDM).mp. or IIDM.ti,ab. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer,

drug manufacturer name]

5. insulin$ secret$ dysfunc$.ti,ab.

6. insulin$ resist$.ti,ab.

7. ((impaired glucose tolerance or glucose intoleran$ or insulin$ resist$) and (DM or DM2)).ti,ab.

8. insulin$ depend$.mp. or insulin?depend$.ti,ab.

9. (non insulin$ depend$ or nonisulin$ depend$ or nonisulin?depend).mp. or non insulin?depend$.ti,ab.

10. (("typ$ 1" or typ$ I) adj6 DM).ti,ab.

11. (("typ$ 2" or typ$ II) adj6 DM).ti,ab.

12. ((juvenil$ or child$ or keto$ or labil$ or brittl$ or earl$ onset) adj6 (DM or DM1)).ti,ab.

13. ((keto$ prone or autoimmun$ or auto immun$ or sudden onset) adj6 (DM or DM1)).ti,ab.

14. ((keto$ resist$ or nonketo$ or non keto$ or adult$ onset or matur$ onset or late$ onset or slow onset or stabl$) adj6 (DM or DM2)).ti,ab.

15. exp Insulin Resistance/

16. (insulin$ defic$ adj6 (absolut$ or relativ$)).ti,ab.

17. metabolic$ syndrom$.ti,ab.

18. (syndrom$ X not (fragil$ X or X linked)).ti,ab.

19. (plurimetabolic$ syndrom$ or pluri metabolic$ syndrom$).ti,ab.

20. or/1-19

21. exp Periodontics/

22. exp Periodontitis/

23. exp Preventive Dentistry/

24. Dental Care.mp. and Chronic$ ill$

25. periodont$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]

26. (surgical flap$ and periodont$).mp.

27. exp Dental Prophylaxis/

28. (scale$ adj4 polish$).mp.

29. (scaling adj4 polish$).mp.

30. ((root$ adj4 planing) or (root$ adj4 plan$)).mp.

31. (gingivitis or gingiva$).mp.

32. ((tooth adj6 scaling) or (teeth adj6 scaling) or (dental adj6 scaling)).mp.

33. (((tooth adj6 scale$) or teeth) adj6 scale$).mp.

34. (((oral adj3 prophylaxis) or dental) adj3 prophylaxis).mp.

35. Mouth Hygiene/

36. (oral hygien$ or oral health$).mp.

37. or/21-36

38. 20 and 37

The above subject search was linked to the Cochrane Oral Health filter for identifying randomised controlled trials in EMBASE via Ovid:

1. random$.ti,ab.

2. factorial$.ti,ab.

3. (crossover$ or cross over$ or cross-over$).ti,ab.

4. placebo$.ti,ab.

5. (doubl$ adj blind$).ti,ab.

6. (singl$ adj blind$).ti,ab.

7. assign$.ti,ab.

8. allocat$.ti,ab.

9. volunteer$.ti,ab.

10. CROSSOVER PROCEDURE.sh.

11. DOUBLE-BLIND PROCEDURE.sh.

12. RANDOMIZED CONTROLLED TRIAL.sh.

13. SINGLE BLIND PROCEDURE.sh.

14. or/1-13

15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

16. 14 NOT 15

CINAHL via EBSCO search strategy

S1 MH “DIABETES MELLITUS+”

S2 TI diabet*

S3 AB diabet*

S4 DKA or IDDM or TI DMI or AB DMI

S5 MODY or DM2 or NIDDM or TI IDDM or AB IDDM

S6 TI insulin* secret* dysfunc* or AB insulin* secret* dysfunc*

S7 TI insulin* resist* or AB insulin* resist*

S8 impaired glucose tolerance or glucose intoleran* or insulin* resist*

S9 TI DM or AB DM or TI DM2 or AB DM2

S10 S9 and S8

S11 insulin* depend* or AB insulin* depend* or TI insulin* depend*

S12 non insulin* depend* or nonisulin* depend* or non isulin* depend*

S13 "typ* 1" or "typ* I"

S14 TI DM or AB DM

S15 S14 and S13

S16 "typ* 2" or "typ* II"

S17 S16 and S14

S18 TI DM or AB DM or TI DM1 or AB DM1

S19 juvenil* or child* or keto* or labil* or brittl* or "earl* onset”

S20 S19 and S18

S21 keto* prone or autoimmun* or auto immun* or "sudden onset"

S22 S21 and S18

S23 keto resist* or nonketo* or non keto* or "adult* onset" or matur* or "late* onset" or "slow onset" or stabl*

S24 S23 and S18

S25 MH INSULIN RESISTANCE

S26 insulin* defic*

S27 TI metabolic* syndrom* or AB metabolic* syndrom*

S28 syndrom* X not (fragil* X or X linked)

S29 TI plurimetabolic* syndrom* or AB plurimetabolic* syndrom* or TI pluri metabolic* syndrom* or AB pluri metabolic* syndrom*

S30 S29 or S28 or S27 or S26 or S25 or S24 or S22 or S20 or S17 or S15 or S12 or S11 or S10 or S7 or S6 or S5 or S4 or S3 or S2 or S1

S31 MH PERIODONTICS or MH PERIODONTITISS or MH PREVENTIVE DENTISTRY or MH DENTAL CARE FOR CHRONICALLY ILL

S32 periodont*

S33 MH SURGICAL FLAPS or surgical flap*

S34 S33 and S32

S35 MH DENTAL PROPHYLAXIS

S36 scale or scaling and polish

S37 root and plan*

S38 gingivitis or gingiva*

S39 (tooth or teeth or dental) and scal*

S40 (oral or dental) and prophylaxis

S41 MH ORAL HYGIENE or oral hygien* or oral health*

S42 S41 or S40 or S39 or S38 or S37 or S36 or S35 or S34 or S32 or S31

S43 S42 and S30

The above subject search was linked to the Cochrane Oral Health filter for identifying controlled trials in CINAHL:

S1 MH Random Assignment

S2 MH Single-blind studies

S3 MH double-blind studies

S4 MH triple-blind studies

S5 MH crossover design

S6 MH factorial design

S7 multicentre study or multicenter study or multi-centre study or multi-center study

S8 TI random or AB random

S9 TI latin square or AB latin square

S10 TI crossover or AB crossover or TI cross-over or AB cross-over

S11 MH placebos

S12 (singl* or doubl* or trebl* or tripl*) and (blind* or mask*)

S13 MH clinical trials

S14 placebo*

S15 clinical and trial

S16 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15

LILACS via BIREME Virtual Health Library search strategy

diabet$ [Palavras]

and periodont$ [Palavras]

The above subject search was linked to the Brazilian Cochrane Centre filter for identifying randomised controlled trials in LILACS:

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM

ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or

tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw

ciego) or (tw double and tw blind)) and tw clinic$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR

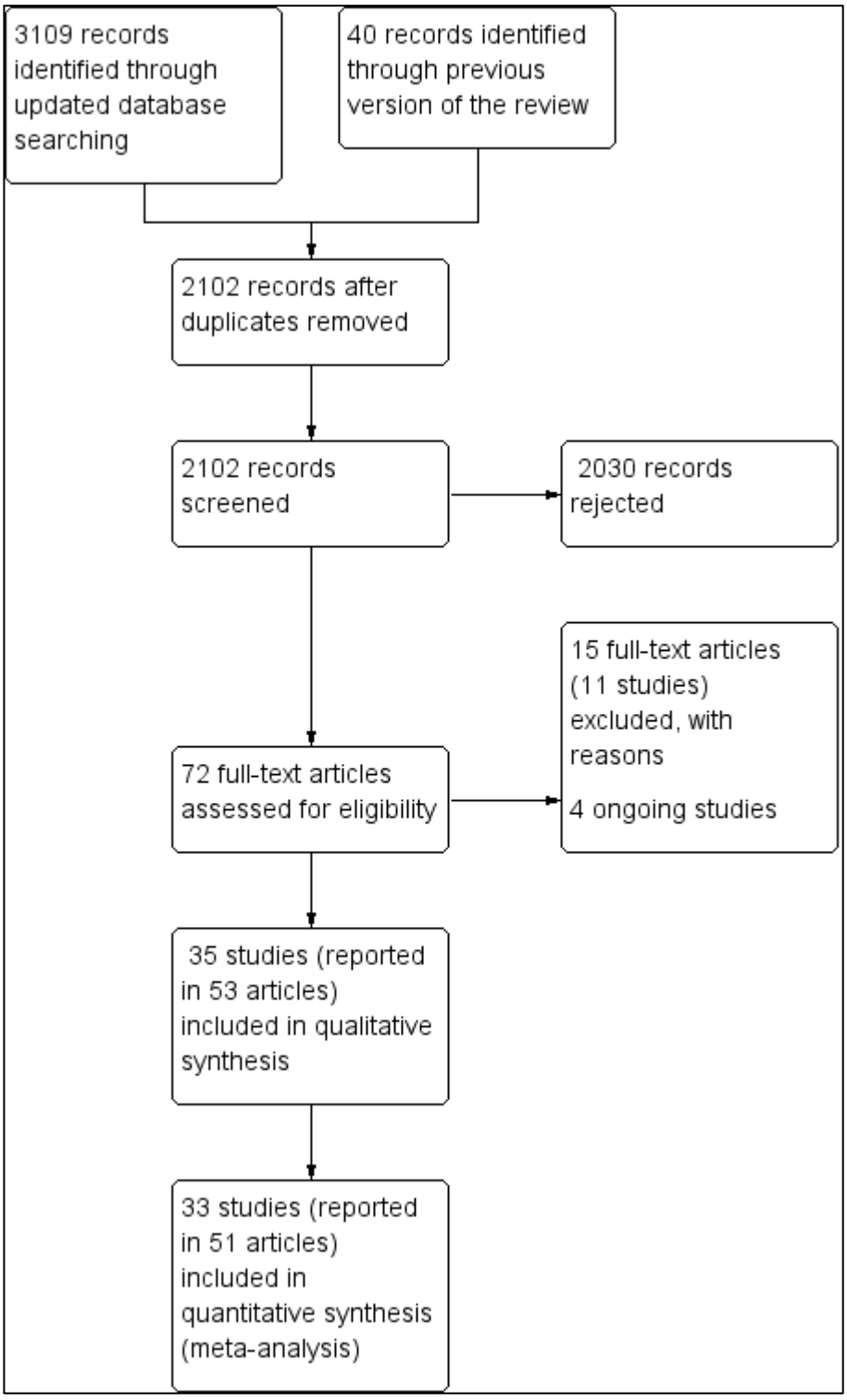
MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Palavras]

ZETOC Conference Proceedings search strategy
diabet* AND periodont*
ISI Web of Knowledge Conference Proceedings search strategy
diabet* AND periodont*

US National Institutes of Health Trials Registry (ClinicalTrials.gov) and WHO International Clinical Trials Registry Platform search strategy
periodontal AND diabetes

Appendix D – Effectiveness evidence study selection

The clinical effectiveness study selection is depicted on the PRISMA diagram bellow.


3109 records identified through updated database searching
40 records identified through previous version of the review
2102 records after duplicates removed
2102 records screened
2030 records rejected
15 full-text articles (11 studies) excluded, with reasons
72 full-text articles assessed for eligibility
4 ongoing studies
35 studies (reported in 53 articles) included in qualitative synthesis
33 studies (reported in 51 articles) included in quantitative synthesis (meta-analysis)

Appendix E – Evidence tables for included studies

The evidence tables, the risk of bias of included studies and publication bias assessment were taken from the Cochrane draft review. These tables cover all the studies included in the Cochrane Review and presented in the evidence review.

Artese 2015	**Artese HPC, Longo PL, Gomes GH, Mayer MPA, Romito GA. Supragingival biofilm control and systemic inflammation in patients with type 2 diabetes mellitus. Brazilian Oral Research (online) 2015;29(1):1-7.**
Study details	Trial design: 2-arm RCT Location: São Paulo, Brazil Number of centres: 1 Recruitment period: February 2011 to December 2013 Funding source: "supported by the Fundação de Amparo à Pesquisa do Estado de SãoPaulo – FAPESP, São Paulo, Brazil, under protocol numbers 2011/06982-4;10057-4;18618-5"
Participants	Inclusion criteria: ≥ 35 years of age, confirmed diagnosis of T2DM for a period of over 3 years, generalised severe chronic periodontitis (number of probing pocket depth [PPD] sites ≥ 30%, clinical attachment level [CAL] > 4 mm, and bleeding on probing), and ≥ 15 teeth Exclusion criteria: pregnant women, smokers, people with body mass index (BMI) > 35 kg/m2 , or those who had received periodontal therapy, systemic antibiotic, or oral antiseptic therapy 6 months prior to the study Age at baseline (yrs): Gp A 54.4 ± 5.8, Gp B 52.0 ± 3.3 Sex (M:F): unclear (authors report Gp A 56.3% female, Gp B 52.0% female) Smoking: none (exclusion criteria) Alcohol consumption: not reported Diabetes type: type 2 DM, diagnosed according to WHO criteria Duration since diabetes diagnosis: minimum of 3 yrs Metabolic control: not reported numerically Other clinical investigations: TNF-α, IL-8, IL-17A, IL-6 MCP-1, ELISA Number randomised: 24 Number evaluated: 24 at 6 months
Interventions	Comparison 1: SRP vs supragingival scaling Gp A (n = 12): supragingival scaling with a shorter appointment ("using an ultrasonic device and periodontal curettes (Hu-Friedy®, Chicago, USA). A Single appointment lasted ~ 60 minutes") Gp B (n = 12): intensive therapy - supragingival and subgingival scaling and root planing with 2 long appointments ("supra- and subgingival scaling and root planing, (in sites with PPD ≥ 4 mm) using an ultrasonic device and periodontal curettes. The

	procedures for the IT group were performed under local anesthesia (3% prilocaine with felypressin), in two appointments lasting ~ 120 minutes each") All participants given OHI every month Duration of follow-up: 6 months "Periodontal therapy was carried out by an experienced periodontist"	
Outcomes measures	Primary: HbA1c Secondary: GBI, VPI, PPD, CAL, BOP. Stratification results presented for PD and CAL. Serum levels of interleukin (IL)-6, IL-17A, IL-8, tumor necrosis factor α(TNF-α), monocyte chemoattractant protein (MCP)-1 enzyme-linked immunosorbent assay (ELISA) Measured at 6 months	
Notes	Sample size calculation: "assuming a reduction of 2 mm in mean pocket depth, with 0.6 mm standard deviation in the IT group, and 1 mm mean pocket depth reduction, with 0.6 mm standard deviation in the ST group (90% statistical power and 5% significance level, the required sample size for each group was determined as 11; 12 participants were recruited to account for potential dropouts and missing data." Data for HbA1c were presented in a graph and it was not possible to extract data from it for inclusion in meta-analysis 1.	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Computer random number generator
Allocation concealment (selection bias)	Low	Allocated by sequentially numbered sealed opaque envelopes
Blinding of participants	High	Not feasible
Blinding of clinical operator	High	Not feasible
Blinding of periodontal outcome assessor	Low	Clinical examinations performed by 2 blinded and calibrated examiners
Incomplete outcome data (attrition bias) All outcomes	Low	All participants accounted for "All patients selected for analysis in the present study completed 6 months of the clinical trial"
Selective reporting (reporting bias)	High	HbA1C was analysed but it was not reported other than in a graph from which data could not be extracted
Other bias	Low	None apparent

Bukleta 2018	Bukleta D, Krasniqi S, Beretta G, Daci A, Nila A, Komoni T, et al. Impact of combined non-surgical and surgical periodontal treatment in patients with type 2 diabetes mellitus-a preliminary report randomized clinical study. Biomedical Research 2017;29(3):633-9.
Study details	Trial design: open label, 4-arm, parallel-group RCT (we included the 2 arms comparing T2DM patients; the other 2 arms compared non-diabetic patients) Location: Endocrinology department of "Peja's Regional Hospital" and Dental Polyclinic in the city of Peja, Slovenia Recruitment period: 2015-16 Funding source: "We would like to thank the Slovenian Human Resources Development and Scholarship Fund (SHRDSF) for the providing scholarship for Dr. Dashnor Bukleta." Aim: "to evaluate the effects of a Non-Surgical Procedure (NSP) in addition to a surgical procedure on systemic inflammation and glycaemic control in patients with T2M and periodontitis and Non-Diabetic (ND) patients with periodontitis"
Participants	Inclusion criteria: age 30-70 yrs, diagnosed with type 2 DM; baseline HbA1c ≥6.5%; at least 10 teeth in the functional dentition (excluding third molars) ; clinical diagnosis of periodontitis with at least 1 site with a probing depth (PD) ≥ 5 mm, 2teeth with attachment loss ≥ 6 mm; no modification in the pharmacological treatment of diabetes during the study period Exclusion criteria: pregnancy or lactation; major diabetic complications; use of antibiotic therapy or non-steroidal anti-inflammatory drug therapy within 4 months before the first visit; and modification in the pharmacological treatment of diabetes during the study period PLEASE NOTE: non-diabetic control arm also reported but not recorded here Age at baseline: 59.49 ± 10.82 across both groups Sex (♂:♀): 50/50 across both groups Smoking: 88 across both groups (also weight, BMI and height recorded as well as oral therapy and insulin) Alcohol consumption: not reported Diabetes type: type 2 DM Duration since diabetes diagnosis: not reported Metabolic control: HbA1c mean % Gp A (test) 9.59 (SD 2.57), Gp B (control) 8.82 (SD 3.01) HbA1c > % Gp A (test group) 9.59 ± 2.57, Gp B (control group) 8.82 ± 3.01 Other clinical investigations: hs-CRP Number randomised: 100 diabetic participants Number evaluated: 100 (50/50) at 3 months
Interventions	Comparison (T2DM subgroups): SRP and tooth extraction vs tooth extraction only Group A – tooth extraction only Group B – tooth extraction and full-mouth SRP

	"...at least one tooth extraction was performed for each patient. Prior to the surgical procedures, an adjunctive, non-surgical periodontal treatment to achieve a full-mouth tooth cleaning was performed for the patients in the treatment groups: Full-Mouth Scaling and Root Planning (FM-SRP) using an ultrasonic device (UDS-J Ultrasonic Scaler, Guilin Woodpecker Medical Instrument) and periodontal curettes for the mechanical debridement of supra and subgingival plaque and calculus. Post-operative rinsing was followed by the use of the antiseptic solution Listerine® (ethanol 21.6%, methyl salicylate 0.06%, menthol 0.042%, thymol 0.064% and eucalyptol 0.092%) as a mouthwash thrice a day for 3 weeks" Duration of follow-up: 3 months	
Outcomes measures	Primary: HbA1c, fasting blood samples for the measurement of high-sensitivity C-Reactive Protein (hs-CRP) Secondary: mean PD, mean attachment level, PI, BOP Measured at baseline and 3 months after treatment	
Notes	Sample size calculation: yes. “A priori sample size calculation was performed given: Effect size δ=0.5, alpha error probability 0.08 and power 0.8 resulting in 26 patients for the group.” The study was registered on Clinical.Trials.gov in 2016 (NCT02874963)	
Risk of Bias	**Authors’ judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Not mentioned
Allocation concealment (selection bias)	Unclear	Not mentioned
Blinding of participants	High	Open label
Blinding of clinical operator	High	Open label
Blinding of periodontal outcome assessor	High	Trial registration states no masking
Incomplete outcome data (attrition bias) All outcomes	High	24 lost to follow-up. Missing data on MAL in control group. Not clear if intention-to-treat analysis was used
Selective reporting (reporting bias)	Low	All prespecified outcomes reported
Other bias	Low	None apparent
Calbacho 2004	**Calbacho V, Carrasco E, Wilckens M, Barboza P, Grant C, Aguirre M, et al. Evaluation of influence of conventional therapy in diabetics type 2. Journal of Dental Research 2004;84((Spec Iss B) Chilean section):65739.**	
Study details	Trial design: 2-arm, parallel-design RCT Location: Chile	

	Setting: primary care Number of centres: not reported Recruitment period: not reported Funding source: not reported
Participants	Inclusion criteria: aged 40-60, diagnosis of T2 DM with poor metabolic control of diabetes and moderate chronic marginal periodontitis diagnosis without treatment of this disease from 1 year or more Exclusion criteria: any other treatment or medication (except diabetes), less than 8 teeth (excluding third molars) Age at baseline (yrs): overall: mean 50.3 (SD 6.2); Gp A mean 52.8 (SD 5.4), Gp B mean 47.8(SD 6.1). No P value reported Sex (M:F): overall 10:14, Gp A 4:8, Gp B 6:6. No P value reported Tobacco use: all non-smokers Alcohol consumption: not reported Diabetes type: all T2 DM Duration since diabetes diagnosis: both groups 10.0 yrs (SD 3.4) Metabolic control: mean HbA1c at baseline: Gp A 7.31% (SD 1.23), Gp B 7.29% (SD 1.55), Gp C 7.25% (SD 1.49) (P > 0.05) Antidiabetic therapy: all in receipt of oral hypoglycaemic medication only HbA1c assessment method: high-performance liquid chromatography Other clinical investigations: mean blood glucose levels Number randomised: 24 (12 per gp) Number evaluated: 24
Interventions	Comparison: SRP + doxycyline versus OHI Gp A: (n = 12) "conventional" periodontal treatment + doxycycline 100 mg daily for 10 days Gp B: (n = 12) OHI only
Outcomes measures	Primary: HbA1c, at baseline, 2 and 4 months Secondary: PPD, PI and BOP
Notes	Only abstract published to date. Full study unpublished. Author states reason as "lack of time to prepare report and excess of work in other areas" Author (Victor Calbacho) provided some details and numerical data via email in May 2013, but his email address is no longer valid, and other authors have been non-responsive to email requests SES: not reported Sample size calculation: not reported Data analysis method: ITT Conflict of interests: not reported Adverse events: not reported

Risk of Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Block randomisation – method unexplained. Quote: "12 were at random assigned to a study group and the rest to a control group"
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low	All completed. ITT analysis
Selective reporting (reporting bias)	High	Secondary outcomes only reported as P values (no means or SDs provided despite repeated email request). Also, no detail of adverse events.
Other bias	Unclear	Insufficient description in abstract and from author's comments to make a judgement
Chen 2012	*** Chen L, Luo G, Xuan D, Wei B, Liu F, Li J, et al. Effects of non-surgical periodontal treatment on clinical response, serum inflammatory parameters, and metabolic control in patients with type 2 diabetes: a randomized study. Journal of Periodontology 2012;83(4):435-43.**	
Study details	Trial design: 3-arm, single-centre, parallel-design RCT Location: Guangzhou Setting: not reported Number of centres: 1 Recruitment period: November 2008 to October 2009 Funding source: 2 grants – both government sponsored: 1) Key Projects in the National Science and Technology Pillar Program (11th 5-year plan periods), Beijing, China and 2) Technology Planning Project of Guangdong Province, China (grant 2010B031600117)	
Participants	Inclusion criteria: diagnosis T2 DM >1 year; no change in TP in the previous 2 months; no major diabetic complication (eg CHD); diagnosis of chronic periodontitis (AAP criteria), ≥16 teeth, ≥1 mm mean CAL; including mild, moderate and severe periodontitis	

	Exclusion criteria: presence of systemic disease other than diabetes that could influence the course of periodontitis; systemic antibiotic administration in last 3 months; pregnancy or lactation; refusal of written consent; active infections other than periodontitis; periodontal treatment in last 12 months Age at baseline (yrs): overall 60.3 (SD 10.02), Gp A mean 59.86 (SD 9.48), Gp B mean 57.91 (SD 11.35), Gp C mean 63.2 (SD 8.51) (P = 0.052) Sex (M:F): overall 66:60, Gp A 23:19, Gp B 26:17, Gp C 17:24 (P = 0.2) Tobacco use: Gp A 7; Gp B 10; Gp C 7 (former smoker: Gp A 1; Gp B 1; Gp C 0) (P = 0.872) Alcohol consumption: Gp A 2; Gp B 4; Gp C 7 (P = 0.169) Diabetes type: 2 Duration since diabetes diagnosis (yrs): Gp A mean 8.69 (SD 5.25); Gp B mean 6.93 (SD 4.31); Gp C mean 9.56 (SD 6.02) (P = 0.066) Metabolic control: mean HbA1c at baseline: Gp A 7.31% (SD 1.23), Gp B 7.29% (SD 1.55), Gp C 7.25% (SD 1.49) (P > 0.05) Antidiabetic therapy: all in receipt of oral hypoglycaemic medication (Gp A 38, Gp B 35, Gp C 36), insulin (Gp A 4, Gp B 5, Gp C 4), or diet (Gp A 0, Gp B 3, Gp C 1) (P = 0.574) Other clinical investigations: gingival recession, FPG (mmol/l), hsCRP (mg/L), TNF-α 9pg/ml), TC (mmol/l), TG (mmol/l), HDL-C (mmol/l), LDL-C (mmol/l) Other medical conditions: none Number randomised: 134 Number evaluated: 126 (loss to follow-up Gp A 3, Gp B 2, Gp C 3)
Interventions	Comparison: SRP + OHI (x 3) + subgingival debridement versus SRP + OHI (x 3) + supragingival prophylaxis versus no intervention Gp A (n = 45): SRP (at baseline; with local anaesthetic, no antibiotics or local antimicrobials, using standard Gracey curettes and ultrasonic instrumentation, and completed in 24 hrs) + OHI (x 3: at 1.5, 3 and 6 months check-ups) + subgingival debridement (at 3 months) Gp B (n = 45): SRP (at baseline; with local anaesthetic, no antibiotics or local antimicrobials, using standard Gracey curettes and ultrasonic instrumentation, and completed in 24 hrs) + OHI (x 3: at 1.5, 3 and 6 months check-ups) + supragingival prophylaxis (at 3 months; no intervention in deep periodontal pockets) Gp C (n = 44): no intervention (delayed treatment until completion of study) Duration of follow-up: 6 months with interim readings taken at 1.5 and 3 months
Outcomes measures	Primary: HbA1c (at baseline, month 1.5, month 3 and month 6) Secondary: PI, BOP, mean PD, sites with PD = 4 to 5 mm, sites with PD ‡6 mm and mean CAL (all at 1.5 months, 3 months and 6 months)
Notes	Sample size calculation: a priori calculation assuming SD of 1% at 80% power – approximately 53 per group

	Data analysis method: per protocol HbA1c assessment method: Boronate-affinity chromatography Conflict of interests: authors report no conflict of interests SES: not reported Adverse events: no adverse events reported by participants	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "...computer-generated list of random numbers prepared by statistician"
Allocation concealment (selection bias)	Unclear	Quote: "Allocation concealed from researcher LC." Allocation overseen by "independent research nurse" Sequentially numbered envelopes used 1-134.Comment: no indication whether envelopes were opaque and sealed
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low	All participants accounted for with reasons provided. Per-protocol analysis
Selective reporting (reporting bias)	Low	No evidence of reporting bias
Other bias	Low	None apparent
D'Aiuto 2018	*** D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. Lancet Diabetes & Endocrinology 2018;6(12):954-65.**	
Study details	Trial design: parallel-group, single-blind (examiner) RCT Location: London, UK Number of centres: 1 Recruitment period: October 2008–October 2012 (4 yrs) Funding source: Diabetes UK and UK NIHR	

Participants	Inclusion criteria: type 2 diabetes (WHO diagnostic criteria) for 6 months or longer, moderate to severe periodontitis (at least or more 20 periodontal pockets with probing pocket depths of more than 4 mm and marginal alveolar bone loss of more than 30%), at least 15 teeth, referred to Eastman Dental Hospital Periodontology Unit, University College Hospital, Ealing and St Mary's Hospitals in London, or from 15 General Medical or dental practices in Greater London area (provided patients were registered with Diabetes Research Network) Exclusion criteria: uncontrolled systemic diseases other than diabetes (cardiovascular diseases including hypertension, liver diseases, pulmonary diseases, end-stage renal failure, or neoplasm), hepatitis B or HIV infection, chronic treatment lasting more than 2 weeks with drugs known to affect periodontal tissues, chronic systemic antibiotic treatment , pregnancy or lactation Age at baseline (yrs): Gp A 58.2 (±9.7), Gp B 55.5 (±10.0) Sex (M:F) Gp A 82:51, Gp B 83:48 Smoking: current Gp A 18, Gp B 19; former Gp A 40, Gp B 42; never Gp A 75, Gp B 70 Alcohol consumption: not reported Diabetes type: type 2 DM Duration since diabetes diagnosis (yrs): Gp A 8.3 (± 7.4), Gp B 8.7 (± 8.4) Metabolic control: Gp A 8.1% (± 1.7), Gp B 8.1% (± 1.7) Other clinical investigations: blood pressure, height, body weight, waist circumference, body fat mass (no data reported) Number randomised: 264 Number evaluated: 264 at 2 months, 6 months and 12 months Numbers lost-to-follow-up: 8 at 2 months (Gp A 5, Gp B 3); 8 at 6 months (Gp A 12, Gp B 8) 12 mths
Interventions	Gp A (n=133) intensive periodontal therapy: essential dental care + OHI + compromised teeth removal (baseline only?); whole-mouth root-surface scaling under local analgesia (at baseline, 2/6/9/12m) subgroup: patients with <20% plaque scores + >1 Gp B (n=131): control - usual care: essential dental care + OHI + compromised teeth removal (baseline only?); full-mouth supragingival scale & polish (at baseline, 2/6/9/12m) Duration of follow-up: 12 months
Outcomes measures	Primary: HbA1c Secondary: recession of gingival margin relative to cementoenamel junction at 6 sites per tooth Periodontal lesions with probing depths of more than 4 mm Supragingival plaque (presence/absence) Adverse effects Quality of life (Audit of Diabetes Dependent Quality of Life; Oral impacts on daily performance, and oral health related quality of life) Diabetic complications

Notes	Sample size calculation: 129 p/gp, for 1% (± 2.1) difference in HbA1c @12m (assuming 10% loss-to-follow-up) Much of the data not in the main paper but in an appendix Conflicts of interests: authors declare no conflict Trial registration: ISRCTN83229304 (retrospectively registered in 2010) Funder stated to have had role in study design, but not in data collection, analyses, interpretation, write-up Trial registration: ISRCTN83229304 (retrospectively registered in 2010 Funder stated to have had role in study design, but not in data collection, analyses, interpretation, write-up.	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Stratified (for diabetes duration, smoking status, sex, periodontitis severity) randomisation by computer-generated table in 1:1 arm distribution ratio
Allocation concealment (selection bias)	Unclear	"Patients were allocated to clinicians in a random order" - conflicting statements, indicates allocation to clinicians rather than treatment? "Allocation to treatment was concealed in an opaque envelope and revealed to the clinician and patient on the day of first treatment" No indication where held/who by and whether windowless
Blinding of participants	High	Participants were not blinded to group allocation
Blinding of clinical operator	High	Dental staff delivering treatment were not blinded to participant group
Blinding of periodontal outcome assessor	High	"With the exception of the study dental staff delivering the treatment and performing the clinical examinations, all other investigators (vascular examiner, nurses collecting anthropometric measures and blood samples, laboratory staff who analysed the serum samples, staff involved with the data collection and analyses, and report authors) were masked to the group allocation."
Incomplete outcome data (attrition bias) All outcomes	Low	ITT analyses undertaken
Selective reporting (reporting bias)	Unclear	Many assessments presented in less accessible appendix publication
Other bias	Low	None apparent

Das 2019	Das AC, Das SJ, Panda S, Sharma D, Taschieri S, Fabbro MD. Adjunctive effect of doxycycline with conventional periodontal therapy on glycemic level for chronic periodontitis with type 2 diabetes mellitus subjects. Journal of Contempory Dental Practice 2019;20(12):1417-23
Study details	Trial design: parallel-group, 3-arm RCT Location: Regional Dental Hospital and Medical College, Guwahati India, Number of centres: 2 Recruitment period: (study performed between) February 2009 to September 2010 Funding source: nil Aim: to assess the use of doxycycline in adjunct to periodontal therapy on the glycemic levels for chronic periodontitis patients with type 2 diabetes mellitus (DM)
Participants	Inclusion criteria: type 2 diabetes with moderate to severe periodontitis (where 30% of teeth have >4mm clinical attachment loss), >30 years of age, no evidence of other oral and systematic diseases, under treatment of endocrinologist Exclusion criteria: uncontrolled DM, undergone perio therapy during last 6 months, antibiotics last 3 months, < 20 teeth, allergic to tetracycline, pregnant and lactating mothers, consuming any tobacco Age at baseline (yrs): Gp A 38±11, Gp B 42±13, GpC 40±12 Sex (M:F) Gp A 10:7, Gp B 8:9, Gp C 11:6 Smoking: all non-smokers Alcohol consumption: not reported Diabetes type: 2 Duration since diabetes diagnosis (yrs): not reported Metabolic control: Gp A 7.58±0.89, Gp B 8.42±1.27, Gp C 8.35±0.96 Other clinical investigations: metabolic parameters FPG, and PPG Number randomised: total 51 (17 per group) Number evaluated: 51 at 3 months (17 per group)
Interventions	Comparison: SRP versus SRP and doxycycline versus no periodontal treatment till 3 months Gp A (SRP) oral hygiene instruction and full mouth SRP (n = 17) Gp B (SRP + doxy): same as Gp A plus 16 doses of doxycycline of 100mg (n = 17) Gp C (control): no treatment control (n = 17) Duration of follow-up: 3 months
Outcomes measures	HbA1c, fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (PPG), PPD, CAL, PI, GI Evaluated at baseline (day 0) and after 3 months (day 90)
Notes	Sample size calculation: “SS of at least 15 patients per group was estimated to achieve 90% power to detect mean difference between groups ($p<0.05$)”

	Abstract conclusion: "The adjunct of doxycycline to conventional periodontal therapy provides additional benefit in reducing glycemic level and improves periodontal health"	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Quote "...randomly categorised into 3 groups by single investigator using block randomisation"
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	The different interventions would be apparent to the participants
Blinding of clinical operator	High	The different interventions would be apparent to the operators
Blinding of periodontal outcome assessor	Unclear	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low	No drop-outs
Selective reporting (reporting bias)	Low	All data reported in full
Other bias	Low	None apparent
El-Makaky 2020	**El-Makaky Y. The effects of non-surgical periodontal therapy on glycemic control in diabetic patients: a randomized controlled trial. Oral Diseases 2020;26(4):822-29. [CRSREF: 19179379; DOI: 10.1111/odi.13256]**	
Study details	Trial design: parallel-group, 2-arm randomised control trial Location: Periodontology Dept, Tanta University, Egypt Number of centres: 1 Recruitment period: June 2015 to March 2016 Funding source: "funded by the authors" Aim: to monitor clinical outcomes and metabolic response of non-surgical periodontal therapy in patients with chronic periodontitis and uncontrolled type 2 diabetes	
Participants	Inclusion criteria: diagnosis of type 2 diabetes for at least 5 years, HbA1c level 7-9%, no changes in diabetes treatment over previous 3 months, 40-70 years old, minimum of 6 teeth excluding third molars. CAL and PD 4 mm in more than 30% of sites, diagnosis with chronic periodontitis, periodontitis diagnosis based on 4 teeth with at least one site with CAL > 3 mm and PPD > 4 mm Exclusion criteria: pregnancy, alcoholism, smoking, presents of systemic disorder other than hypertension and diabetes, major diabetic complications, antimicrobial or periodontal therapy over last 6 months, allergy to metronidazole and amoxicillin	

	Age at baseline (yrs): Gp A 53±7, Gp B 52±7 Sex (M:F) Gp A 18:26, Gp B 20:24 Smoking: all non-smokers Alcohol consumption: not reported (alcoholics excluded) Diabetes type: 2 Duration since diabetes diagnosis (yrs): at least 5 Metabolic control: Gp A 8.12±0.74, Gp B 8.21±0.71 Other clinical investigations: not reported Number randomised: total 88 (44 per group) Number evaluated: 88 at 3 months (44 per group)	
Interventions	Comparison: SRP + antibiotics + OHI Gp A (SRP+ antibiotics) oral hygiene instruction, full mouth SPR, metronidazole 400 mg 3X daily for two weeks and amoxicillin 500 mg 3X daily for 2 weeks (n = 44) ("one-stage scaling and root planning, a combination of systemic antibiotics (amoxicillin 500 mg and metronidazole 400 mg), and oral hygiene instructions") Gp B (control) delayed periodontal therapy control (n = 44) Duration of follow-up: 3 months	
Outcomes measures	Primary: HbA1c Secondary: periodontal attachment level (CAL mm); BOP (% sites); visible plaque index (Y/N); PPD mm Measured at baseline and 3 month	
Notes	Sample size calculation: not reported First sentence of Results: "None of the patients in the test group reported significant side effects after periodontal therapy."	
Risk of Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low	Quote "...closed envelopes were used by the study coordinator to randomly allocate the patients to the test and control group"
Allocation concealment (selection bias)	Unclear	Quote: "The random series was hidden from the principal investigator who screened the patients. The same periodontics specialist treated all the patients in both groups."
Blinding of participants	High	The different interventions would be apparent to the participants.
Blinding of clinical operator	High	The different interventions would be apparent to the operators.

Blinding of periodontal outcome assessor	Low	"single blinded" "clinical parameters in both studied groups were recorded by the same examiner (SH) who was blinded to metabolic parameter data and the intervention protocol"
Incomplete outcome data (attrition bias) All outcomes	Low	All data reported in full
Selective reporting (reporting bias)	Low	No drop-outs
Other bias	Low	None apparent
Engebretson 2013	**Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, et al. The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. JAMA 2013;310(23):2523-32.**	
Study details	Trial design: 2-arm, multicentre, parallel-design RCT Location: USA Setting: Community Number of centres: 5 - diabetes and dental clinics and communities associated with academic medical centres (deliberately selected for geographic diversity): University of Alabama, Birmingham, Alabama; University of Minnesota and Hennepin County Medical Center, Minneapolis, Minnesota; University of Texas Health Science Center, San Antonio, Texas; Stony Brook University, New York; University of Texas Health Science Center, Houston, Texas Recruitment period: November 2009 – March 2012 (originally designed to run until May 2012). Enrolment stopped earlier than anticipated due to futility. Trial stopping rule based on power threshold of 40% demonstrating interim test statistic of < -0.12t-test for HbA1c was -0.37, consequently monitoring board recommended cessation of recruitment Funding source: 2 x NIH/NIDCR grants: U01 DE018902 (awarded to S Engebretson); U01 DE018886 (awarded to L Hyman) No detail re: provider/manufacturer of chlorhexidine mouthrinse to compare to conflict of interests declarations	
Participants	Inclusion criteria: age 35 yrs or over; with physician-diagnosed type 2 diabetes (duration of >3 months); an HbA1c value between 7-<9% at screening; under care of physician for management of diabetes; diagnosed with moderate-advanced chronic periodontitis (CAL/PD >5 mm in 2 or > quadrants); minimum of 16 natural teeth; received no periodontal treatment in prior 6 months; and agreed to continue current diabetes medications (unless medically indicated otherwise); and avoid pregnancy during the trial period Exclusion criteria: treatment required for extensive caries, abscess, or oral infection; limited life expectancy (<1 year); diabetes-related emergency in prior 30 days; NSAID use (>7 days in prior 2 months. Except low-dose aspirin: 75-325 mg/d); systemic immunosuppressant use; systemic antibiotic use (>6 days during 30 days after enrolment); receiving dialysis; increased risk of bleeding complications; heavy alcohol consumption (mean >2 drinks/day for females and >3 drinks/day for males)	

	Age at baseline (yrs) overall: mean 57.3 (SD 10.1), Gp A mean 56.7 (SD 10.5), Gp B mean 57.9 (SD 9.6). No P value reported Sex (M:F): overall: 277:237, Gp A 143:114; Gp B 134:123. No P value reported Tobacco use: Gp A: never 129, former 89, current 39; Gp B: never 144, former 86, current 27 Weight: Gp A mean 99.5 kg (SD 24.3), Gp B mean 97.5 kg (SD 21.7) BMI: Gp A 34.7 (SD 7.5), Gp B 34.2 (SD 6.7) Alcohol consumption: not reported Diabetes type: all T2 DM Duration since diabetes diagnosis (yrs): Gp A mean 12.3 (SD 8.2), Gp B 11.3 (SD 8.4) Metabolic control: Overall: <7.0% 22; >7.0%-<8.0% 297; >8.0%-<9.0% 179; >9.0%-<10.0% 16 Gp A: <7.0% 12; >7.0%-<8.0% 143; >8.0%-<9.0% 93; >9.0%-<10.0% 9 Gp B: <7.0% 10; >7.0%-<8.0% 154; >8.0%-<9.0% 86; >9.0%-<10.0% 7 Antidiabetic therapy: all but 11 participants (2% of 514 participants) were in receipt of oral hypoglycaemic medication, insulin, or combination treatment. Overall: no diabetes medications 11; oral agents only 244; insulin only 80; combination of medications 179Gp A: no diabetes medications 7; oral agents only 117; insulin only 40; combination of medications 93Gp B: no diabetes medications 4; oral agents only 127; insulin only 40; combination of medications 86 Other investigations: change in insulin, fasting glucose levels, HOMA2 scores and diabetes medication from baseline; participants requiring periodontal/diabetes rescue therapy Other medical conditions: Overall: angina 32; myocardial infarction 43; stroke 24; hypertension 364; kidney disease 26 Gp A: angina 21; myocardial infarction 22; stroke 12; hypertension 180; kidney disease 14Gp B: angina 11; myocardial infarction 21; stroke 12; hypertension 184; kidney disease 12 Number randomised: 514 (Gp A 257, Gp B 257) Number evaluated: ITT analysis (HbA1c outcome only):Baseline, 3 and 6 months: Gp A 257, Gp B 257 Per-protocol analysis (all outcomes – all participants with HbA1c data at 6-month visit):Baseline: Gp A 240, Gp B 2353 months: Gp A 233, Gp B 227 (missed 3-month visit: Gp A 6, Gp B 7. Periodontal data missing: Gp A 1, Gp B 1)6 months: Gp A 240, Gp B 233 (periodontal data missing: Gp A 0, Gp B 2)
Interventions	Comparison: SRP (x 3) + OHI (x 3) + chlorhexidine (0.5 oz bid) versus OHI (x 3) Gp A (n = 257): SRP (at baseline, 3 and 6 months: initial SRP >160 min treatment with local anaesthesia over 2 or more sessions, and completed within 42 days of initial baseline visit; SRP at 3 and 6 months comprised of a single 1 hour session each time) + OHI and provision of 0.12% chlorhexidine gluconate oral rinse (0.5 oz twice daily for 2 weeks), toothbrush, toothpaste, and dental floss

	Gp B (n = 257): OHI at baseline, 3 months and 6 months (followed by offer of SRP after 6-month visit) Duration of follow-up: 6 months	
Outcomes measures	Primary: HbA1c Secondary: GI, BOP, PPD and CAL Measured at baseline, 3 and 6 months)	
Notes	Sample size calculation: 468 participants required (90% power: 2-tailed, 2-sample t-test, .05 type I error). Accounting for attrition rate of 20%, planned sample size was 600 (300 in each arm) Data analysis: ITT (periodontal data provided per-protocol analysis; however, all periodontal parameters provided as tertiles, therefore not able to use per-protocol data in meta-analysis) SES: ethnicity data provided Overall: Black 146; White 280; Hispanic 166; other 88Gp A: Black 76; White 140; Hispanic 81; other 41Gp B: Black 70; White 140; Hispanic 85; other 47 Adverse events: Quote: "No study-related serious adverse events occurred" Reported symptoms were consistent with common discomfort following SRP Diabetes rescue therapy required by 1.7% in Gp A (4/241), and 2.1% in Gp B (5/236) during the trial Change in medication from baseline required by 45.0% in Gp A (105/233), and 40.2% in Gp B (92/229) HbA1c assessment method: Whole-blood samples iced and analysed within 4 days by high-performance liquid chromatography (Tosoh HPLC G7 Glycohemoglobin Analyzer, Tosoh Medics Inc) Conflict of interests: No conflict declaration from lead author (Dr Engebretson), but available for others: Quote: "Dr Gelato reported receiving travel/meeting expenses from the Endocrine Society. Dr Seaquist reported serving as a board member and President Elect of Science and Medicine for the American Diabetes Association; serving as a consultant for AMG Medical, Sanofi-aventis, SkyePharma, and Merck; receiving grants or grants pending from the American Diabetes Association, Eli Lilly, and the National Institutes of Health; and receiving payment for lectures from the Japan Diabetes Society, the American Diabetes Association, Intellyst Medical Education, Pediatric Academic Societies, the Association of Specialty Professors, and the International Society for Neurochemistry. Dr Lewis reported receiving a grant or grant pending from Novo Nordisk. Dr Katancik reported serving as a consultant for the Texas Healthy Baby Initiative 2011 and receiving a grant or grant pending, and travel/meeting expenses, fromZimmer Dental. Dr Paquette reported serving as a board member for Colgate-Palmolive; receiving a speakers honorarium from Colgate-Palmolive; and serving as a consultant for MIS Implant Technologies" Trial ID: NCT00997178 (trial referred to as Diabetes and Periodontal Therapy Trial (DPTT))	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "Randomization was conducted centrally by the CC using a site-specific randomization assignment sequence generated prior to the start of the study. Assignments to the Treatment and Control Groups were created through a custom

		computer program using a permuted block randomization scheme stratified by Clinical Site using block sizes of 2, 4 or 6"
Allocation concealment (selection bias)	Low	Quote: "..randomization assignments by individual participant were accessible in Velos eResearch only to the necessary CC personnel and the Clinical Site Coordinators. Participant IDs did not contain treatment assignment codes" "Once eligibility for an individual was confirmed, the CC Study Coordinator generated the randomization assignment electronically and notified the Clinic Coordinator by email or fax. The Clinic Coordinator then contacted the participant with the treatment group assignment. No other Clinical Site personnel other than the Study Therapist were informed of the assignments"
Blinding of participants	High	Quote: "Double masking would have required us to provide some type of "sham" periodontal therapy to control participants, which, to the best of our knowledge, had not been done in any previous trial in periodontology" "Periodontal therapy also frequently results in gingival (gum) recession and tooth sensitivity, especially to hot and cold temperatures. Treatment also removes the discolored calcified deposits that form at and just beneath the gum line. These signs and symptoms, which can be readily noticed by patients, would not be expected following some type of "sham" treatment. Thus, it is unlikely that the provision of a sham treatment would adequately mask control participants either"
Blinding of clinical operator	High	Quote: "An endpoint of treatment is the complete removal of hard and soft deposits from the tooth and root surfaces. Thus it is not possible to mask therapists"
Blinding of periodontal outcome assessor	Low	Quote: "Periodontal examiners and laboratory personnel who performed the HbA1c analyses were masked to treatment group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low	93% completed the study (476/514), similar retention across both arms Gp A: 240/257 (93.4%); Gp B: 236/257 (91.8%). ITT analysis of HbA1c data. Periodontal data provided per-protocol analysis
Selective reporting (reporting bias)	Low	All reported (albeit via supplementary material available online). Adverse events reported
Other bias	Unclear	Conflict of interest declaration reported for all authors except lead author
Felipe 2015	**Felipe MEMC. Effect of non-surgical periodontal treatment on glycemic control, inflammatory mediators and adipokines in patients with type 2 diabetes and severe chronic periodontitis (Thesis) [Efeito do tratamento periodontal não-cirúrgico sobre o controle glicêmico, mediadores inflamatórios e adipocinas em pacientes com diabetes mellitus**	

	tipo 2 e periodontite crônica severa]. Rio de Janeiro 2015;pesquisa.bvsalud.org/portal/resource/pt/biblio-910208 (accessed 1 September 2021).
Study details	Trial design: 2-arm RCT Location: University Hospital Pedro Ernesto/UERJ, Brazil Number of centres: 1 Recruitment period: 14 months (October 2013 – December 2014) Funding source: none declared
Participants	Inclusion criteria: diagnosis of T2 DM; minimum treatment time for DM of 1 year; severe chronic periodontitis (AAP); minimum 10 teeth present; at least 2 sites with PD ≥ 6mm and 2 sites with CAL ≥ 5mm Exclusion criteria: periodontal or antibiotic therapy within the last 6 months; presentation with rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis or Chron´s disease. Age at baseline (yrs): Gp A 58.1 ± 8.4, Gp B 54.1 ± 9.9 (P = 0.26) Sex (M:F): Gp A 11:10, Gp B 14:6 (P = 0.2) Smoking: not reported Alcohol consumption: not reported Duration since diabetes diagnosis: not reported No of standing teeth: Gp A 21.4 ± 3.7, Gp B 18.2 ± 4.9 HbA1c Gp A 7.1% ± 1.9, Gp B 8.2% ± 2.3 Other clinical investigations: periodontal clinical examination Number randomised: 41 Number evaluated: 41 at 3 months (21/20)
Interventions	Comparison: Gp A (n = 21) oral hygiene advice + non-surgical supra and subgingival scaling under local anaesthesia Gp B (n = 20) no treatment up to the 90th day of study Duration of follow-up: 3 months Data extraction by translator Professor Sinval A Rodrigues Junior
Outcomes measures	Primary: HbA1c Secondary: clinical periodontal parameters (PD, CAL, BOP, PI), inflammatory markers (interleukin - 1β and -6, tumor necrosis factor-α, resistin, leptin and adiponectin), other markers (total cholesterol (TC), HDL, LDL and triglycerides)
Notes	Sample size calculation: no rationale Intra and interrater agreement of 88% and 73%, respectively, for PD and CAL No protocol registration

Risk of Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	"Participants were randomly allocated to groups" – no description
Allocation concealment (selection bias)	Unclear	No description
Blinding of participants	High	No description, but not possible
Blinding of clinical operator	High	No description, but not possible
Blinding of periodontal outcome assessor	High	"The clinical periodontal exam was performed by two examiners (ME and RM) previously calibrated… All patients were treated by examiner RM, while examiner ME monitored the patient management and blood collection." The clinical operators were the outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear	"Two patients from the control group and three from the test group did not show up for the second blood exam. Only one patient from the control group did not show up to the clinical periodontal exam and was excluded" – no reason given for the losses
Selective reporting (reporting bias)	Low	All outcome data reported for both groups
Other bias	Unclear	Hypertension, heart disease, smoking habit, family history, medicine use and lifestyle data unreported.
Gay 2014	**Gay IC, Tran DT, Cavender AC, Weltman R, Chang J, Luckenbach E, et al. The effect of periodontal therapy on glycaemic control in a Hispanic population with type 2 diabetes: a randomized controlled trial. Journal of Clinical Periodontology 2014;41(7):673-80.**	
Study details	Trial design: 2-arm, single-centre, parallel-design RCT Location: USA Setting: Hospital Number of centres: 1, University of Texas Health Science Center, Houston, Texas Recruitment period: not reported Funding source: "...funded by National Institutes of Health Clinical and Translational Award ULI RR024148 and KL2 RR024149 from the National Center for Research Resources"	

Participants	Inclusion criteria: >18 yrs old; diagnosed T2 DM; possessing HbA1c value >6.5% at screening (although initial values of 5.7-6.5% were included if taking hypoglycaemic medication: n = 16 (note: unsure of allocation between groups)); Hispanic; presence of local or general severe chronic periodontitis (AAP criteria) Exclusion criteria: smokers; dental treatment within prior 12 months; systemic antibiotics within 6 months of recruitment (not specified if a pre- or post-recruitment requirement) Age at baseline: overall: mean 52.8 yrs (SD 9.7), Gp A mean 51.5 (SD 9.0), Gp B 54.0 (SD 10.2). No P value reported Sex (M:F): overall 55:71, Gp A 30:36, Gp B 25:35. No P value reported Tobacco use: smokers were excluded from participation in the trial Weight: not reported BMI: not reported Alcohol consumption: not reported Diabetes type: all T2 DM Duration since diabetes diagnosis: not reported Metabolic control: mean HbA1c at baseline - Gp A 9.00% (SD 2.30), Gp B 8.40% (SD 2.00) Antidiabetic therapy: all except 26 participants (21% of 126) were in receipt of "diabetic treatment" with no further description: Gp A 78.8% (52), Gp B 80.0% (48). Of diabetic treatment recipients, 21 were on insulin therapy: Gp A 21% (14); Gp B 12% (7) Other investigations: distance from free gingival margin to cementoenamel junction (FGM-CEJ) Other medical conditions: not reported Number randomised: 154 (Gp A 77, Gp B 77) Number evaluated: 126 (Gp A 66, Gp B 60) Note: All data (including baseline) only presented for evaluated participants, rather than those randomised Attrition: Gp A: dropped out 2; lost to follow-up 8 (1 participant not accounted for); Gp B dropped out 12; lost to follow-up 2; excluded for unreliable data 2 (1 participant not accounted for)
Interventions	Comparison: SRP + OHI (x 2) versus OHI Gp A (n = 77): OHI at baseline (including modified Bass technique, interdental brush/floss use), + SRP 4-6 weeks later (ultrasonic scaler, Gracey curettes, on 2 quadrants, local anaesthetic, by 2 calibrated periodontists) when OHI repeated Gp B (n = 77): OHI at baseline (including modified Bass technique, interdental brush/floss use), + repeat OHI 4-6 weeks later Duration of follow-up: 4 months
Outcomes measures	Primary: HbA1c (at baseline and 4 months) Secondary: BOP, PD and CAL (at baseline and 1 month)
Notes	Sample size calculation: 123 participants required (90% power: 2-sided t-test, .05 type I error). Accounting for attrition rate of 20%, planned sample size was 154 (77 in each arm) Data analysis: per protocol SES: not reported specifically except that all participants were of Hispanic origin

	Adverse events: not reported Change in medication from baseline required by Gp A 27.3% (18), Gp B 21.7% (13) HbA1c assessment method: Afinion AS100 Analyzer. High value samples run in duplicate, and several other samples run in duplicate for compliance Conflict of interests: authors declare no conflict of interests Trial ID: NCT01128374	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Computer-randomised sequence generation Quote: "Permuted blocks randomization with varying block sizes using Stata 11 was performed by a statistician (DT) to generate allocation sequences"
Allocation concealment (selection bias)	Low	Quote: "These sequences were used by the research coordinator (AC) to recruit and blindly randomize 154 participants either to a control (n = 77) or experimental group (n = 77) with a 1:1 allocation ratio" Assumed adequate
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	Not reported
Incomplete outcome data (attrition bias) All outcomes	High	All data (including baseline) only presented for evaluated (n = 126) patients, rather than those randomised (n = 154) 1 participant from each group not accounted for Attrition: Gp A: dropped out 2; lost to follow-up 8 (1 participant not accounted for); Gp B: dropped out 12; lost to follow-up 2; excluded for unreliable data 2 (1 participant not accounted for) Per-protocol analysis
Selective reporting (reporting bias)	Unclear	All initially stated outcomes reported on in results/tables, albeit only including those evaluated. No adverse events reported
Other bias	Low	No other apparent biases
Jones 2007	*** Jones JA, Miller DR, Wehler CJ, Rich SE, Krall-Kaye EA, McCoy LC, et al. Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study. Journal of Clinical Periodontology 2007;34(1):46-52.**	

Study details	Trial design: 2-arm, multicentre, parallel-design RCT (at 4 months) Location: USA Setting: Primary care Number of centres: 4, New England Recruitment period: not stated Funding source: grants from Veterans Affairs Health Services Research and Development Service and Boston University (VA HSR&D QUERI DII-99.206 and NIH K24 DE00419). Dentsply International provided ultrasonic scalers, and Colgate Oral Pharmaceuticals provided the Gluconate rinse (PerioGards)
Participants	Inclusion criteria: a repeat HbA1c of 8.5% or above; a minimum of 8 natural teeth; periodontal treatment need as evidenced by the Community Periodontal Index of Treatment Need CPITN scores of 3 or 4 in at least 2 sextants on examination; and sufficient health and willingness to complete the 12–16-month study Exclusion criteria: grave medical or psychiatric illness or severe immune compromise (eg HIV or cancer) Age at baseline (yrs): mean 58.36. Gp A 57.79, Gp B 58.96. 4-month gp 58.08, 12-month gp 58.39 Sex (M:F): Overall 97%:3%; Gp A 100%:0%; Gp B: 94%:6% Tobacco use: Overall: 24%; Gp A: 29.5%; Gp B: 18.8% Alcohol consumption: Overall 1.8 drinks p/wk (SD 5), Gp A 2.2 drinks p/wk (no SD), Gp B 1.43 drinks p/wk (no SD) Diabetes type: assumed majority T2 DM Quote: "Because all participants were veterans whose admission to military service was on the basis of their health, and thus developed diabetes after the beginning of military service, we reasoned that the vast majority of them had Type 2 diabetes" Duration since diabetes diagnosis (yrs): Gp A 11.4, Gp B 14.1 (no SDs provided by group) Metabolic control: poor mean HbA1c at baseline - Gp A 10.07%, Gp B 10.29% Antidiabetic therapy: all in receipt of oral hypoglycaemic medications, insulin, or combination Other medical conditions: many comorbidities (comorbidity index: Gp A 5.95, Gp B 6.11), high levels of hypertension, hypercholesterolaemia, obesity, atherosclerosis Number randomised: 193 Number evaluated: 165 (Gp A 82, Gp B 83)/132 depending on outcome
Interventions	Comparison: SRP + doxycycline + chlorhexidine rinse versus usual treatment Gp A (n = 98): SRP + doxycycline (100 mg qid for 14 days) + chlorhexidine rinse (0.12% twice daily for 4 months) Gp B (n = 95): usual treatment (described only as "usual medical and dental care") Duration of follow-up: 4 months
Outcomes measures	Primary: change in HbA1c (not fully reported) Secondary: GI, gingival recession
Notes	Sample size calculation: "The study was designed to have 300 participants. Allowing for 33% attrition, we expected 200 patients studied, 100/group. We anticipated 80% power to detect a moderate-sized effect (ES δ=0.40) of the intervention in 2-

	sided tests at the 5% level. For the analysis at 4 months comparing the proportion of patients in Early Treatment and Usual Care groups who experienced a greater than 1% drop in their HbA1c levels, we expected similar power" Data analysis: per protocol Adverse events:Chlorhexidine: disturbance in taste (15%); tooth staining (13.6%); sore mouth/tongue irritation (5%); swelling of lips, face, tongue and throat also reported in a small number of participants. Also shortness of breath Doxycyline: diarrhoea (7.1%); abdominal pain (3.6%); nausea (2.9%) "Compliance with the study drug regimen was not universal. Eighty-three percent used both chlorhexidine and doxycycline, another 8% used chlorhexidine only, and 7% used doxycycline only. Thus, over 90% in the treatment group used each study drug. Among users of chlorhexidine, 17 participants reported less than daily use, 19 reported daily use, and 29 reported twice daily use. One chlorhexidine user had four bottles left, nine had two to three bottles left, 16 had one left, and 41 used all the chlorhexidine. Among doxycycline users 50 reported using all the pills, two had 10 pills left (of 14), and five had more than 10 pills left" SES: race is reported, although only as % of white participants: Overall 97%; Gp A 84%, Gp B 79% HbA1c assessment method: not reported Conflict of interests: not reported Means data for analysis provided by lead author in 2007	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "We used PROC PLAN in Statistical Analysis Systems (SAS) Version 8.1, Cary, NC, USA) to obtain 12 blocks of eight, using a seed of 020348. Group assignments were put on white cards and sealed in white envelopes and numbered consecutively. Study staff took the top envelope to assign study group"
Allocation concealment (selection bias)	Low	See above
Blinding of participants	High	Participants knew which group they are allocated to
Blinding of clinical operator	High	Quote: "...by seeking physicians' concurrence, in essence we notified each participant's primary care provider that his or her patient's diabetes was under poor control. Because of this notification, some providers likely became more aggressive in treating these patients"
Blinding of periodontal outcome assessor	Low	Quote: "The study examiner...did not know to which study group participants were assigned
Incomplete outcome data (attrition bias) All outcomes	High	193 participants recruited, 28 excluded after randomisation for reasons not related to interventions. Numbers from each group not reported. 165 in study providing baseline data then 33 withdrawals, reasons given but not by group

		Potentially, such high drop-out rates within the short study duration may reflect the reported adverse events experienced by Gp A (relating to doxycycline and chlorhexidine) Per-protocol analysis: not all participants analysed in groups randomised to, regardless of intervention actually received
Selective reporting (reporting bias)	High	No mean HbA1c values at 4 months reported, only 2 dichotomous outcomes. No reporting of SD for each group, only overall reported Author supplied means and SDs in correspondence Adverse events only reported for Gp A All characteristics data (including baseline) only presented for evaluated patients (varies for each characteristic) (n = 154-165), rather than those randomised (n = 193) 1 patient from each group not accounted for
Other bias	High	Baseline differences with respect to smoking, history of stroke, TIAs, diabetes with nephropathy. Unclear what usual care could be
Kapellas 2017	**Kapellas K, Mejia G, Bartold PM, Skilton MR, Maple-Brown LJ, Slade GD, et al. Periodontal therapy and glycaemic control among individuals with type 2 diabetes: reflections from the PerioCardio study. International Journal of Dental Hygiene 2017;15(4):e42-e51.**	
Study details	Trial design: 2-arm RCT Location: Australia's Northern Territory Number of centres: 4 locations Recruitment period: June 2010-January 2012 (with final annual assessment in December 2012) Funding source: the National Health and Medical Research Council: Project grant #627100. MRS is supported by a Future Leader Fellowship from the National Heart Foundation of Australia #100419. KK received a University of Adelaide Divisional Scholarship to participate in this research	
Participants	Inclusion criteria: Aboriginal Australian participants aged 18 years or older without a previous history of cardiovascular disease, a minimum of 5 natural teeth and moderate/severe periodontitis defined using the joint Centers for Disease Control and Prevention and American Academy of Periodontology case definition Exclusion criteria: individuals receiving periodontal treatment in the preceding 6 months, those with cardiovascular disease history, rheumatic fever or any other medical condition requiring preventive antibiotic prophylaxis, pregnant women, or people with clinically visible endodontic or orofacial infections Age at baseline: Gp A 45.5 ± 10.9, Gp B 46.4 ± 9.1	

	Sex (♂:♀) Gp A 18:17, Gp B 17:10 Smoking: smoker/ex-smoker/never Gp A 12/2/13, Gp B 7/6/3 Alcohol consumption: not recorded Diabetes type: 2 Duration since diabetes diagnosis: Gp A, ± Gp B ± Metabolic control: HbA1c Gp A 70.3 mmol/mol 8.6% ± 4.4, Gp B 60.8 mmol/mol 7.7% ± 4.0 Other clinical investigations: C-reactive protein (CRP)IL-6, total cholesterol, HDL cholesterol, BMI, waist-to hip ratio Number randomised: 62 (Gp A 35, Gp B 27) Number evaluated: 44 at 3 months (Gp A 24, Gp B 20)	
Interventions	Comparison: single episode of non-surgical periodontal therapy comprising supra- and subgingival scaling using hand instruments and ultrasonic device under LA versus delayed treatment (12 months) Gp A (n= 35) Gp B (n= 27) Duration of follow-up: 3 months	
Outcomes measures	Primary: HbA1c Secondary: gingival bleeding, PPD ≥4mm, CAL ≥3mm no of sites of each /total sites	
Notes	Sample size calculation: post hoc power calculation for change in HbA1c at 3 months using the two sample means feature of PROC POWER in SAS 9.3 for Windows, Cary, N.C., USA	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Randomised on 1:1 basis to either intervention or control group using permuted block randomisation with variable block sizes, stratified by recruitment location. Randomisation database created by member of the Clinical Trials branch, Baker IDI Heart and Diabetes Institute, Melbourne, who had no other involvement
Allocation concealment (selection bias)	Low	Allocated by study clinicians unaware of block sizes by entering study participant ID and date of baseline measure into randomisation database
Blinding of participants	High	Stated that not blinded
Blinding of clinical operator	High	Stated clinicians not blinded
Blinding of periodontal outcome assessor	High	Stated dental clinicians not blinded. Inter-examiner kappa score 0.75 [95% CI 0.70-0.80]
Incomplete outcome data (attrition bias) All outcomes	High	18 lost to follow-up

		Treatment: 11 (10 loss-to-follow up, 1 withdrawn) Control: 7 (6 loss-to-follow up, 1 moved away)
Selective reporting (reporting bias)	Low	All outcomes reported
Other bias	Low	None apparent
Katagiri 2009		
Study details	Trial design: 2-arm, multicentre, parallel-design RCT Location: Japan Setting: Hospital Number of centres: 5 diabetic clinics: Tokyo Medical and Dental University Hospital, Kagoshima University Medical and Dental Hospital, Aichi Gakuin University Dental Hospital, Tokyo Medical University Hospital and Kyoto Prefecture Medical University Hospital. Recruitment period: not reported Funding source: supported by Grants-in Aid from the Ministry of Health and Welfare of Japan (H16- Iryo-020) and the Mitsui Sumitomo insurance foundation	
Participants	Inclusion criteria: Aged 39–75 years, HbA1c 6.5–10.0%; at least 11 remaining teeth, at least 2 pocket sites with probing depth 4 mm or more (indicated as mild to severe periodontitis), no periodontal treatment during the preceding 6 months Exclusion criteria: Severe diabetic complications; evidence of systemic diseases other than diabetes as a risk factor for periodontitis; systemic antibiotics during the preceding 3 months; pregnancy or lactation; allergy to tetracycline; smoking; modifications in the treatment of diabetes during the preceding 2 months Age at baseline: Overall: 59.7 yrs (SD 7.4); Gp A: mean 60.3 yrs (SD 9.9); Gp B: mean 59.0 yrs (SD 4.8) Sex (M:F): Overall: M27:F22; Gp A: M21:F11; Gp B: M6:F11 Tobacco use: Non-smokers Alcohol consumption: Not stated Diabetes type: T2 DM Duration since diabetes diagnosis: Gp A: 11.3 yrs (SD 6.4); Gp B: 8.8 yrs (SD 7.5) Metabolic control: Good mean HbA1c at baseline: Gp A: 7.2 (SD 0.9); Gp B: 6.9 (SD 0.9) Antidiabetic therapy: All in receipt of oral hypoglycaemic medication, insulin, or diet Diet: Overall: n = 3; Gp A: n = 1; Gp B: n = 2 Oral hypoglycaemic medication: Overall: n = 27; Gp A: n = 15; Gp B: n = 12 Insulin: Overall: n = 19; Gp A: n = 16; Gp B: n = 3 Other medical conditions: None reported	

	Number randomised: 49 (Gp A 32; Gp B 17) Number evaluated: 49	
Interventions	Comparison: SRP + minocycline + OHI versus OHI Gp A (n = 32): Mechanical debridement of the subgingival plaque and calculus was performed using piezoelectric ultrasonic scalers, and 10 mg of minocycline ointment (Periofil1, Showa Yakuhin Co., Tokyo, Japan) was administered topically in every periodontal pocket at the end of each visit. The intensive periodontal treatment was completed over the course of 4 visits within 2 months. Additional periodontal treatment including instructions for brushing, supra- and sub-gingival debridement without topical administration of antibiotics were performed, if necessary Gp B (n = 17): Instructions for brushing their teeth, including the use of interproximal cleaning aids, such as floss and interdental brushes, depending on their individual needs After the completion of 2 months of intensive period periodontal treatment, all participants visited the respective medical and dental clinics at 1, 3 and 6 months Duration of follow-up: 6 months	
Outcomes measures	Primary: HbA1c at 1 month, 3 months and 6 months Secondary: change in PPD at 1 month (Delta PPD), change in BOP at 1 month (Delta BOP) and intervention of periodontal treatment on the change in HbA1c at 6 months	
Notes	Sample size calculation: Not reported Data analysis: ITT HbA1c assessment method: High-performance liquid chromatography (Kyotokagaku Co, Japan) Adverse events: Not reported SES: Not reported Conflict of interests: Authors declare no conflict of interests	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Quote: "randomly allocated by envelope method" - method of sequence generation not described
Allocation concealment (selection bias)	High	Envelope method. Dentists knew the allocations to each group (from correspondence with the author)
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	Not mentioned

Incomplete outcome data (attrition bias) All outcomes	Low	All randomised participants included in outcome evaluation. ITT analysis
Selective reporting (reporting bias)	Unclear	HbA1c not reported by group but details later supplied by the lead author. Adverse events not reported.
Other bias	Low	None apparent
Kaur 2015	**Kaur PK, Narula SC, Rajput R, K Sharma R, Tewari S. Periodontal and glycemic effects of nonsurgical periodontal therapy in patients with type 2 diabetes stratified by baseline HbA1c. Journal of Oral Science 2015;57(3):201-11.**	
Study details	Trial design: double-blind (operator and assessor), parallel, 5-arm RCT (stratified by poor and good glcaemic control) Location: Dept of Periodontics and Oral Implantology, Rohtak, India Number of centres: 1 Recruitment period: 23 month duration (Feb 2010-Jan 2012) Funding source: none declared	
Participants	Inclusion criteria: receipt of treatment for at least 1yr after T2DM diagnosis, aged 45-60yrs, presence of ≥12 teeth (excluding third molars), no change in medication use (oral hypoglycemics/insulin/etc.) in 2 months prior or during study, clinical diagnosis of moderate or severe generalised chronic periodontitis. Exclusion criteria: cardiovascular disease, chronic respiratory disease, rheumatoid arthritis, systemic disease influencing periodontitis course, pregnancy, lactating, current/ex smokers, major diabetic complications, use of systemic antibiotics in prior 3 months, periodontal treatment in prior 6 months Age at baseline (yrs): Gp A 51.82 ± 5.85, Gp B 52.94 ± 6.03 Sex (M:F) Gp A 22:28, Gp B 26:24 Smoking: "current or past smokers were excluded from our study" Alcohol consumption: not reported Diabetes type: type 2 DM Duration since diabetes diagnosis (yrs): Gp A 8.57 ± 6.39, Gp B 7.05 ± 4.43 HbA1c (%; mean ± SD): Gp A 8.17 ± 2.49, Gp B 7.87 ± 2.56 Other clinical investigations: FPG, PPG Number randomised: 100 Number evaluated: 3 months 100, 6 months 100 Attrition: Gp A 5 LTFU (non-attending), Gp B 4 LTFU (non-attending)	
Interventions	Comparison: SRP versus no treatment Gp A (n=50): SRP (4 sessions over 2 wks, additional supportive SRP as necessary during study) + OHI (at each visit) Gp B (n=50): no intervention (delayed treatment until completion of study)	

	Duration of follow up: 6 months	
Outcomes measures	Primary: HbA1c Secondary: PI, GI, PPD, CAL, BOP Assessed at baseline, 3 months and 6 months	
Notes	Sample size calculation: on the basis of an expected mean difference in HbA1c of approximately 0.4% between groups and a standard deviation of 0.4, they calculated that at least 22 patients would be required in each group to detect a difference with 90% power and a two-sided type 1 error of 5% Compliance and AEs seem not to have been assessed nor reported	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	May be computerised. Not clear if re-randomised to treatment and non-treatment groups after initial stratification but minimisation appears to have occurred
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Low	"Periodontal treatment of patients in treatment groups was carried out by a different trained examiner (PKK) to avoid any bias in the evaluations." "A single examiner (SCN) blinded to the group allocation, was responsible for recording periodontal parameters throughout the study."
Incomplete outcome data (attrition bias) All outcomes	Low	"The nine patients who withdrew after 3 months (five from T group and four from NT group) were included in intention-to-treat analysis by carrying their last observation forward."
Selective reporting (reporting bias)	Low	All assessed outcomes fully presented
Other bias	Low	None apparent
Kiran 2005	**Kiran M, Arpak N, Unsal E, Erdogan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. Journal of Clinical Periodontology 2005;32(3):266-72.**	
Study details	Trial design: 2-arm, single-centre, parallel-design RCT Location: Turkey Setting: Hospital	

	Number of centres: 1, Ankara University Faculty of Medicine, Department of Metabolic Diseases and Endocrinology Recruitment period: Not reported Funding source: Not reported
Participants	Inclusion criteria: Patients with type 2 DM with glycated haemoglobin (HbA1c) values: 6%-8%; creatinine values o1.4 mg/dl; liver function tests not > 3 x the normal range Exclusion criteria: Major diabetic complications; systemic antibiotics administered within prior 3 months; periodontal treatment within prior 6 months Sex (M:F): Overall: M18:F26; Gp A: M10:F12; Gp B: M8:F14 Age at baseline: Overall 54.39 yrs (SD 11.27); Gp A: mean 55.95 yrs (SD 11.21); Gp B: mean 52.82 yrs (SD 12.27) Tobacco use (daily): Overall: n = 7 (15.9%); Gp A n = 5 (22.7%); Gp B n = 2 (9.1%) Alcohol consumption: Not reported Diabetes type: T2 DM Duration since diabetes diagnosis: Overall mean 8.68 yrs (SD 7.18). Gp A: 9.32 yrs (SD 11.21); Gp B: 8.05 yrs (SD 5.90) Metabolic control: mean HbA1c at baseline. Mean HbA1c at baseline: Gp A: 7.31% (SD 0.74); Gp B: 7.00% (SD 0.72) Antidiabetic therapy: All in receipt of oral hypoglycaemic medication (Gp A: 64%; Gp B: 72%), insulin (Gp A: 9%; Gp B: 9%), diet (Gp A: 9%; Gp B: 5%) or combination (Gp A: 18%; Gp B:14%). No P values presented Other clinical investigations: Gingival recession; fasting plasma glucose; 2-hour post-prandial glucose; total cholesterol; triglyceride; HDL-cholesterol (HDL); LDL-cholesterol (LDL); microalbuminurea Other medical conditions: None reported Number randomised: 44 Number evaluated: 44
Interventions	Comparison: SRP + OHI versus no intervention Gp A (n = 22): OHI and full mouth SRP performed under local anaesthesia Gp B (n = 22): No periodontal treatment during study period (delayed treatment offered, if required, after conclusion of study) Duration of follow-up: 3 months
Outcomes measures	Primary: HbA1c, at baseline, at 1 month and 3 months Secondary: PI, GI, PPD, CALs, and BOP were recorded at baseline, at 1 month and 3 months
Notes	Sample size calculation: Not reported Data analysis: ITT HbA1c assessment method: Not reported SES: Not reported Adverse events: Not reported Conflict of interests: Not reported

	Clarification supplied by author Note: teeth with periapical lesions were allocated additional treatment: Gp A: 9 patients, 9 teeth: 4 extractions, 5 root canal treatment Gp B: 5 patients, 5 teeth: 5 root canal treatment	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "A list was prepared in advance using random numbers. The list was transferred to a series of sealed envelopes each containing the allocation on the card" (from correspondence with a co-author)
Allocation concealment (selection bias)	Low	Quote: "The clinician opened the envelope in the series when the patient entered the trial" (from correspondence with a co-author)
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Low	"The examining investigator was unaware of group assignments"
Incomplete outcome data (attrition bias) All outcomes	Low	ITT analysis, although subjects who had surgical treatment were excluded from statistical analysis. All participants underwent periodontal examination at baseline and 9/22 and 5/22 had periapical lesions requiring treatment prior to study start. Correspondence with co-author indicates: "HbA1c data was recorded for all 44 trial participants, 22 for test and 22 for control patients. There were no patients lost in the follow up period"
Selective reporting (reporting bias)	Low	All planned outcomes reported
Other bias	Low	None apparent
Koromantzos 2011	*** Koromantzos PA, Makrilakis K, Dereka X, Katsilambros N, Vrotsos IA, Madianos PN. A randomized, controlled trial on the effect of non-surgical periodontal therapy in patients with type 2 diabetes. Part I: effect on periodontal status and glycaemic control. Journal of Clinical Periodontology 2011;38(2):142-7.**	
Study details	Trial design: 2-arm, single-centre, parallel-design RCT Location: Greece Setting: Hospital Number of centres: 1, outpatient university diabetes clinic, Laiko Hospital, Athens	

	Recruitment period: January 2006 to December 2008 Funding source: European National Fund and National Resources (EPEAEK 2 PYTHAGORAS)
Participants	Inclusion criteria: diabetes type: type 2 DM with HbA1c levels ranging from 7-10%; moderate-to severe periodontitis; > 16 teeth present; PPD with at least 8 sites ≥ 6 mm and CAL ≥ 5 mm in at least 4 sites distributed to at least 2 quadrants Exclusion criteria: systemic antibiotic usage in last 3 months; non-surgical periodontal treatment during last 6 months; surgical periodontal treatment over last 12 months; current medication including usage of calcium channel blockers, phenytoin or cyclosporine; history of stroke or acute cardiovascular event over the past 12 months; renal dysfunction determined by creatinine levels > 1.5 mg/dl or liver dysfunction defined as AT/ALT levels > 2.5 times ULN Age at baseline: overall: mean 59.52 yrs (SD 8.88); Gp A: mean 59.62 yrs (SD 7.95); Gp B: mean 59.42 yrs (SD 9.8) Sex (M:F): overall M33:F27; Gp A M17:F13; Gp B M16:F14 Tobacco use: recorded at 3 levels – current, ex and non Gp A: 4(13.3%)/13(43.3%)/13(43.3%); Gp B: 7(23.3%)/16(53.3%)/7(23.3%) Alcohol consumption: Not recorded Duration since diabetes diagnosis: overall 7.8 yrs (SD 5.7); Gp A 7.76 yrs (SD 4.3); Gp B 7.84 yrs (SD 6.8) Metabolic control: mean HbA1c at baselineMean HbA1c at baseline: Gp A 7.87% (SD 0.74); Gp B 7.59 (SD 0.66) (P value not reported) Antidiabetic therapy: insulin Gp A 12/30 (40%), Gp B 7/30 (23.3%) (P value not reported); OHA Gp A 21/30 (70%), Gp B 27/30 (90%) (P value not reported) Mean BMI (kg/m2): Gp A 27.76 (SD) 3.68, Gp B 27.51 (SD) 3.83 (P value not reported) Mean remaining teeth 23.52 (SD) 3.99, 24.23 (SD) 3.78 (P value not reported) Other clinical investigations: total cholesterol, total triglycerides, LDL-cholesterol, HDL-cholesterol Number randomised: 60 Number evaluated: 60 (4 lost to follow-up in Gp A, 3 in Gp B)
Interventions	Comparison: SRP + OHI versus supragingival cleaning + OHI Gp A (n = 30): OHI (at baseline, 1 month and 3 months) + SRP (2 sessions, 1 week apart at baseline, using ultrasonic scaler and hand instruments, under local anaesthesia) + additional supportive SRP (at 1 month and 3 months) if required Gp B (n = 30): OHI (at baseline, 1 month and 3 months) + supragingival cleaning (described as "supragingival removal of all deposits (plaque and calculus) with an ultrasonic scaler." Delayed SRP provided to all after conclusion of study) Duration of follow-up: 6 months
Outcomes measures	Primary: HbA1c (recorded at baseline, 1 month, 3 and 6 months) Secondary: CAL, PPD, BOP and GI (recorded at baseline, 1 month, 3 and 6 months)
Notes	Sample size calculation: 19 required in each arm to detect mean difference reduction in HbA1c between groups of 0.4% (90% power, 2-sided type 1 error of 5%) HbA1c assessment method: high-performance liquid chromatography

	Data analysis: ITT SES: all Greek patients, no further details Adverse events: not reported Conflict of interests: authors declare no conflict of interests Notes: Gp A: 2/30 had extractions at baseline	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Computer assignment undertaken by 1 author (PK) before recruitment using a computer programme Quote: "The randomization sequence was generated by one author (P.K.) before patient recruitment. Numbers from 1 to 60 were assigned to patients according to their recruitment date (first recruited patient would be number 1 and last would be number 60). Random assignment into two groups of 30 patients each was then accomplished with the use of a computer program"
Allocation concealment (selection bias)	Low	4 containers numbered 1-60, designated for each visit of each patient maintain masking Quote: "Containers (numbered 1–60, four for each visit of each patient) were designated to maintain examiner blinding"
Blinding of participants	High	Not possible Quote from correspondence with author: "Every patient after the screening examination was assigned to control or treatment groups according to their rank in that sequence (first that was recruited, 2nd, 3rd etc.). The participants did not know what category they were assigned in until they received SRP or prophylaxis, they were informed that they would have treatment at the beginning or at the end of the study"
Blinding of clinical operator	High	Quote from correspondence with author: "The periodontist that performed SRP or prophylaxis (same for all patients, P.K.) knew the allocation group of the patients, right after the baseline visit"
Blinding of periodontal outcome assessor	Unclear	"Patients were examined dentally through the course of the study by the same examiner"
Incomplete outcome data (attrition bias) All outcomes	Low	100% completion. ITT analysis

Selective reporting (reporting bias)	Unclear	No change data for triglycerides, total cholesterol, LDL-cholesterol and HDL-cholesterol. Adverse events not reported Quote from correspondence with author: "...in our study we divided pocket depth and CAL in 3 categories, (percentage of shallow, medium and deep pockets) and there is no available information in overall pocket depth or CAL." Despite this, PPD and CAL data not considered to be a source of bias
Other bias	Low	No other apparent biases
Kothiwale 2013	**Kothiwale SV, Kothiwale VA, Bhargava PV. Effect of non-invasive periodontal therapy on glycaemic control in type 2 diabetes mellitus patients - a randomized control trial. Diabetes 2013;62(Suppl 1):Abstract No A229. [**	
Study details	Trial design: 2-arm, single-centre, parallel-design RCT Location: India Setting: Hospital Number of centres: 1, Department of Periodontics, KLE VK Institute of Dental Sciences, Belgaum Recruitment period: Unknown Funding source: Unknown	
Participants	Inclusion criteria: aged 25 or older; known cases of type 2 diabetes (minimum duration of 2 years); possessing >20 natural teeth; and receiving oral hypoglycaemic medications Exclusion criteria: history of smoking, haemoglobinopathies, or hypertension; receiving insulin therapy, renal dialysis or requiring hospitalisation; undergone periodontal therapy in prior 6 months; antibiotic/anti-inflammatory drugs taken in prior 3 months; have abnormal hepatic function; pregnant or lactating Age at baseline: Gp A: mean 57.7 yrs (SD 8.61); Gp B: mean 56.4 yrs (SD 11.53) Sex (M:F): Overall: M32:F18; Gp A: M15:F10; Gp B: M17:F8 Tobacco use: Excluded from participation if possess history of smoking Weight: Not reported BMI: Gp A: 23.7 (SD 1.92); Gp B: 23.85 (SD 1.65) Alcohol consumption: Not reported Diabetes type: All T2 DM Duration since diabetes diagnosis: Gp A: mean 5.3 yrs (SD 2.76); Gp B: 5.2 yrs (SD 2.20) Metabolic control: Mean HbA1c at baseline: Gp A: 8.16 (SD 0.61); Gp B: 7.94 (SD 0.66) Antidiabetic therapy: all in receipt of oral hypoglycaemic medication. Quote: "The oral hypoglycemic drugs for diabetes, diet and physical therapy was unchanged throughout the course of the study as monitored by the physician" Other investigations: change in periodontal status (by CPI and LOA scores) Other medical conditions: not reported	

	Number randomised: 50 (Gp A n = 25; Gp B n = 25) Number evaluated: not reported	
Interventions	Comparison: SRP + OHI versus no treatment Gp A (n = 25): SRP after baseline examination (by ultrasonic scaler, hand scaler and curette across varying numbers of sessions - dependent of treatment needs of individual patients), followed a further SRP session (unspecified time point) by same investigator, and provision of OHI Gp B (n = 25): No treatment (followed by SRP and OHI after end of study) Duration of follow-up: 3 months	
Outcomes measures	Primary: Change in HbA1c from baseline to 3 months Secondary: None	
Notes	Sample size calculation: Not reported Data analysis: Per-protocol SES: Education status data provided: Overall: Illiterate n = 11 (22%); primary school n = 14 (28%); high school n = 15 (30%); graduate n = 10 (20%)Gp A: Illiterate n = 5 (20%); primary school n = 10 (40%); high school n = 6 (24%); graduate n = 4 (16%)Gp B: Illiterate n = 6 (24%); primary school n = 4 (16%); high school n = 9 (36%); graduate n = 6 (24%) Adverse events: Not reported HbA1c assessment method: High-pressure liquid chromatography (HPLC) Conflict of interests: Not reported	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Simply states 50 patients randomly assigned into 2 groups. No indication of method
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not reported, but assumed not possible as only intervention group patients would have received care
Blinding of periodontal outcome assessor	Unclear	Not reported
Incomplete outcome data (attrition bias) All outcomes	High	No patient flow provided or any drop-outs indicated, although states "After the non-surgical therapy was completed, patients were revaluated for surgical

		treatment needs. The data concerning the group of patients who had surgical treatment were excluded in the statistical analysis" Per-protocol analysis: not all participants analysed in groups randomised to regardless of intervention actually received.
Selective reporting (reporting bias)	Low	Planned outcomes reported on
Other bias	Unclear	None apparent; however, it is unpublished data, and therefore without peer review. Author indicated intention to publish study in full in near future
Lee 2020	**Lee JY, Choi YY, Choi Y, Jin BH. Efficacy of non-surgical treatment accompanied by professional toothbrushing in the treatment of chronic periodontitis in patients with type 2 diabetes mellitus: a randomized controlled clinical trial. Journal of Periodontal Implant Science 2020;50(2):83-96.**	
Study details	Trial design: preliminary report of a double-blinded 3-arm parallel RCT Location: Community Healthcare Centre in Gwangjin-gu Public Health Centre, Seoul, Korea Number of centres: 1 Recruitment: June 2013 - June 2014 Funding source: supported by the Health Promotion Fund, Ministry of Health and Welfare, Republic of Korea (#13-15) Aim: to evaluate clinical benefit of additional toothbrushing accompanying non-surgical periodontal treatment on oral and general health in patients with T2DM	
Participants	Inclusion criteria: teeth with sites with a PD >5 mm and attachment loss in at least 2 quadrants; BOP at these sites; at least 20 remaining teeth; 4). HbA1c level ≥ 6.5%; non-smoking status; diagnosed with periodontitis Exclusion criteria: current abuse of alcohol or drugs; chronic liver disease including hepatitis; body mass index (BMI) ≥40 kg/m2 Patients' age, BMI, HbA1c level, endotoxin level, interleukin-1 beta (IL-1β) level, and oral health status were recorded Number randomised: 75 (25 per gp) Number evaluated: 60 (20 per gp) Age at baseline (yrs): Gp A SRP = 71.15±8.61, GpB SRPAT = 72.45±8.20, GpC Control = 74.15±7.21 Sex (M:F): GpA 10:10, Gp B 10:10, Gp 10:10 Smoking: excluded Alcohol consumption: not reported Diabetes Type: T2DM diagnosed as per WHO criteria Duration since diabetes diagnosis: not reported Metabolic control: HbA1c at baseline Gp A 6.64± 0.29, Gp B 6.68±0.23, Gp C 6.76±0.39 HbA1c >/= 6.5 % Other clinical investigations: Number randomised: 75	

	Number evaluated: 60 at 3 months (20 per gp)	
Interventions	SRP vs SRPAT vs control SRPSRP with additional toothbrushing (SRPAT) group (additional toothbrushing by toothpick methods - Watanabe method - once a week from the first visit through the fifth visit) Control GpA SRP: after a baseline oral examination, oral health education including toothbrush instruction was conducted to eliminate bias in oral health behaviours. In the SRP group, supragingival scaling was performed only on the first visit by 2 trained dentists working together simultaneously. After 2 weeks, root planing was performed to remove the subgingival calculus. At 12 weeks, patients were recalled to re-check their oral health status. If they required additional periodontal treatment, it was done at 12 weeks. GpB SRPAT: after a baseline oral examination, oral health education including toothbrush instruction was conducted to eliminate bias in oral health behaviours. In the SRPAT group, additional toothbrushing (Watanabe method) with a 2-row toothbrush was applied on the first visit by a trained dentist. On the second visit, subgingival calculus was removed as appropriate according to the patient's oral health condition. Additional toothbrushing (Watanabe method) was performed once a week from the first visit through the fifth visit. GpC Control: group received no other treatments beyond medical screening for diabetes. However, all groups received oral health education including toothbrush instruction at the baseline visit to eliminate intergroup bias associated with routine oral health behaviours. Gp A (n=25) Gp B (n=25) Gp C (n=25) Duration of follow-up: 3 months	
Outcomes measures	Changes in HbA1c levels, serum endotoxin levels, interleukin-1 beta levels Periodontal health status: PPD, calculus index, BOP Primary: HbA1c Secondary: IL-1β, Endotoxin, PD, CI (calculus index), BOP (%) Measured up to 12 weeks following treatment	
Notes	The paper is described as a 'preliminary report'. Sample size calculation: "We estimated that a total of 72 patients with diabetes would be needed to detect a difference among 3 groups, with an α of 0.05, a (1-β) of 0.80, and an effect size of 0.40, with a drop-out rate of 10%."	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Not described
Allocation concealment (selection bias)	Unclear	Not described
Blinding of participants	High	

Blinding of clinical operator	High	
Blinding of periodontal outcome assessor	Unclear	All microbiological and immunological laboratory procedures were performed by blinded analysts. Do not know about periodontal outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear	"15 participants dropped out of the study (Figure 1) due to old age and the long intervention period" 5 participants from each group
Selective reporting (reporting bias)	Low	None noted
Other bias	Low	None apparent
Li 2011	**Li Z, Sha YQ, Zhang BX, Zhu L, Kang J. [Effect of community periodontal care intervention on periodontal health and glycemic control in type 2 diabetic patients with chronic periodontitis]. [Chinese]. Beijing da Xue Xue Bao (Yi Xue Ban/Journal of Peking University. Health Sciences) 2011;43(2):285-9.**	
Study details	Trial design: 3-arm, multicentre, parallel-design RCT Location: Peking, China Setting: Community Number of centres: 6 community healthcare centres Recruitment period: Not reported Funding source: National Key Project of Science and Technical Supporting Programs of China, National Natural Science Foundation of China, "211" Project Foundation, Mega-projects of Science Research for the 10th Five-year Plan	
Participants	Inclusion criteria: Type 2 DM (the diagnostic criteria was 1999 WHO DM diagnostic criteria) with chronic periodontitis (at least 1 tooth with PD ≥3 mm and AL ≥3 mm). The number of residual teeth must have exceeded 16 and no receipt of any periodontal treatment within 1 year Exclusion criteria: Aggressive periodontitis, severe chronic or debilitating disease; long-term usage of antibiotics or steroids Age at baseline: Gp A: 60.86 yrs (SD 10.22); Gp B: 64.21 yrs (SD 5.99); Gp C: 61.64 yrs (SD 9.6) Sex (M:F): Overall M28:F38; Gp A M9:F13; Gp B M8:F11;Gp C M11:F14 Tobacco use: Gp A (9.1%); Gp B (15.8%); Gp C (12%) Alcohol consumption: Not reported Diabetes type (I/II): Gp A (0/22); Gp B (0/19); Gp C (0/25) Duration since diabetes diagnosis: Gp A 6.5 (SD) 5.1 yrs; Gp B 8.84 (SD) 5.77 yrs; Gp C 7.92 (SD) 5.14 yrs Metabolic control: Mean HbA1c at baseline: Gp A: 7.64 (SD 1.77); Gp B: 8.15 (SD 1.97); Gp C: 8.12 (SD 1.88) Antidiabetic therapy: Gp A (oral hypoglycaemic agents: 77.3%/insulin injection: 27.3%); Gp B (78.9%/21.1%); Gp C (76%/16%)	

	Other clinical investigations: FBG (fasting blood glucose); modified bleeding index Other medical conditions: Diabetes complications Gp A (27.3%); Gp B (21.1%); Gp C (32%) Number randomised: 66 Number evaluated: Not reported	
Interventions	Comparison: Non-surgical periodontal treatment versus supragingival scaling versus no intervention Gp A (n = 22): Periodontal initial therapy: periodontal non-surgical treatment given by periodontists (details not given) Gp B (n = 19): Professional mechanical tooth cleaning: coronal/supragingival scaling given by oral hygienists (details not given) Gp C (n = 25): Non-clinical therapy: no active intervention Duration of follow-up: 6 months	
Outcomes measures	Primary: HbA1c (at baseline, 6 weeks, 3 and 6 months) Secondary: Probing depth, attachment loss, plaque index - change data only for periodontal parameters	
Notes	Sample size calculation: Not reported Data analysis: Assumed ITT SES: Not reported Adverse events: Unknown, was a stated secondary outcome in paper HbA1c assessment method: Not reported Conflict of interests: Not reported Translation by Chunjie Li, May 2014	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	"randomized" - No further information
Allocation concealment (selection bias)	Unclear	No information
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	"blinded" - no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear	No information
Selective reporting (reporting bias)	Unclear	No information

Other bias	Unclear	No way to verify if other biases exist due to translation of data extraction components
Mauri-Obradors 2018	**Mauri-Obradors E, Merlos A, Estrugo-Devesa A, Jané-Salas E, López-López J, Viñas M. Benefits of non-surgical periodontal treatment in patients with type 2 diabetes mellitus and chronic periodontitis: a randomized controlled trial. Journal of Clinical Periodontology 2018;45(3):345-53.**	
Study details	Trial design: single-blind 2-arm RCT Location: not clear - University Hospital Barcelona, Spain Number of centres: 3 Recruitment period: 6 months Funding source: partially funded by a research grant from SEPA and by a research grant from the University of Barcelona	
Participants	Inclusion criteria: type 2 diabetes (diagnosed at least 1.5 years prior the study) and generalised chronic periodontitis (Armitage, 1999) at least 9 teeth present and >30% of the probed gingiva with a depth and clinical attachment level ≥4 mm Exclusion criteria: antibiotic treatment during the previous 15 days or for periods >10 days during the last 3 months, non-surgical periodontal treatment within the past 6 months, pregnancy, significant changes in diabetes medication during the course of the study, and evidence of other serious systemic disease (ASA III or IV) Age at baseline (yrs): Gp A 61 ± 11, Gp B 62 ± 10 Sex (♂:♀): Gp A 17:25, Gp B 20:28 Smoking: smoker/ex-smoker/never Gp A 15/13/14, Gp B 3/22/23 Alcohol consumption: not reported Diabetes type: 2 Duration since diabetes diagnosis (yrs): Gp A 10, Gp B 11 (median) Metabolic control: mean HbA1c % 7.7 (SD 1.13) Other clinical investigations: bacterial assays (P. intermedia, A. actinomycetemcomitans, P. gingivalis, T. forsythia) DNA and PCR testing Number randomised: 90 Number evaluated: 80 at 3 months, 79 at 6 months	
Interventions	Comparison: Test: SRP and OHI (48) Control: OHI (modified Bass technique) and supragingival plaque and calculus removal with ultrasonic scaler (42) Duration of follow-up: 6 months	
Outcomes measures	Primary: HbA1c, fasting plasma glucose Secondary: bacterial assessment, PPD, PI, GI	

	Measured at baseline, 3 months and 6 months. HbA1c at 3 months not reported or provided	
Notes	Sample size calculation: power calculation using expected 0.8% improvement in HbA1c in test and 0.45% in control. Also planned for 20% drop out during study Severity of periodontitis. Discussion only mentioned moderate periodontitis Treatment protocol did not indicate thoroughness of OHI, and did not mention interdental cleaning instruction - only modified bass technique No indication as to who did the SRP and their level of training Limited information on delivery of SRP Other data form: Sample size calculation: Up to a 0.80% improvement of HbA1c levels was expected in the TG and a 0.45% in the CG (response to hygiene control and dental intervention). With a power of 80% and an α-error of 5%, and accepting an α-risk 0.05 and a β-risk of <0.2 in a bilateral contrast, 36 patients would be needed in each group to detect statistically significant differences. An estimated rate of 20% loss of patients during follow-up was considered. Thus, a total of 48 patients were assigned to CG and the rest (42) to the TG	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Computer generated
Allocation concealment (selection bias)	Unclear	Not mentioned
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Low	Single examiner blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear	11 dropouts (4 Gr A 7 Gr B)
Selective reporting (reporting bias)	High	Not all periodontal data reported BoP not recorded just GI. No assessment of plaque control reported Full mouth PPD reported rather than breakdown of change in moderate and deep pockets. Difficult to assess the quality of the treatment provided HbA1c not reported or provided at 3 months, although article implies it was measured

Other bias	Low	None apparent
Mizuno 2017	**Mizuno H, Ekuni D, Maruyama T, Kataoka K, Yoneda T, Fukuhara D, et al. The effects of non-surgical periodontal treatment on glycemic control, oxidative stress balance and quality of life in patients with type 2 diabetes: a randomized clinical trial. PLoS One 2017;12(11):e0188171.**	
Study details	Trial design: 2-arm RCT (single blind) Location: Japan Setting: Nephrology, Diabetology and Endocrinology Department of Okayama University Hospital Number of centres: 1Recruitment period: April 2014 to March 2016Duration: 6 months Funder: Japanese Ministry of Health, Labour and Welfare grant number 25110601 Aim: "to investigate the effects of non-surgical periodontal treatment on hemoglobinA1c (HbA1c) levels, oxidative stress balance and quality of life (QOL) in patients with type 2 diabetes mellitus (T2DM) compared to no periodontal treatment (simple oral hygiene instructions only)"	
Participants	Inclusion criteria: aged >= 30 years; physician-diagnosed T2DM (diagnosed at least 2 months prior to the study); ability to make hospital visits throughout the trial, were in the care of a physician for their diabetes; agreement to not change their diabetes medications during the trial unless medically indicated; diagnosis of mild to advanced chronic periodontitis, defined as <2 interproximal sites with CAL >3mm and 2 interproximal sites with PPD >4mm (not on the same tooth) or one site with PPD 5mm Exclusion criteria: pregnancy, inappropriate status for the trials, such as limited life expectancy and diabetes-related emergency, and receiving periodontal treatment in the prior 6 months Age at baseline: 61.2 ± 9.2 vs. 62.8 ± 12.1 Sex (♂:♀) : 28:9 Smoking: 7/37 Alcohol consumption: 14/37 Diabetes type: 2 Duration since diabetes diagnosis: not reported Metabolic control: HbA1c > %: 7.5 ± 1.7 vs. 7.7 ± 1.2 Other clinical investigations: glycated albumin, oxidative index Number randomised: 40 Number evaluated: at 3 months 37 (Gp A 20, Gp B 17) (complete data for 31: Gp A 17, Gp B 14); at 6 months 28 (Gp A 15, Gp B 13)	
Interventions	Comparison: SRP + OHI + SPT versus OHI only Periodontal treatment group (n = 20): non-surgical periodontal therapy, including scaling and root planing plus oral hygiene instructions, and consecutive supportive periodontal therapy at 3 and 6 months	

	Control group (n = 17): only oral hygiene instructions without treatment during the experimental period	
Outcomes measures	Primary: change in HbA1c levels from baseline to 3 months (also measured at 6 months) Secondary outcomes: changes in oxidative stress balance (Oxidative-INDEX), the Diabetes Therapy-Related QOL and clinical periodontal parameters from baseline to 3 months and baseline to 6 months	
Notes	Trial registration: Current Controlled Trials UMIN-ICDR UMIN 000013278 (Registered April 1, 2014)	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Randomisation stratified by levels of HbA1c (< 8% vs. 8%), insulin (use vs no use) and the number of medications (2 vs >2). Each selected patient received a code number and one of the study co-ordinators used a computer-generated table to randomly allocate people to 1 of the 2 groups (control and periodontal treatment group as below) (allocation ratio 1:1)
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Low	Study personnel, including the periodontal examiners, laboratory personnel who performed the HbA1c analyses and the investigator responsible for the data analysis were blinded to the treatment assignment. Code breaking was performed after the final statistical analysis
Incomplete outcome data (attrition bias) All outcomes	Low	Attrition low and not a concern
Selective reporting (reporting bias)	Low	All expected outcomes reported
Other bias	Low	None apparent
Moeintaghavi 2012	**Moeintaghavi A, Arab HR, Bozorgnia Y, Kianoush K, Alizadeh M. Non-surgical periodontal therapy affects metabolic control in diabetics: a randomized controlled clinical trial. Australian Dental Journal 2012;57(1):31-7.**	
Study details	Trial design: 2-arm, single-centre, parallel-design RCT Location: Iran	

	Setting: Hospital Number of centres: 1, Periodontics Department, Mashhad Dental School Recruitment period: June 2007 to September 2008 (Parsian Diabetes Clinic and Mashhad Diabetics Centre) Funding source: Grant from Mashhad University of Medical Sciences
Participants	Inclusion criteria: Mild-moderate periodontitis (AAP criteria); diagnosis of T2 DM with HbA1c >7%; no major complications of diabetes; controlled by OHA (glybenglamide and metformin) but not insulin administration; no periodontal treatment or antibiotic administration in last 6 months Exclusion criteria: Presence of systemic diseases other than T2 DM that could influence course of periodontitis; intake of immunosuppressive drugs, steroids, hydantoin, or NSAIDs; tobacco use; pregnancy or intention to become pregnant during study period; fixed orthodontic appliances; refusal or inability to give informed consent Age at baseline: Overall: 50.29 yrs (SD 3); M 52.48 yrs (SD 3); F 48.1 yrs (SD 3) (by sex P = 0.9) No detail of age by group allocation Sex (M:F): Overall M20:F20; Gp A M9:F13; Gp B M11:F7 (P = 0.341) Tobacco use: Excluded Alcohol consumption: Not reported, although consumption of alcohol is illegal in Iran Diabetes type: T2 DM Duration since diabetes diagnosis: Not reported Metabolic control: Mean HbA1c at baseline: Gp A 8.15% (SD 2.22); Gp B 8.72% (SD 1.82) (P = 0.304) Antidiabetic therapy: All in receipt of oral hypoglycaemic medication (no insulin) Other clinical investigations: Biochemical markers TG, TC (total cholesterol), LDL, HDL, FPG Number randomised: 40 Number evaluated: 40
Interventions	Comparison: SRP versus no intervention Gp A (n = 22): SRP (ultrasonic device, standard periodontal curettes, local anaesthetic and no limitation on time) Gp B (n = 18): No treatment (delayed SRP provided after completion of trial) Duration of follow-up: 3 months
Outcomes measures	Primary: HbA1c (at baseline and 3 months) Secondary: CAL, PPD, PI and GI (at baseline and 3 months)
Notes	HbA1c assessment method: Cobas Integra 700; Roche Diagnostics, Germany Data analysis: ITT Conflict of interests: Not reported Adverse events: Not reported SES: Not reported

	Sample size calculation: A priori calculation based on Kiran 2005 and Rodrigues 2003 of 20 per group (α = 0.05 and β = 0.2) Trial ID: NCT01252082	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "Patients were randomly divided into treatment and non-treatment (control) groups by the study research assistant (KK) using a computer generated random numbers table"
Allocation concealment (selection bias)	Unclear	Examiner (AMT) at baseline "blinded to subjects' group assignment. "Although 'AMT' blinded, randomisation statement relates to 'KK' and therefore unclear if allocation concealment occurred
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low	ITT analysis. All patients completed the study, however several non-planned treatments occurred: Reported extractions – 1 per group. Endodontic treatment to 1 in Gp A
Selective reporting (reporting bias)	Unclear	Age differences not reported between group but by sex instead Adverse events not reported
Other bias	Low	No other apparent biases
Qureshi 2021	**Qureshi A, Bokhari SAH, Haque Z, Baloch AA, Zaheer S. Clinical efficacy of scaling and root planing with and without metronidazole on glycemic control: three-arm randomized controlled trial. BMC Oral Health 2021;21(253).**	
Study details	Trial design: 3-arm RCT Location: Dow University of Health Sciences Karachi, Pakistan Number of centres: 1 Recruitment period: December 2018 to December 2020 (author supplied info) Funding source: Higher Education Commission of Pakistan through their National Research Program for Universities (NRPU) Grants [Grant No.: 7143] Research protocol registered with the Protocol Registration and Results System at ClinicalTrials.gov [NCT 03343366] on 17/11/2017	

Participants	Inclusion criteria: ≥ 2 interproximal sites having ≥ 5 mm PPD or ≥ 4 mm of clinical attachment loss (CAL) with at least 16 natural teeth on examination, having moderate to severe periodontitis, HbA1c level ≥ 6.5% and >14% at baseline with T2DM diagnosed at least a year ago prior to the study. Patients under either or both types of diabetes management (insulin and/ or oral glycaemic therapy) were suitable for inclusion. Exclusion criteria: pregnant or nursing mothers, patients with gestational diabetes, undergoing dialysis therapy, alcoholics, those with any serious concurrent disease or with complications requiring emergency treatment were excluded. Patients under any anti-inflammatory or antibiotic drugs (daily for >7 consecutive days) within the last two months of examination, other than low dose aspirin prescribed for cardiovascular disease, were also excluded. (not reported in the final paper but available at doi.org/10.5455/JPMA.22016) Age at baseline (yrs): Gp A 52.72 (SD 8.00), Gp B 51.24 (SD 8.27), Gp C 52.82 (SD 6.38) Sex (M:F): Gp A 20:30, Gp B 23:27, Gp C 25:25 Tobacco use (Y:N): Gp A 2:47, Gp B 2:46, Gp C 4:43 Alcohol consumption: not recorded Diabetes type: T2DM Duration since diabetes diagnosis: not recorded Other measures at baseline: comorbidity, diet, medication (diabetic management, education and BMI Metabolic control: Gp A % 9.11 (SD 1.52), Gp B % 9.09 (SD 1.75), Gp C 8.88 (SD 1.65) Other clinical investigations: FBG Number randomised: 150 Number evaluated: 97 at 3 mths; 74 at 6 mths
Interventions	Comparison: SRP + antibiotics + OHI vs SRP + OHI vs OHI (delayed periodontal treatment) Randomly allocated to either: Intervention 1: SRP + metronidazole (MET) + OHI (50) Intervention 2: SRP + OHI (50) Control: OHI (50) Gp A - SRP through a combination of ultrasonic scaling (average 60 min on medium intensity full mouth in single sitting) and hand instrumentation (using sharpened and sterilized curettes) to smoothen irregular areas of root surface until the surfaces were smooth followed by MET 400 mg×3 for 10 days along with warm salt water rinses for 3 to 5 days and OHI Gp B - received the same intervention as test group-1 except MET Gp C - OHI (delayed periodontal treatment) Duration of follow-up: 6 mths
Outcomes measures	Mean change in HbA1c (at 3 and 6 months), fasting blood glucose, periodontal variables BOP, PPD, CAL (states L is loss in this paper) at 1 and 3 months.

Notes	Sample size calculation: minimum sample size determined was n = 105 with 35 participants in each group with a ratio of 1:1:1; however, the number was increased to 150 participants	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Computer-generated random number table
Allocation concealment (selection bias)	Low	"Independent allocator using Sequentially Numbered and Opaque Sealed Envelopes (SNOSE) containing detailed instructions for each intervention that were opened only by the chair side dental assistant. These envelops were kept confidential and sent back to the allocator by the dental assistant which were disclosed at the time of statistical analysis to check the type of intervention performed."
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Low	"...the periodontal examiners and biochemist were unaware of the type of intervention performed by the periodontal therapist!
Incomplete outcome data (attrition bias) All outcomes	High	Large dropout. Loss to follow-up of 76 of the 150 by month 6. ITT and PP analysis undertaken "Per protocol (PP) analysis was performed on data of only those participants who showed compliance with study protocol. Intent-to-treat (ITT) analysis was applied to assess any bias in the results due to attrition." "On the 1st follow-up visit by approximately 30 days [mean = 31.73 [+ or -] 4.55 days], 100% response was achieved. Out of 150 participants, 97 [64.66%] participants reported on 3-month follow-up. Further 23 participants were lost on 6th month follow-up leaving behind total 74 participants with n = 24, n = 26 and n = 24 in the two test and control arms respectively."
Selective reporting (reporting bias)	Low	ITT and PP analysis undertaken
Other bias	Low	None apparent
Raman 2014	**Raman RP, Taiyeb-Ali TB, Chan SP, Chinna K, Vaithilingam RD. Effect of nonsurgical periodontal therapy versus oral hygiene instructions on Type 2 diabetes subjects with chronic periodontitis: a randomised clinical trial. BMC Oral Health 2014;14(1):2-19.**	

Study details	Trial design: 2-arm, multicentre, parallel-design RCT Location: Malaysia Setting: Hospital Number of centres: 2, patients recruited from outpatient Diabetes Clinic of the University of Malaya Medical Centre, then treated at Periodontology Clinic at the Faculty of Dentistry, University of Malaya Recruitment period: recruitment period not explicit, although states screening and treatment from May 2010-April 2011 Funding source: 2 research grants from University of Malaya (P0027/2009B and RG/11HTM)
Participants	Inclusion criteria: moderate-advanced chronic periodontitis; at least 12 teeth; 5 or more > PD 5 mm or > and attachment loss 4 mm or > in at least 2 quadrants which bleed on probing Exclusion criteria: systemic antibiotic use in prior 4 months; pregnancy; current smoker; cardiovascular/cerebrovascular event in prior 12 months; diabetes medication change during study; non-surgical periodontal therapy in prior 6 months; surgical periodontal therapy in prior 12 months Age at baseline: overall 56.2 yrs (SD 8.1); Gp A: 57.7 yrs (SD 9.9); Gp B: 54.6 yrs (SD 6.2) Sex (M:F): overall M20:F12; Gp A M11:F4; Gp B: M9:F8 Tobacco use: current smokers excluded from participation Alcohol consumption: not reported Diabetes type: all type 2 Duration since diabetes diagnosis: overall: <7 yrs n = 7 (21.9%), 7-12 yrs n = 8 (25.0%), >12 yrs n = 17 (53.1%); Gp A: <7 yrs n = 4 (26.7%), 7-12 yrs n = 4 (26.7%), >12 yrs n = 7 (46.7%); Gp B: <7 yrs n = 3 (17.6%), 7-12 yrs n = 4 (23.5%), >12 yrs n = 10 (58.8%) Metabolic control: Mean HbA1c at baseline: Gp A: 7.80 (SD 1.50); Gp B: 7.60 (SD 1.50) Antidiabetic therapy: not reported fully. Only a quote: "All subjects who completed the study were on oral hypoglycaemic drugs" Other medical conditions: not reported Other clinical investigations: systemic hs-CRP, GBI Number randomised: 40 Number evaluated: 32 (Gp A n = 15; Gp B n = 17)
Interventions	SRP + OHI (x 3) + adjunctive chlorhexidine mouthrinse versus OHI (x 3) Gp A (n = 20): repeat OHI (modified Bass technique, soft-bristled toothbrush, compact-tuft toothbrush, interdental brush, floss (using TePe oral hygiene education set)) until PI <20%, followed by SRP (single visit, ultrasonic scaler, Gracey curettes) and 0.12% chlorhexidine mouthrinse (Hexipro, Evapharm, Kuala Lumpur, Malaysia) 3 x 15 ml p/d for 14 days. OHI repeated at each monthly visit Gp B (n = 20): OHI (modified Bass technique, soft-bristled toothbrush, compact-tuft toothbrush, interdental brush, floss (using TePe oral hygiene education set)). OHI repeated at each monthly visit Duration of follow-up: 3 months

Outcomes measures	Primary: HbA1c at baseline and 3 months Secondary: PI, PPD, PAL (corresponds to CAL) at baseline, 2 months, and 3 months	
Notes	Sample size calculation: 30 required (15 per arm; 80% power). Accounting for attrition, recruited 40 (20 per arm). Results confirm arms were sufficiently powered after accounting for attrition. Quote: "This gave a within group analyses power of 80% for the NSPT group [Gp A] and 88% for the OHI group [Gp B]" Data analysis: per-protocol SES: ethnicity data provided. Overall: Malay n = 9 (28.1%); Chinese n = 8 (25%); Indian n = 6 (46.9%)Gp A: Malay n = 5 (33.3%); Chinese n = 4 (26.7%); Indian n = 6 (40.0%) Gp A: Malay n = 4 (23.5%); Chinese n = 4 (23.5%); Indian n = 9 (52.9%) Adverse events: not reported HbA1c assessment method: not reported. Assessed by private laboratory, using 15 ml venous blood Conflicts of interest: authors declare no conflict of interests Trial ID: NCT01951547	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "All subjects were assigned via block randomisation to age matched NSPT and OHI groups. Following randomisation, baseline values for hs-CRP and HbA1c were obtained"
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	States "not double-blinded." Not reported further
Incomplete outcome data (attrition bias) All outcomes	High	Per-protocol analysis: not all participants analysed in groups randomised to, regardless of intervention actually received. Gp A: lost 5 participants. 2 due to medication change during study (exclusion criteria); 2 withdrew for unspecified reasons; and 1 unable to attend recall due to distance Gp B: lost 3 participants. 1 due to medication change during study; and 2 withdrew for unspecified reasons
Selective reporting (reporting bias)	Low	All planned outcomes fully reported
Other bias	High	Quote: "..during the randomization of subjects, more participants with poor metabolic control were placed in the NSPT group. In the OHI group, there was equal distribution of participants with poor and good metabolic control"

Rapone 2021	Rapone B, Ferrara E, Corsalini M, Qorri E, Converti I, Lorusso F, et al. Inflammatory status and glycemic control level of patients with type 2 diabetes and periodontitis: a randomized clinical trial. International Journal of Environmental Research and Public Health 2021;18(6):3018.
Study details	Trial design: parallel-group, 2-arm RCT Location: Tirana, Albania Number of centres: 1 Recruitment period: June 2018 and January 2020 Funding source: no external funding
Participants	Inclusion criteria: diagnosis of type 2 diabetes and therapy had not changed over previous 3 months, having diagnosis of periodontitis if CAL affected > 2 non-adjacent teeth or buccal/oral CAL of > 3mm with pocketing of > 3mm was detectable in > 2 teeth Exclusion criteria: insulin dependent diabetes or higher chronic disease, smoking or consuming alcohol, antibiotics, or anti-inflammatory drugs over previous 6 months, pregnant or lactating women, having received periodontal treatment over previous year Age at baseline: Gp A 53±11; Gp B 56±7 Sex (♂:♀): Gp A 40:50; Gp B 36:54 Smoking: all non-smokers Alcohol consumption: not reported (alcoholics excluded) Diabetes type: 2 Duration since diabetes diagnosis (yrs): at least 5 Metabolic control: Gp A 8.08±1.97; Gp B 8.77 ± 8.51 SDerror in paper Other clinical investigations: CRP- C-reactive protein Number randomised: total 187 (93/94 per A, B group) Number evaluated: 6 months 180 (90 per group)
Interventions	Comparison: SRP versus no treatment (delayed) Gp A (SRP) oral hygiene instruction, full-mouth SPR delivered in 4 sessions (n = 90) Gp B (control) delayed periodontal therapy control (n = 90) Duration of follow-up: 6 months
Outcomes measures	Primary: HbA1c Secondary: periodontal attachment level (CAL mm); GI (% sites); visible plaque index; PPD mm Outcomes measured at baseline, 3 months, and 6 months
Notes	Sample size calculation: “determined setting type 1 error at 0.05, and type ii error at 0.02 and power 80%”..."sample size calculation was determined to detect difference in change of HbA1c of 0.5%,...based on SD of 0.1%”

Risk of Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low	Quote "...randomisation was done using computer generated series of numbers..."
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low	Low number of drop-outs in both group Gp A 4, Gp B 3
Selective reporting (reporting bias)	High	Data not reported in full for any outcome
Other bias	Low	None apparent
Rodrigues 2015	**Rodrigues RMJ. Effect of periodontal therapy on serum osteocalcin levels in patients with type 2 diabetes and severe chronic periodontitis [Efeito do tratamento periodontal nos niveis de osteocalcina serica em pacientes com diabetes tipo 2 e periodontite cronica severa [thesis]]. Rio de Janeiro 2015. www.bdtd.uerj.br:8443/bitstream/1/14058/1/TESE_FINAL_ROSA_MARIA_JARDIM_RODRIGUES_com%20alteracao%20%282%29.pdf (accessed 6 September 2021).**	
Study details	Trial design: 2-arm RCT Location: University Hospital Pedro Ernesto/UERJ, Brazil Number of centres: 1 Recruitment period: not reported Funding source: none declared	
Participants	Inclusion criteria: diagnosis of T2 DM (WHO) for, at least, 1 year; severe chronic periodontitis (International Workshop for Classification of Periodontal Disease) - at least 2 sites with PD ≥ 6mm and 2 sites with CAL ≥ 5mm; minimum age of 35 years; minimum 8 teeth present Exclusion criteria: smokers; diagnosed with osteopenia or osteoporosis; presenting immunological or hepatic disorders; pregnant or lactating; periodontal or antibiotic therapy within the last 6 months Age at baseline:	

	Gp A 59.4 ± 8.4, Gp B 55.8 ± 8.4 (P = NS) Sex (♂:♀) Gp A 9/4, Gp B 5/8 Alcohol consumption: not reported Duration since diabetes diagnosis: not reported Number of standing teeth: Gp A 20.2 ± 4.8, Gp B 16.8 ± 7.3 HbA1c Gp A 10.9% ± 13.3, Gp B 8.2% ± 3.0 Other clinical investigations: periodontal clinical examination? Number randomised: 26 Number evaluated: 26 at 3 months (13/13)	
Interventions	Comparison: Gp A (n = 13) 4 to 6 sessions of scaling and root planing Gp B (n = 13) biofilm control and advices on oral hygiene Duration of follow-up: 3 months	
Outcomes measures	Primary: HbA1c Secondary: serum osteocalcin level, clinical periodontal parameters (PD, CAL, BOP, PI), glycaemic level (glycose, estimated glycaemia), lipidic profile (total cholesterol (TC), HDL, LDL, and triglycerides)	
Notes	Sample size calculation: no rationale. Intra and interrater agreement of 88% and 73%, respectively, for PD and CAL. No protocol registration	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	No description. "The 26 initially selectioned patients were randomly divided into group test and control"
Allocation concealment (selection bias)	Unclear	No description
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	High	"Clinical periodontal exams were performed by two examiners (RM and ME) previously calibrated… All patients were treated by examiner 1, while examiner 2 monitored the management of the patient and blood collection" – the clinical operators were the outcome assessors.

Incomplete outcome data (attrition bias) All outcomes	Low	No dropout or patient loss registered
Selective reporting (reporting bias)	Low	All outcome data reported for both groups – although the items described below were collected and were not reported
Other bias	Unclear	Skin colour, educational level, marital status, family history of diabetes data unreported
Singh 2008	**Singh S, Kumar V, Kumar S, Subbappa A. The effect of periodontal therapy on the improvement of glycaemic control in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. International Journal of Diabetes in Developing Countries 2008;28(2):38-44.**	
Study details	Trial design: 3-arm, single-centre, parallel-design RCT Location: India Setting: Hospital Number of centres: 1, Department of Periodontics, JSS Dental College, Mysore, India Recruitment period: Not reported Funding source: Quote: "Source of support: Nil"	
Participants	Inclusion criteria: ≥30 years old, either sex; T2 DM; moderate to advanced periodontitis (30% or > of examined teeth with ≥4 mm probing depth); absence of any major diabetic complications; no evidence of any systemic disease (other than diabetes) being a risk factor for periodontitis Exclusion criteria: Uncontrolled DM; periodontal treatment in prior 6 months; antibiotic administration in prior 3 months; <16 remaining natural teeth Age at baseline: Not reported Sex (M:F): Not reported Tobacco use: Not reported Alcohol consumption: Not reported Diabetes type: Type 2 DM Duration since diabetes diagnosis: Not reported Metabolic control: Mean HbA1c at baseline: Gp A: mean 7.9% (SD 0.7); Gp B mean 8.3% (SD 0.7); Gp C mean 8.08% (SD 0.7) Antidiabetic therapy: Not specifically reported. All in receipt of antidiabetic therapy but no indication what form ("Exclusion criteria: Patients with uncontrolled DM") Other clinical investigations: FPG, PPBG Number randomised: 45	

	Number evaluated: 45	
Interventions	Comparison: SRP + OHI versus SRP + OHI + doxycycline versus no treatment Gp A (n = 15): Full mouth SRP (under local anaesthesia) + OHI Gp B (n = 15): Full mouth SRP + OHI + systemic doxycycline (200 mg on treatment day, followed by 100 mg p/d x 14 days)Gp C (n = 15): No treatment Note: Additionally "after oral examination the teeth with poor prognosis were extracted." No indication which Gps or how many patients received extractions, or whether this may have affected treatment outcomes Duration of follow-up: 3 months	
Outcomes measures	Primary: HbA1c (at baseline and 3 months) Secondary: PI, GI, PPD, CAL (at baseline and 3 months)	
Notes	Sample size calculation: Not reported Data analysis: Assumed ITT SES: Not reported Adverse events: Quote: "None of the patients in our study experienced any adverse side effects with doxycycline" HbA1c assessment method: Liquid chromatography Conflict of interests: Authors declare no conflict of interests exists	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Quote: "They were randomly divided into three groups of 15 patients each" Comment: No further detail
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low	No patients was reported as lost to follow-up. Analysis assumed to have been ITT, but not specifically reported

Selective reporting (reporting bias)	Unclear	Planned outcomes reported for 3 months; however, assessed at 1 month and not reported. Furthermore, no adverse events reported other than for doxycycline use (Gp B) relating to SRP (Gps A+B) or no treatment (Gp C)
Other bias	Unclear	No patient characteristics presented therefore unknown if baseline imbalances between groups. Also, no indication of how many patients in each arm received tooth extractions as part of treatment protocol as wound healing may potentially affect results
Sun 2011	**Sun WL, Chen LL, Zhang SZ, Wu YM, Ren YZ, Qin GM. Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis. Internal Medicine 2011;50(15):1569-74.**	
Study details	Trial design: 2-arm, single-centre, parallel-design RCT Location: China Setting: Hospital Number of centres: 1, Second Affiliated Hospital, College of Medicine, Zhejiang University, China Recruitment period: August 2008 to November 2010 Funding source: Grants from public research organisations: Zhejiang Science and Technology Projects (2009C33168), Natural Science Foundation of Zhejiang Province (Y2100077), Zhejiang Education Committee Projects (Y201017607), National Natural Science Foundation of China (30872884) and Zhejiang Health Bureau Fund (2009A104)	
Participants	Inclusion criteria: Patients diagnosed with T2 DM at least 1 year prior to study; moderately poor glycaemic control (HbA1c between 7.5% and 9.5%); aged 70 years; BMI 19-26 kg/m2 in women, BMI 20-27 kg/m2 in men; no medication changes during the 3 months of study; not smoking; without severe complications, such as diabetic nephropathy, stroke, angina, myocardial infarction and so on. The diagnosis of periodontitis met the following conditions: at least 20 teeth, PD >5 mm, >30% teeth with attachment loss (AL) over 4 mm, or > 60% teeth with PD >4 mm and AL >3 mm; no periodontal treatment in the previous 6 months; no antibiotics or non-steroidal anti-inflammatory drugs administered in previous 3 months; no serious systemic diseases or complications Exclusion criteria: Patients with systemic inflammatory diseases (rheumatoid arthritis, etc.), blood disease, liver damage, kidney disease or trauma Age at baseline: Gp A mean 55.13 yrs (SD 11.16); Gp B mean 54.23 yrs (SD 10.85) Sex (M:F): Overall: M67:F90; Gp A: M35:F47; Gp B: M32:F43 Tobacco use: Smokers excluded Alcohol consumption: Not reported Diabetes type: All T2 DM Duration since diabetes diagnosis: >1 year Metabolic control: Poor mean HbA1c at baseline. Mean HbA1c at baseline: Gp A: 8.75% (SD 0.67); Gp B: 8.70% (SD 0.65)	

	Antidiabetic therapy: Not reported, only study requirement for no medication changes during study period Other medical conditions: None Other clinical investigations: Sulcus bleeding index; fasting plasma glucose; triglycerides; total cholesterol; high-density lipoprotein cholesterol; low-density lipoprotein cholesterol; FINS, fasting insulin; homeostasis model assessment of insulin resistance; high-sensitivity C reactive protein; tumour necrosis factor; interleukin-6; adiponectin Number randomised: 190 Number evaluated: 157	
Interventions	Comparison: SRP + OHI + antibiotics versus no intervention Gp A (n = 82 after removal of patients not completing the study): OHI, full mouth scaling (supragingival and subgingival scaling), root planing, periodontal flap surgery when indicated, and extraction of hopeless teeth, restore of balanced occlusion. Antibiotics (tinidazole 1.0 g, bid, po and ampicillin 0.25 g, qid, po) were prescribed for 3 days before and after periodontal intervention. All periodontal interventions were performed by 1 periodontist Gp B (n = 75 after removal of patients not completing the study): No periodontal treatment (no indication if OHI delivered) Duration of follow-up: 3 months	
Outcomes measures	Primary: HbA1c at baseline and 3 months Secondary: PD, CAL, BI, PI at baseline and 3 months	
Notes	Sample size calculation: Not reported Data analysis: Per-protocol SES: Not reported Adverse events: Not reported HbA1c assessment method: Immunoturbidimetry Conflict of interests: Authors declare no conflict of interests exists Note: Not detailed anywhere how many were originally in each group. Quote: "A total of 33 patients did not finish the study. The reasons for dropping out included withdrawal due to personal reasons (such as sickness, no available time) (12 patients), later follow-up visit (21 patients, over 3 months). The data of these patients have been excluded from the data at the baseline (Table 1, 2)"	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Quote; "..patients were randomly divided into two Groups." This is the only information reported. The study is not even described as being an RCT
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Quote: "study was not blinded"
Blinding of clinical operator	High	Quote: "study was not blinded"

Blinding of periodontal outcome assessor	High	Quote: "study was not blinded"
Incomplete outcome data (attrition bias) All outcomes	High	Per-protocol analysis: not all participants analysed in groups randomised to, regardless of intervention actually received. All losses accounted for by rationale, but not indicated which arm withdrawals are from: personal reasons n = 12; postponed follow-up visit n = 21, over 3 months
Selective reporting (reporting bias)	Low	All planned outcomes fully reported
Other bias	Low	No other apparent biases
Telgi 2013	**Telgi RL, Tandon V, Tangade PS, Tirth A, Kumar S, Yadav V. Efficacy of nonsurgical periodontal therapy on glycaemic control in type II diabetic patients: a randomized controlled clinical trial. Journal of Periodontal & Implant Science 2013;43(4):177-82.**	
Study details	Diabetic Centre in Moradabad, India	
Participants	Inclusion criteria: with DM2, blood sugar controlled only with oral hypoglycemic agents, mild to moderate periodontitis (pocket depth of 4-5 mm), presence of a minimum of 28 teeth, no systemic antibiotic administration, no periodontal treatment in last 6 months Exclusion criteria: with systemic diseases other than DM2, tobacco and alcohol users, and suffering from oral disease and needing emergency treatment Age 35-45 years Number randomised: 60 (20 in each group)	
Interventions	Gp A: scaling, mouthwash, and brushing Gp B: mouthwash and brushing Gp C: brushing only	
Outcomes measures	HbA1c, fasting blood sugar, PPD, GI, PI, relevant drug history At baseline and after 3 months of intervention	
Notes		
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	"Randomly divided equally among 3 groups"
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Not possible

Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Low	Examiner blinded
Incomplete outcome data (attrition bias) All outcomes	Low	No dropouts
Selective reporting (reporting bias)	Low	All outcomes reported
Other bias	Low	None apparent
Tsobgny-Tsague 2018	**Tsobgny-Tsague NF, Lontchi-Yimagou E, Nana ARN, Tankeu AT, Katte JC, Dehayem MY, et al. Effects of nonsurgical periodontal treatment on glycated haemoglobin on type 2 diabetes patients (PARODIA 1 study): a randomized controlled trial in a sub-Saharan Africa population. BMC Oral Health 2018;18(1):28.**	
Study details	Trial design: 2-arm RCT Location: Yaounde Central Hospital, Cameroon Number of centres: 1 Recruitment period: Dec 2014-May 2015 (5 months) Funding source: none	
Participants	Inclusion criteria: poorly controlled T2D, moderate to severe chronic periodontitis according to the 2012 CDC-AAP classification and having at least 11 teeth Exclusion criteria: periodontal treatment (scaling and root planning) or experimented any alteration of the diabetes treatment 6 months prior to the study, onset of systemic diseases or an acute condition, use of immunosuppressive medications or other drugs or presence of conditions able to alter periodontitis, clinical features (pregnant women, alcohol users, smokers, and acute anaemia) Age at baseline: Gp A 51.2 ± 7.8, Gp B 51.7 ± 9.9 Sex (♂:♀) Gp A 8:7, Gp B 5:10 Smoking: not admitted to the study Alcohol consumption: not admitted to the study Diabetes type: type 2 DM (poorly controlled) Duration since diabetes diagnosis: Gp A, 5.0 ± 3.86 Gp B 4.26 ± 0.825, converted from months to years HbA1c: Gp A 9.7% ± 1.6, Gp B % 8.9 ± 0.9 Other clinical investigations: none	

	Number randomised: 34 Number evaluated: 3 months = 30 (evaluations also at 6 weeks)	
Interventions	Comparison: FMSP/OHI* followed by a sub-gingival irrigation with a 10% povidone iodine solution vs no treatment (time-weighted) Gp A (n=15) Gp B (n=15) Duration of follow-up: 3 months *All participants of the treatment group received dental floss and chlorhexidine gluconate 0.2% as mouth wash (10 ml twice daily for 5 days). All participants were instructed in oral hygiene methods: using of the modified Bass technique for tooth brushing, and using of soft bristled toothbrush	
Outcomes measures	Primary: HbA1c Secondary: O'Leary Plaque index (PI), Aainamo and Bay Bleeding Index (GBI), PD & CAL Stratification by methods to control hypoglycaemia: Gp A Diet = 15 OAD = 13 Insulin = 10 Insulin + OAD = 8 Gp B Diet = 15 OAD = 7 Insulin = 11 Insulin + OAD = 3	
Notes	Sample size calculation: 14 participants per treatment arm would provide 90% power to detect a minimum difference of 1% (SD 0.8) change in HbA1c level between the treatment and the control group.	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Block randomisation "The randomization was made using a permuted block method with a block size of six. This method consisted of drawing one block out of the six non-distinguishable blocks contained in a non-transparent bag without replacement. The blocks are divided into two equal types and marked of two letters A and B (A = treatment and B = control). Therefore, the bag contained 3 blocks A and 3 blocks B. Participants were assigned to one group or the other depending on the block drawn by the researchers, who were aware of the block drawn."

Allocation concealment (selection bias)	Unclear	Drawn from a bag with six blocks. Researchers were then however aware of which block was allocated to each group
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Low	"The periodontal examiners were masked to participants' assignment"
Incomplete outcome data (attrition bias) All outcomes	Low	2 lost to follow-up in each group, reasons provided
Selective reporting (reporting bias)	Low	All outcomes reported
Other bias	Low	None apparent
Vergnes 2018	**Vergnes JN, Canceill T, Vinel A, Laurencin-Dalicieux S, Maupas-Schwalm F, Blasco-Baqué V, et al. The effects of periodontal treatment on diabetic patients: The DIAPERIO randomized controlled trial. Journal of Clinical Periodontology 2018;45(10):1150-63.**	
Study details	Trial design: RCT Location: Diabetology Depts in South-western France (Toulouse-Rangueil & Bordeaux Haut-Leveque) Number of centres: 2 Recruitment period: 54 months (Feb 2010–August 2015) Funding source: French Ministry of Health Clinical Research Program 2008. Equipment by Acteon Group and Oral –B France endowment for part–time staff	
Participants	Inclusion criteria: type 1 or 2 DM of at least one year duration. HbA1c between 7.0 & 9.5% uncontrolled. Unchanged treatment regimen for 3/12 ≥ 6 permanent natural teeth. A diagnosis of periodontitis with at least 4 teeth standing and with at least one probed site with PPD ≥ 4mm and CAL ≥3mm Exclusion criteria: none stated Age at baseline: Results analysed in Type1 and Type 2 DM diagnoses separately: Type 1 Gp A n=32 Gp B n = 35 Gp A Age 50.9 (± 9.4) Gp B 53.7 (± 13.8)	

	Sex (♂:♀) Gp A 19/13, Gp B± 20/15 Smoking: Gp A 7, Gp B 8 Alcohol Consumption: No record Duration since diabetes diagnosis: Gp A 25.0 (±11.0), Gp B 25.2 (±13.9) Metabolic control: HbA1c Gp A 7.84% (±0.65) , Gp B 7.83% (±0.64) Type 2 Gp A n=13 Gp B n = 11 Gp A Age 68.3 (± 9.3) Gp B 63.1 (± 4.0) Sex (♂:♀) Gp A 5/8, Gp B 2/9 Smoking: Gp A 2, Gp B 0 Alcohol Consumption: No record Duration since diabetes diagnosis (years): Gp A 18.1 (±11.2), Gp B 19.9 (±13.0) Metabolic control: HbA1c Gp A 7.96% (±0.84), Gp B 7.78% (±0.52) Other clinical investigations: fructosamine, weight (kg) & QOL Number randomised: 91 (type 1 = 67, type 2 = 24) Number evaluated: 3 months = 88 (type 1 = 65, Type 2 = 23)	
Interventions	Comparison: separate analysis Type 1 and Type 2 DM Gp A (immediate treatment) non-surgical scaling root planning (SRP), systemic antibiotics (amoxicillin 2g/day for 7 days), scaling carried out over 10 days, OHI , subging CHX Gp B (delayed treatment) then same intervention as above Duration of follow-up: 3 months	
Outcomes measures	Primary: HBA1c Secondary: PPD, CAL, BOP (also recession, periodontal epithelial surface area PESA (mm), periodontal inflamed surface area), QoL	
Notes	Sample size calculation: power calculation assuming 0.5% difference in HbA1c and fructosamine at 80%power. 64 per group assuming 150 recruited with 75 per group and a 15% drop out rate	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Not described
Allocation concealment (selection bias)	Unclear	Not described
Blinding of participants	High	Not possible

Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	High	Not possible due to time weighting for periodontal parameters
Incomplete outcome data (attrition bias) All outcomes	Low	Data were presented and analysed on ITT basis
Selective reporting (reporting bias)	Low	Data separately presented as type 1, type 2 and combined
Other bias	Unclear	Trial was stopped early with only 91 recruited. Per protocol analysis excluded participants who reported not toothbrushing twice a day
Wang S 2017	**Wang S, Liu J, Zhang J, Lin J, Yang S, Yao J, et al. Glycemic control and adipokines after periodontal therapy in patients with Type 2 diabetes and chronic periodontitis. Brazilian Oral Research 2017;31:e90.**	
Study details	Trial design: parallel-group, 2-arm RCT Location: Xiamen Dentistry Hospital, China Number of centres: 1 Recruitment period: June 2014 to December 2014 (6 months) Funding source: Xiamen Health Bureau (grant number: WSK 2012-01) and the National Institute of Hospital Administration (the hierarchical medical treatment policy in diabetes project)	
Participants	Inclusion criteria: T2DM >1 year, HbA1c between 6.5 – 10%, chronic periodontitis with >30% teeth, PPD ≥5 mm and CAL >4 mm, or >60% teeth PPD >4 mm and CAL ≥3 mm ≥15 teeth Exclusion criteria: periodontal treatment past 6 months, antibiotic or NSAID past 3 months, serious systemic diseases/complications Age at baseline: Gp A 61.58 ± 4.69 Gp B 61.9 ± 6.75 Sex (♂:♀) Gp A 12:7, Gp A 14:6 Smoking: Gp A 6 (32%), Gp B 3 (15%) Alcohol consumption: no: Gp A 12 (61%), Gp B 17 (75%), seldom: Gp A 3 (16%), Gp B 2 (10%), often: Gp A 4 (21%), Gp B 1 (5%) Diabetes type: 2 Duration since diabetes diagnosis: Gp A 8.5 y ± 3.1, Gp B 7.7y ± 4.7 Metabolic control: Gp A 7.63 ± 0.89, Gp B 7.70 ± 1.32 Other clinical investigations: TNF a, IL-6, APN, FGF21 Number randomised: 44	

	Number evaluated: 3 months Gp A = 19, Gp B = 20	
Interventions	Comparison: Gp A (n=22) OHI, full mouth supra/subgingival scaling, extraction of hopeless teeth, occlusal equilibration Gp B (n=22) no treatment Duration of follow-up: 3 months	
Outcomes measures	Primary: HbA1c Secondary: periodontal parameters – 6PPD, CAL; various biomarkers (not relevant for this review)	
Notes	Sample size calculation: none Per protocol analysis Single, calibrated examiner for periodontal outcomes	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	44 random numbers generated using SPSS version 17.0
Allocation concealment (selection bias)	Low	"These numbers were used to recruit and blindly randomize 44 subjects" but no details of allocation concealment given
Blinding of participants	High	Not possible due to nature of intervention
Blinding of clinical operator	High	Not possible due to nature of intervention Outcome assessors: not clear who measured HbA1c or whether blinded to group allocation
Blinding of periodontal outcome assessor	High	"All periodontal interventions were completed by a single periodontist (Jingsong Liu) within two weeks" "All measurements were performed by a single examiner (Jingsong Liu)"
Incomplete outcome data (attrition bias) All outcomes	Low	Low dropout rates (3 in intervention group and 2 in control) and reasons provided, although per protocol analysis
Selective reporting (reporting bias)	Low	All prespecified outcomes reported in full (per protocol)
Other bias	Low	None apparent
Wang Y 2017	**Wang Y, Liu HN, Zhen Z, Yiu KH, Tse HF, Pelekos G, et al. Periodontal treatment modulates gene expression of endothelial progenitor cells in diabetic patients. Journal of Clinical Periodontology 2017;44(12):1253-63.**	
Study details	Trial design: 2-arm RCT Location: Dept of Medicine, Queen Mary Hospital, Hong Kong	

	Number of centres: 1, but periodontal screening in Prince Philip Dental Hospital (PPDH) Recruitment period: June 2015 - August 2016 Funding source: none Aim: to investigate the effects of periodontal treatment on immuno-inflammatory gene expression of endothelial progenitor cells (EPCs) in diabetic patients	
Participants	Inclusion criteria: clinical diagnosis of DM for at least 5 years with HbA1c level more than 6.5%; (consistent anti-diabetic treatment 3 months prior to the study; and at least 40 years old Moderate to severe chronic periodontitis criteria (Li et al., 2009) were met, including more than 6 sites with probing depth (PD) ≥ 4 mm and over 25% of sites with interproximal clinical attachment loss (CAL) ≥ 5 mm as well as at least 10 teeth present Exclusion criteria: history of cardiovascular disease, people with antibiotic/anti-inflammatory treatment within 3 months prior to the study or those requiring antibiotic prophylaxis Age at baseline: Gp A 65 ± 8, Gp B 68 ± 3 Sex (♂:♀): Gp A 6:5, Gp B 3:4 Smoking (Y:N): Gp A 1/10, Gp B 1/6 Alcohol consumption: not recorded Diabetes type: 2 Duration since diabetes diagnosis: Gp A 19 ± 6, Gp B 18 ± 8 Metabolic control: mean HbA1c % Gp A 7.96 (SD 0.72), Gp B 7.95 (SD 0.94) Other clinical investigations: main outcomes 9 inflammatory mediators like IL-6 and IL-8 Number randomised: 18 (from 41 recruits) Number evaluated: at 6 months 18	
Interventions	Comparison: OHI, extraction, scaling and RSD (hand and ultrasonic) versus delayed treatment. Reviewed every 4-6 weeks Gp A (n=11) Gp B (n=7) Duration of follow up: 6 months. 1 loss to follow up (control group)	
Outcomes measures	Primary: HbA1c (main outcomes 9 inflammatory mediators like IL-6 and IL-8) Secondary: CAL, PD, BOP & PI Peripheral blood samples taken to analyse EPCs at baseline and 6 months after treatment	
Notes	Sample size calculation: none	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Restricted randomised approach to prevent imbalance in age, sex, DM duration and severity of periodontitis. Due to small sample size, it is unclear how this would be done.

Allocation concealment (selection bias)	Unclear	Generated by Primary investigator
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Low	Both periodontal and medical tests were conducted as blinded. Periodontal assessor calibrated for intra-examiner reproducibility
Incomplete outcome data (attrition bias) All outcomes	Low	All accounted for
Selective reporting (reporting bias)	Low	HbA1c was not the main focus of the study
Other bias	Low	None apparent
Yun 2007	**Yun F, Firkova EI, Jun-Qi L, Xun H. Effect of non-surgical periodontal therapy on patients with type 2 diabetes mellitus. Folia Medica 2007;49(1-2):32-6.**	
Study details	Trial design: 2-arm, single-centre, parallel-design RCT Location: China Setting: hospital Number of centres: 1, periodontal department of Guanghua College of Stomatology, Sun Yat-sen University, China Recruitment period: not reported Funding source: not reported	
Participants	Inclusion criteria: patients with newly diagnosed type 2 diabetes and no history of another major illness, no antibiotics or other medications received for at least 3 previous months; at least 14 standing teeth, pocket probing depth was >5 mm, but <8 mm in at least 1 site in 4 teeth in at least 2 different quadrants; bleeding and/or suppuration on probing; no periodontal treatment for 6 months prior to baseline examination Exclusion criteria: pregnancy or lactation Age at baseline: Gp A mean 53.41 (SD 2.42) years, Gp B mean 55.10 (SD 2.64) years Sex (M:F): overall: M22:F24; Gp A: M10:F13; Gp B: M12:F11 Tobacco use: not reported Alcohol consumption: not reported Diabetes type: T2 DM Duration since diabetes diagnosis: "newly diagnosed"	

	Metabolic control: Mean HbA1c at baseline:Gp A 8.26% (SD 0.31); Gp B 8.22% (SD 0.45) Antidiabetic therapy: not specifically reported.Quote: "These groups were well matched for...oral hypoglycaemic medication, the proportion of patients prescribed diet control" Other medical conditions: no history of other major illness Number randomised: 46 Number evaluated: 46	
Interventions	Comparison: SRP + OHI + doxycycline versus doxycycline alone Gp A (n = 23): patients were treated weekly with 5 1-hour sessions on a weekly basis. First session OHI and supragingival scaling and polishing, then on subsequent sessions OHI reinforced and SRP under topical anaesthesia on quadrant by quadrant basis. Doxycycline 100 mg/day for 14 days. Reassessed 8 weeks last session (3 months post-baseline) Gp B (n = 23): doxycycline 100 mg/day for 14 days. This group received periodontal treatment as above after the end of the study Duration of follow-up: 4 months	
Outcomes measures	Primary: HbA1c (at baseline and 4 months) Secondary: BOP, PPD, CAL, PI (at baseline and 4 months)	
Notes	Sample size calculation: mot reported Data analysis: ITT Adverse events: not reported Conflict of interests: not reported SES: not reported HbA1c assessment method: high pressure liquid chromatography	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Quote: "randomly divided"
Allocation concealment (selection bias)	Unclear	Not reported
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Unclear	Not reported

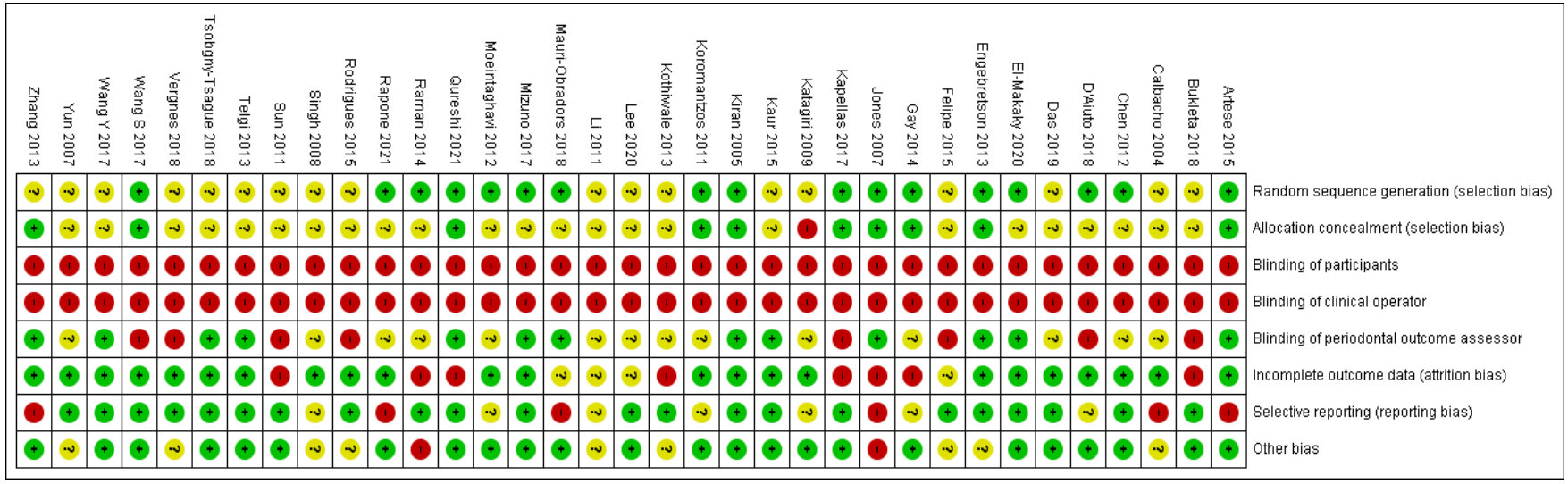
Incomplete outcome data (attrition bias) All outcomes	Low	Not reported, but there do not seem to be any dropouts. ITT analysis
Selective reporting (reporting bias)	Low	All planned outcomes fully reported
Other bias	Unclear	Poorly reported
Zhang 2013	**Zhang H, Li C, Shang S, Luo Z. Scaling and root planing with enhanced root planing on healthcare for type 2 diabetes mellitus: A randomized controlled clinical trial. Journal of Dental Sciences 2013;8(3):272-80.**	
Study details	Trial design: 2-arm, single-centre, parallel-design RCT Location: China Setting: Hospital Number of centres: 1, Hubei Provincial Govt Hospital, Hubei, China Recruitment period: July 2010 to May 2011 Funding source: 11th 5-year National Science and Technology Support Project (2007BAI18B02)	
Participants	Inclusion criteria: chronic periodontitis and had been diagnosed to have T2 DM for more than 1 year. A diagnosis of T2 DM should meet at least 1 of the following criteria: (1) postprandial plasma glucose 200 mg/dL (11.1 mmol/L); (2) fast plasma glucose (FPG) 126 mg/dL (7.0 mmol/L); (3) 2-hour oral glucose tolerance test 200 mg/dL (11.1 mmol/L). In addition, patients should have the following attributes: 35 to 80 years old; with at least 16 natural teeth; with at least 4 teeth with PPD = 5 mm, CAL = 4 mm, and BOP, distributed in 2 or more oral quadrants; and the HbA1c level within 3 months before recruitment should at least be 5.5% Exclusion criteria: accompanied with other systemic immune diseases; administered with antibiotics, immunomodulators, contraceptives, or any other form of hormone within the past 3 months; underwent modified diabetes treatment strategy within 3 months; had periodontal treatment within the past 12 months; needed extraction or endodontic treatment; smokes more than 4 cigarettes per day; pregnant or lactating women. Patients were dropped from the study if these conditions were met during the study course: diabetes treatment scheme was changed; drugs were systemically administered; patients could not revisit on time; participants were lost on follow-up Age at baseline: Gp A mean 60.4 yrs (SD 9.77); Gp B mean 62.7 yrs (SD 10.7) (P = 0.377) Sex (M:F): Overall: M31:F40; Gp A: M21:F28; Gp B: M10:F12 (P = 0.838) Tobacco use: Overall: n = 18 (25%); Gp A: n = 12 (24%); Gp B: n = 6 (27%) Alcohol consumption: Overall: n = 20 (28%); Gp A: n = 13 (27%); Gp B: n = 7 (32%) Diabetes type: T2 DM Duration since diabetes diagnosis: Gp A 8.63 yrs (SD 4.20); Gp B 7.29 yrs (SD 5.61)(P = 0.305) Metabolic control: Mean HbA1c at baseline: Gp A 7.68% (SD 1.22); Gp B 7.38 (SD 1.30)	

	Antidiabetic therapy: All in receipt of oral hypoglycaemic medication, insulin or combinationOverall: oral medication n = 55 (77%); insulin n = 41 (58%); Gp A: oral medication n = 40 (82%); insulin n = 30 (61%); Gp B: oral medication n = 15 (68%); insulin n = 11 (50%) Other medical conditions: n/a Other clinical investigations: FPG Number randomised: 75; Gp A n = 50; Gp B n = 25 Number evaluated: 3 months n = 72; 6 months n = 71	
Interventions	Comparison: SRP + OHI versus no intervention (delayed 'initial periodontal treatment') Gp A (n = 50): SRP (supra/subgingival scaling (Cavitron Bobcat Pro, Dentsply, USA); manual curettage (Hu-Friedy, USA)) + OHI (within 2 weeks of baseline examination) Gp B (n = 25): Delayed treatment Gp A subdivided at 3 months into Gp C (n = 25; SRP + OHI + "sub-enhanced root planing" ("sub-ERP")) and Gp D = 25; SRP + OHI + "subprophylaxis" - HbA1c not reported with this further breakdown) Duration of follow-up: 6 months	
Outcomes measures	Primary: HbA1c (at baseline, 3 and 6 months) Secondary: BOP, PPD, CAL, PI (at baseline, 3 and 6 months)	
Notes	Sample size calculation: Preliminary trial on 5 subjects per group SRP versus no treatment. A priori calculation at 80% power 20 in control and 40 in treatment group at 95% significance Data analysis: Per-protocol Adverse events: Not reported Conflict of interests: Not reported SES: Not reported HbA1c assessment method: Ion exchange chromatography (Drew Scientific DS5, England)	
Risk of Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Pre-prepared randomisation in group A , B and C. No description of sequence generation
Allocation concealment (selection bias)	Low	Number coded-envelopes
Blinding of participants	High	Not possible
Blinding of clinical operator	High	Not possible
Blinding of periodontal outcome assessor	Low	Blinded examiner

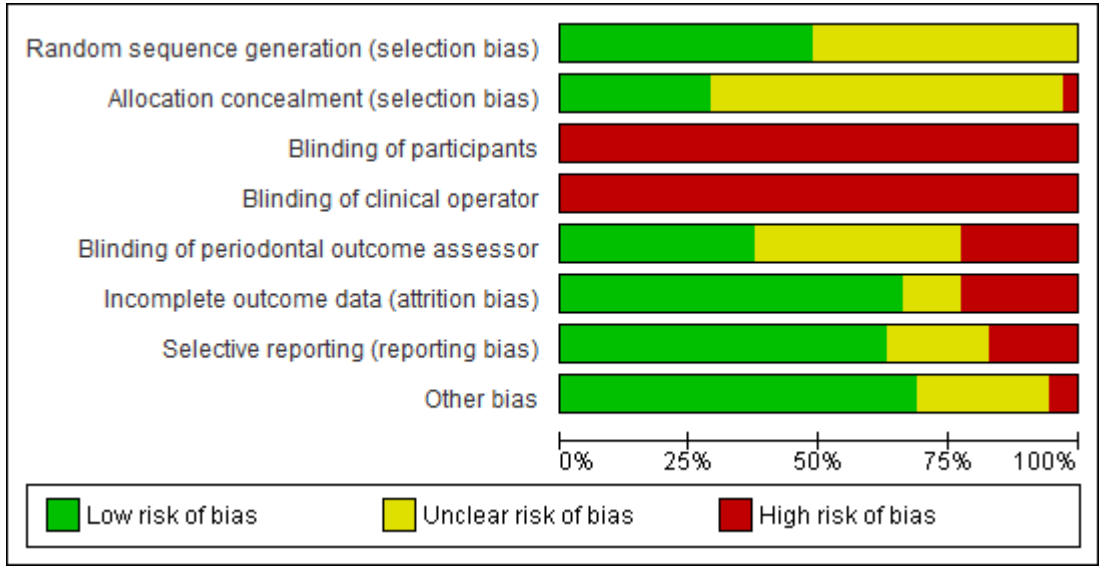
Incomplete outcome data (attrition bias) All outcomes	Low	4 lost to follow-up: Gp A: 1 lost at evaluation 2 (3 months); Gp B: 2 lost at evaluation 2 (3 months), and 1 at evaluation 3 (6 months). Reasons provided. Per-protocol analysis
Selective reporting (reporting bias)	High	HbA1c data presented inconsistently, adverse effects not reported, periodontal outcomes presented as graphs without data. Email to authors bounced
Other bias	Low	No other apparent biases

BOP = bleeding on probing; CAL = clinical attachment level; or loss GI = gingival index; Grp = group; OHI = oral hygiene instruction; PI = plaque index; PPD = probing pocket depth; RCT = randomised controlled trial; SD = standard deviation; SRP = scaling and root planing; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

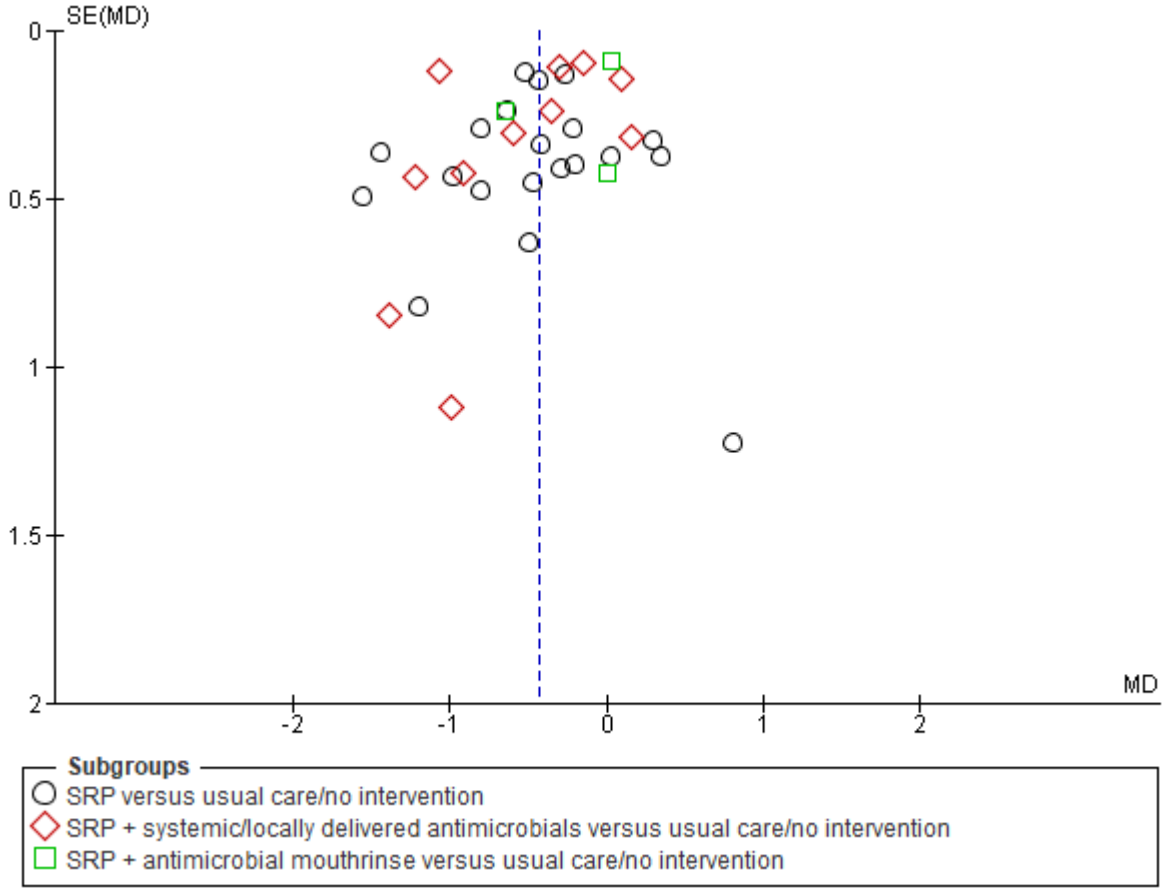
Risk of bias summary: Judgements about risk of bias domains for each included study



Risk of bias graph: Judgements about risk of bias domains presented as percentages across all included studies



Funnel plot of comparison: Periodontal therapy versus no active intervention/usual care at 3-4 months



Overall study risk of bias and applicability

The overall risk of bias and directness of the RCTs included in the Cochrane draft review were assessed by the NICE Guideline Development Team and are presented below:

Study name	Risk of bias	Directness
Artese 2015	Low/Moderate[1]	Directly applicable
Bukleta 2018	Moderate/High[2]	Directly applicable
Calbacho 2004	Moderate/High[3]	Directly applicable
Chen 2012	Low/Moderate[4]	Directly applicable
D'Aiuto 2018	Low/Moderate[4]	Directly applicable
Das 2019	Low/Moderate[4]	Directly applicable
El-Makaky 2020	Low	Directly applicable
Engebretson 2013	Low	Directly applicable
Felipe 2015	Moderate/High[3]	Directly applicable
Gay 2014	Low	Directly applicable
Jones 2007	Moderate/High[5]	Directly applicable
Kapellas 2017	Low/Moderate[6]	Directly applicable
Katagiri 2009	Moderate/High[7]	Directly applicable
Kaur 2015	Low/Moderate[8]	Directly applicable
Kiran 2005	Low	Directly applicable
Koromantzos 2011	Low	Directly applicable
Kothiwale 2013	Moderate[9]	Directly applicable
Lee 2020	Low/Moderate[4]	Directly applicable
Li 2021	Moderate/High[10]	Directly applicable
Mauri-Obradors 2018	Moderate[11]	Directly applicable
Mizuno 2017	Low	Directly applicable
Moeintaghavi 2012	Low/Moderate[4]	Directly applicable
Qureshi 2021	Low	Directly applicable
Raman 2014	Moderate[11]	Directly applicable
Rapone 2021	Moderate[11]	Directly applicable
Rodrigues 2015	Moderate[11]	Directly applicable
Singh 2008	Moderate/High[10]	Directly applicable
Sun 2011	Moderate/High[2]	Directly applicable

Telgi 2013	Low/Moderate[12]	Directly applicable
Tsobgny-Tsague 2018	Low/Moderate[12]	Directly applicable
Vergnes 2018	Moderate[11]	Directly applicable
Wang S 2017	Low	Directly applicable
Wang Y 2017	Low/Moderate[12]	Directly applicable
Yun 2007	Moderate/High[2]	Directly applicable
Zhang 2013	Moderate[13]	Directly applicable

1. Due to poor reporting of the primary outcome.
2. Due to lack of information on selection bias and high risk for periodontal assessor blinding and of attrition bias.
3. Due to the lack of information regarding selection bias, blinding of periodontal assessors and other bias and high risk of selective reporting.
4. Due to the lack of information on the details of selection bias and blinding of periodontal assessors.
5. Due to high risk of attrition, reporting and other bias.
6. Due to high risk for blinding of periodontal assessors and attrition bias.
7. Due to high risk of selection bias, and lack of information for blinding of periodontal assessors and selective reporting.
8. Due to the lack of information regarding the methods of randomisation and allocation concealment
9. Due to the lack of information regarding the methods of randomisation and allocation concealment, blinding of periodontal assessors and selective reporting, and high risk of attrition bias.
10. Due to lack of information across all domains of risk of bias.
11. Due to lack of information on allocation concealment and attrition bias and high risk of selective reporting.
12. Due to the lack of information regarding the methods of randomisation and allocation concealment.
13. Due to the lack of information regarding the methods of allocation concealment and high risk for selective reporting.

ROBIS Risk of bias assessment summary of the Cochrane systematic review

The risk of bias and applicability assessment was performed by the NICE Guideline Development Team using the ROBIS risk of bias checklist for systematic reviews and meta-analysis of interventional studies. This is presented in below:

Table: ROBIS risk of bias and applicability assessment

Section	Question	Answer
Study eligibility criteria	**Concerns regarding specification of study eligibility criteria**	**Low** *(Considerable effort has been made to clearly specify the review question and objectives, and to pre-specify and justify appropriate and detailed eligibility criteria that have been adhered to during the review)*

Section	Question	Answer
Identification and selection of studies	**Concerns regarding methods used to identify and/or select studies**	**Low** *(Given the review question and eligibility criteria as assessed in Domain 1, a substantial effort has been made to identify as many relevant studies as possible through a variety of search methods using a sensitive and appropriate search strategy and steps were taken to minimise bias and errors when selecting studies for inclusion.)*
Data collection and study appraisal	**Concerns regarding methods used to collect data and appraise studies**	**Low** *(Given the studies included in the review as assessed in domain 2, risk of bias was assessed using appropriate criteria, data extraction and risk of bias assessment involved two reviewers, and relevant study characteristics and results were extracted.)*
Synthesis and findings	**Concerns regarding the synthesis and findings**	**Low** *(The synthesis is unlikely to produce biased results, because any limitations in the data were overcome and potential biases accounted for.)*
Overall study ratings	**Overall risk of bias**	**Low** *(The findings of the review are likely to be reliable. Phase 2 did not raise any concerns with the review process or concerns were appropriately considered in the review conclusions. The conclusions were supported by the evidence and included consideration of the relevance of included studies.)*
Overall study ratings	**Applicability as a source of data**	**Fully applicable**

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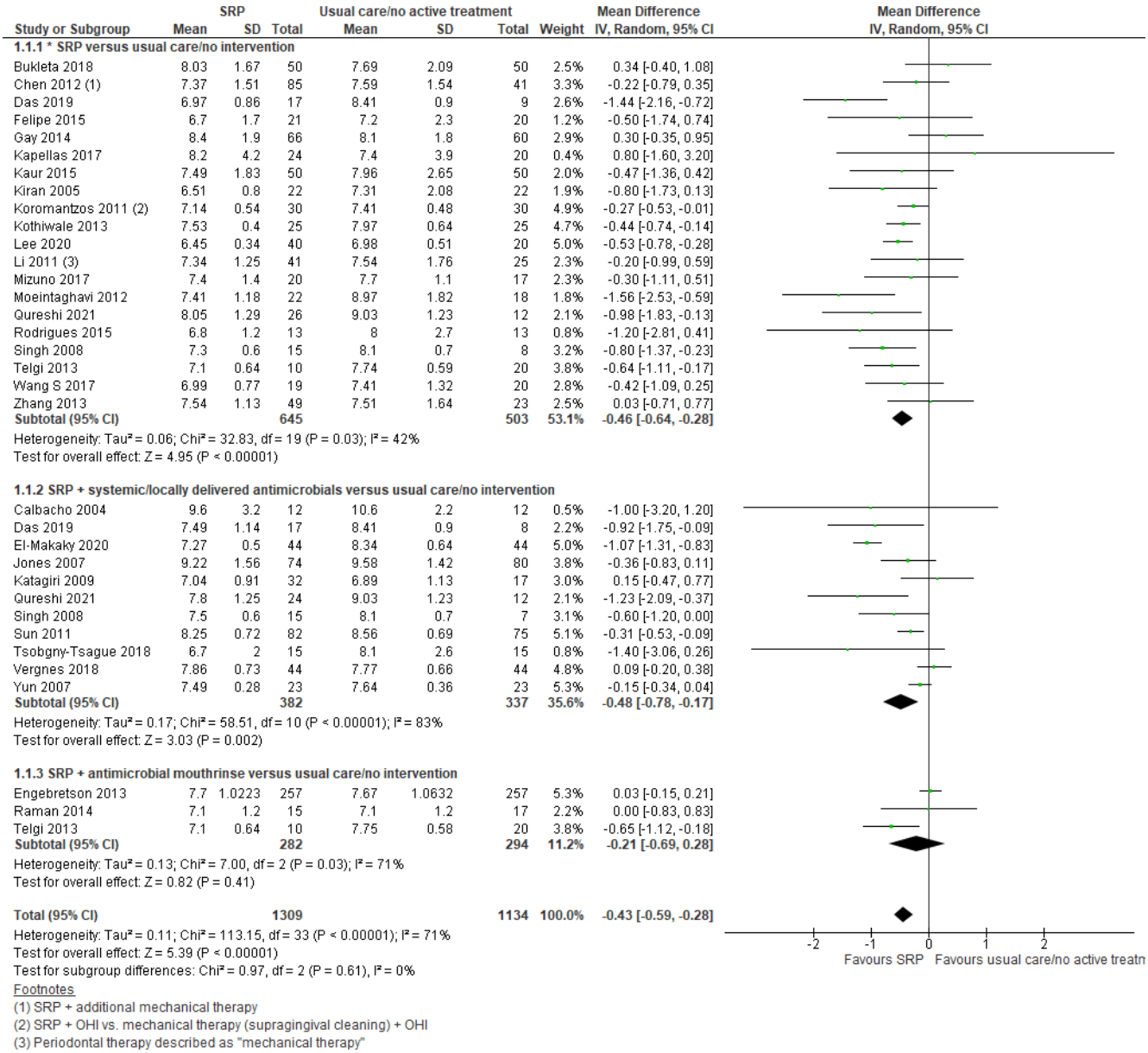
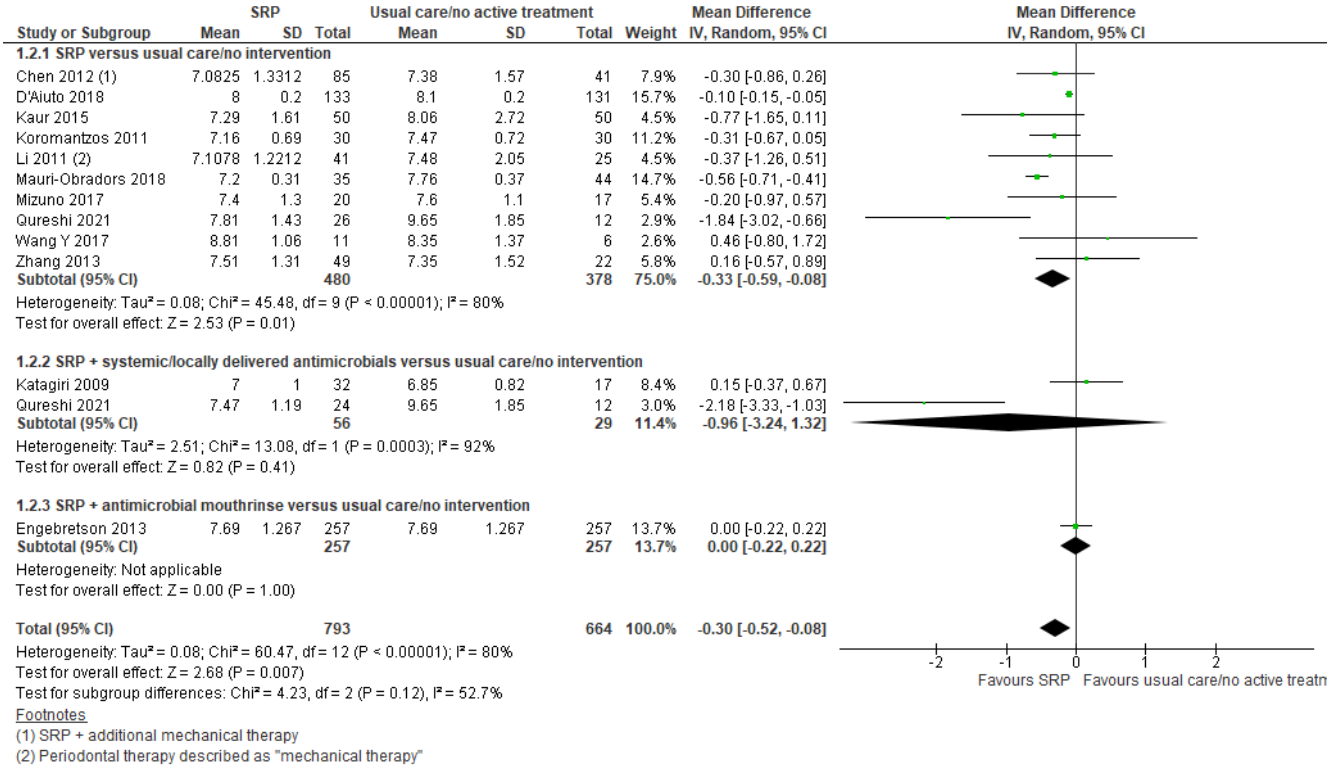
Appendix F – Forest plots

These forests plots are based on data from the Cochrane draft review. In the GRADE tables, the subgroups marked with " * " are presented using fixed effects model in line with the NICE methods (Appendix B).

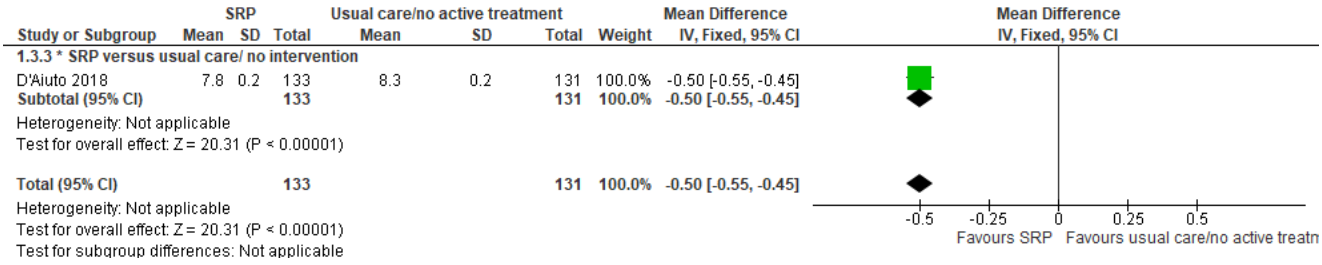
Effects of periodontal treatment versus usual care/no active intervention on HbA1c at 3-4 months



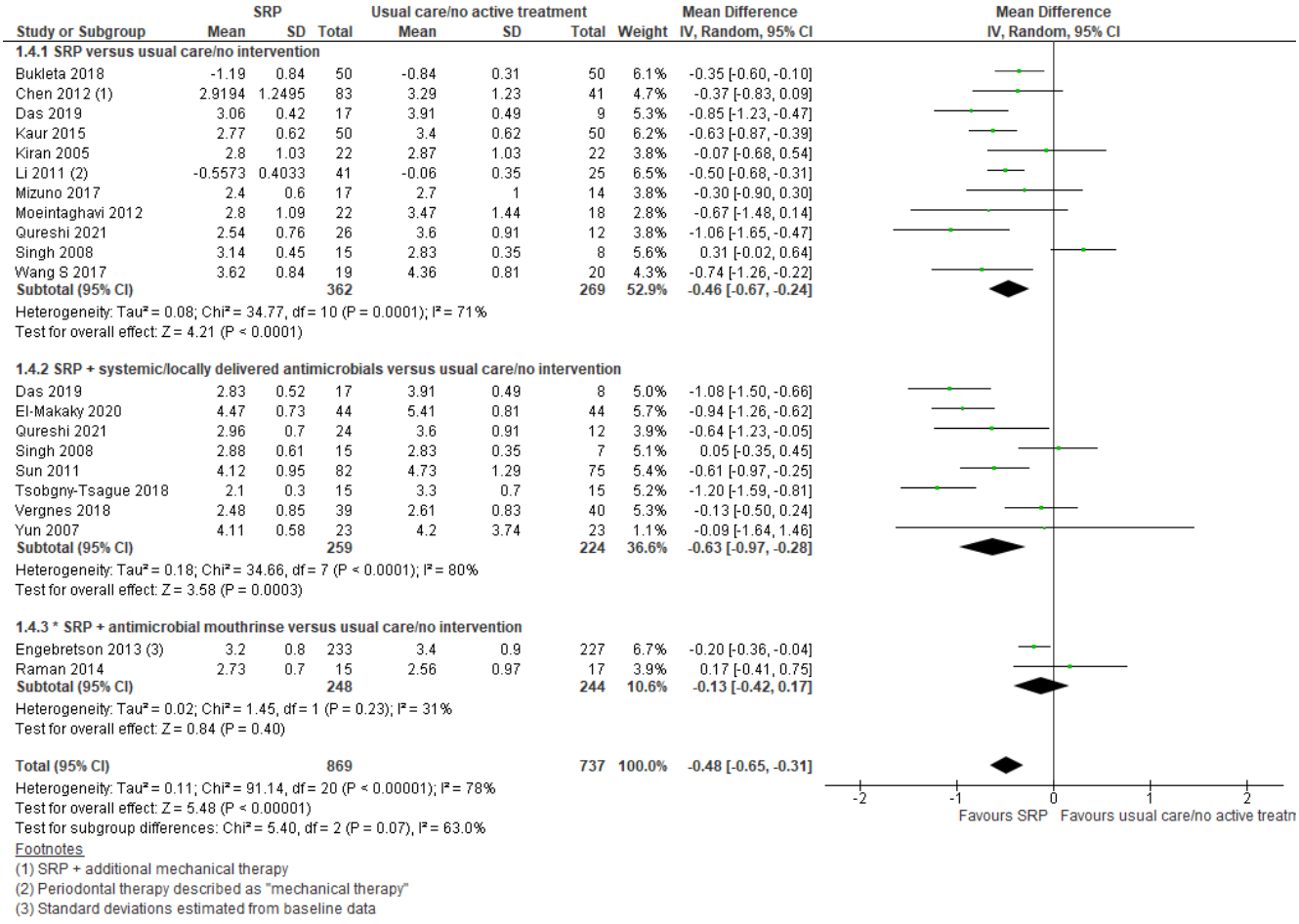
Effects of periodontal treatment versus usual care / no active intervention on HbA1c at 6 months



Effects of periodontal treatment versus usual care / no active intervention on HbA1c at 12 months



Effects of periodontal treatment versus usual care / no active intervention on Clinical attachment loss (CAL) at 3-4 months



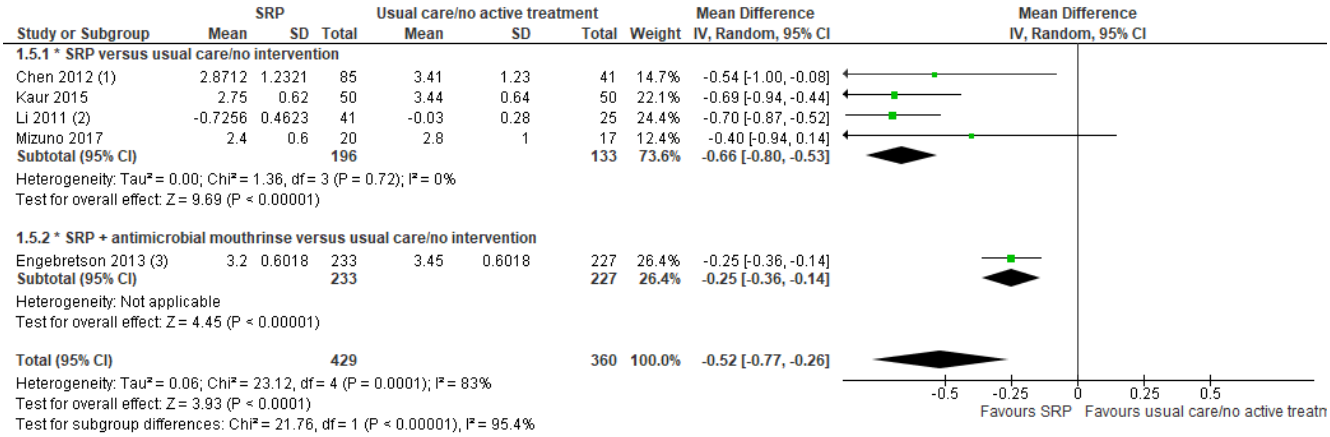
Footnotes

(1) SRP + additional mechanical therapy

(2) Periodontal therapy described as "mechanical therapy"

(3) Standard deviations estimated from baseline data

Effects of periodontal treatment versus usual care / no active intervention on Clinical attachment loss (CAL) at 6 months



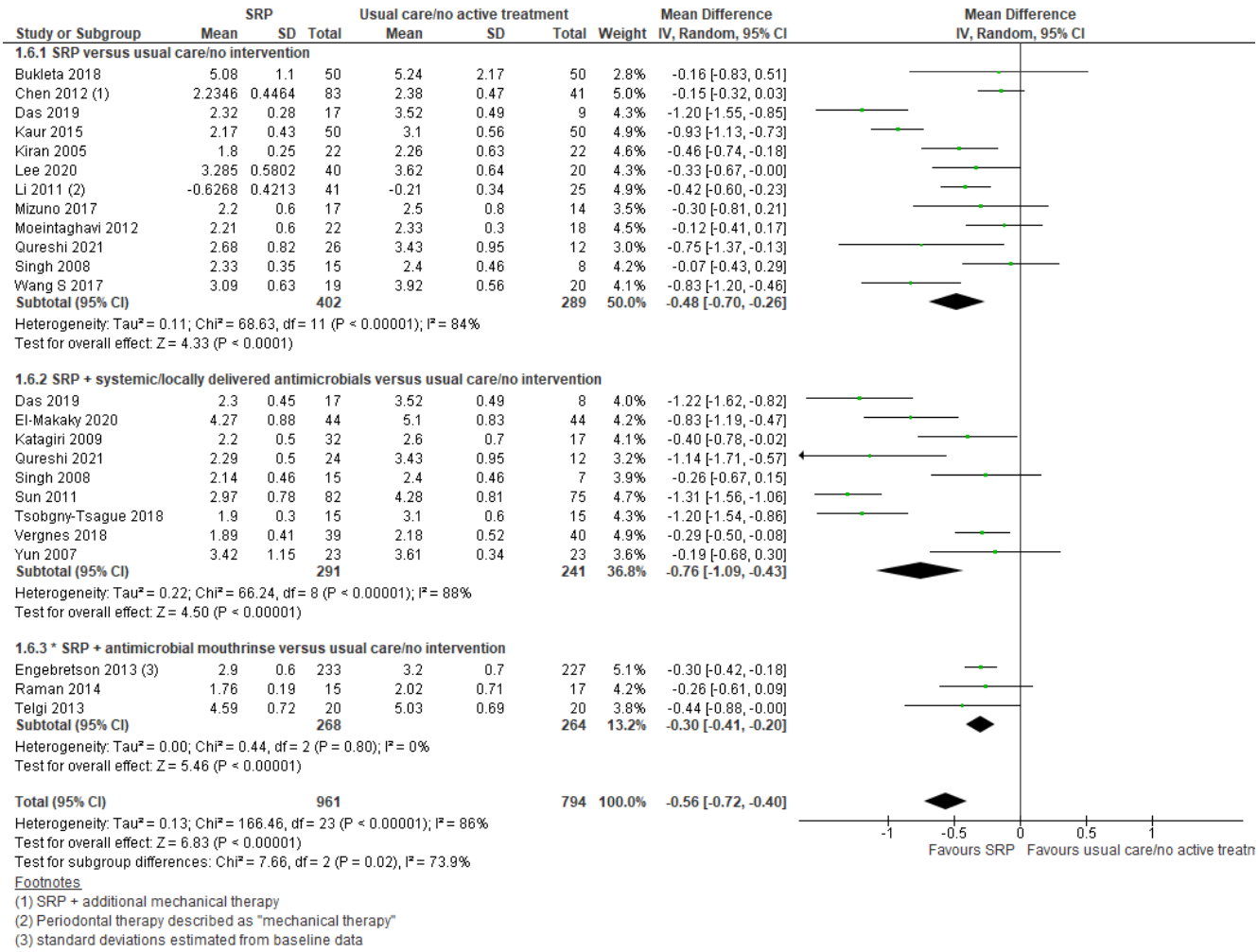
Footnotes

(1) SRP + additional mechanical therapy

(2) Periodontal therapy described as "mechanical therapy"

(3) Adjusted data used

Effects of periodontal treatment versus usual care / no active intervention on Probing pocket depth (PPD) at 3-4 months



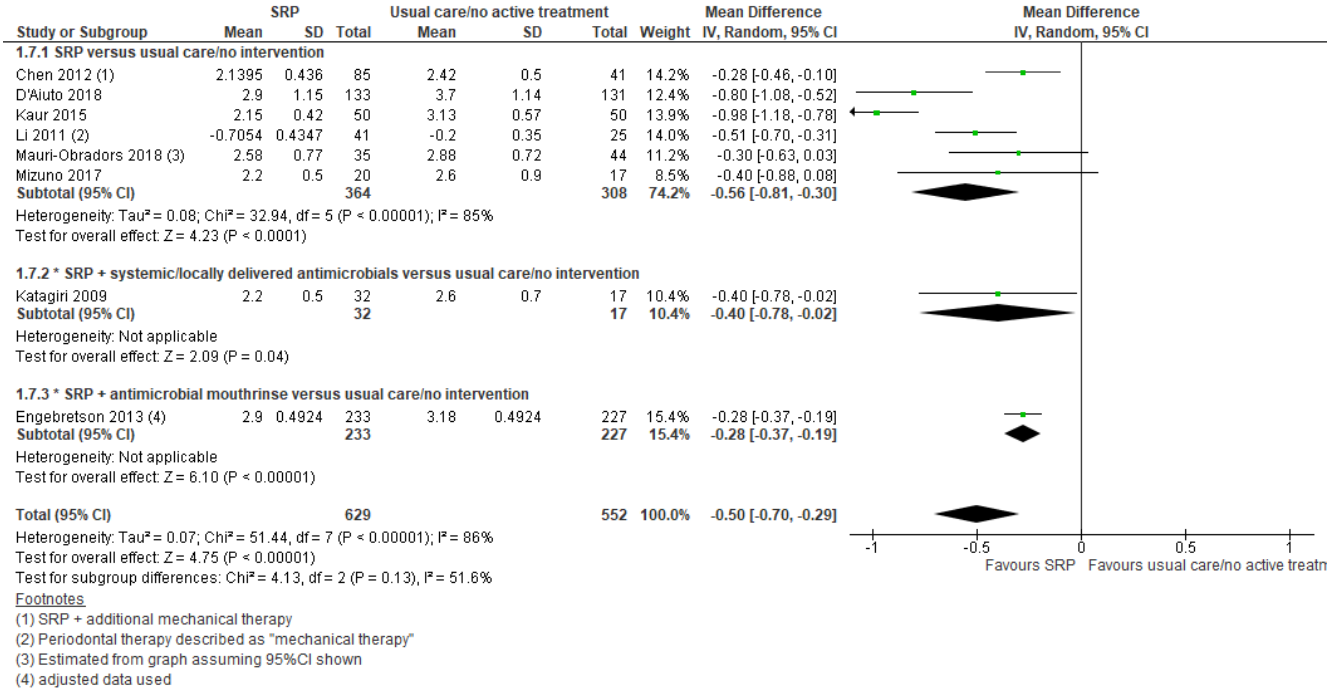
Footnotes

(1) SRP + additional mechanical therapy

(2) Periodontal therapy described as "mechanical therapy"

(3) standard deviations estimated from baseline data

Effects of periodontal treatment versus usual care / no active intervention on Probing pocket depth (PPD) at 6 months



Footnotes

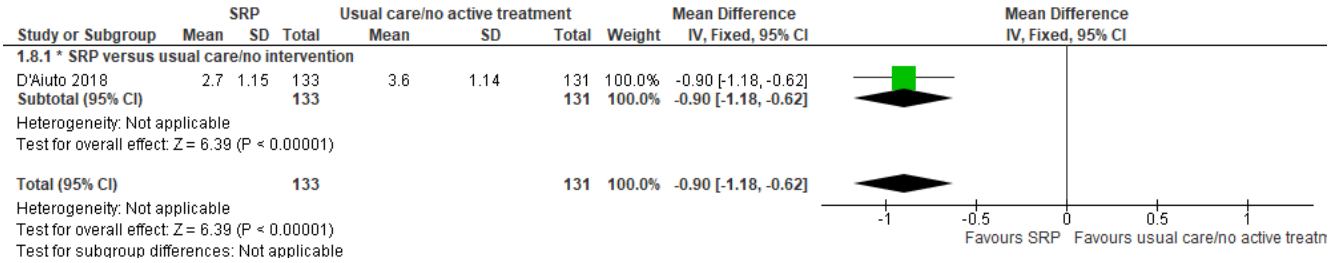
(1) SRP + additional mechanical therapy

(2) Periodontal therapy described as "mechanical therapy"

(3) Estimated from graph assuming 95%CI shown

(4) adjusted data used

Effects of periodontal treatment versus usual care / no active intervention on Probing pocket depth (PPD) at 12 months



* Subgroups in GRADE reported using fixed effect model due to I^2<50% (as per the NICE methods, Appendix B)
SRP=subgingival scaling and root planing

Appendix G – GRADE tables for pairwise data

The GRADE tables were compiled by the NICE Guideline Development Team. Fixed and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence (in line with NICE methods in Appendix B).

Effects of periodontal treatment versus usual care/no active intervention on HbA1c

No. of studies	Study design	Sample size	MIDs	Effect size MD (95% CI)	Absolute risk: control (95% CI)	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
HbA1c (% change from baseline) at 3-4 months: periodontal treatment versus usual care/no active intervention (MD<0 favours periodontal treatment)											
30	RCT	2443	+/- 0.50	-0.43 [-0.59, -0.28]	-	-	Not serious	Very serious[1]	Not serious	Serious[2]	Very low
HbA1c (% change from baseline) at 6 months: periodontal treatment versus usual care/no active intervention (MD<0 favours periodontal treatment)											
12	RCT	1457	+/- 0.50	-0.30 [-0.52, -0.08]	-	-	Not serious	Very serious[1]	Not serious	Serious[2]	Very low
***HbA1c (% change from baseline) at 12 months: periodontal treatment versus usual care/no active intervention (MD<0 favours periodontal treatment)**											
1	RCT	264		-0.50 [-0.55, -0.45]			Not serious	NA[3]	Not serious	Serious[2]	Moderate

* Reported using fixed effect model due to I^2<50% (as per NICE methods, Appendix B). NA = not applicable. SRP=subgingival scaling and root planning

1. I^2 > 66.7%
2. 95% confidence intervals cross one end of the defined MIDs
3. Only one study, inconsistency not applicable

Effects of periodontal treatment versus usual care/no active intervention on Clinical attachment loss (CAL)

No. of studies	Study design	Sample size	MIDs	Effect size MD (95% CI)	Absolute risk: control (95% CI)	Absolute risk: interven (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
CAL (mm change from baseline) at 3-4 months: periodontal treatment versus usual care/no active intervention (MD<0 favours SPR)											
18	RCT	1606	+/- 0.41	-0.48 [-0.65, -0.31]	-	-	Serious[1]	Very serious[2]	Not serious	Serious[3]	Very low
CAL (mm change from baseline) at 6 months: periodontal treatment versus usual care/no active intervention (MD<0 favours SPR)											
5	RCT	789	+/- 0.32	-0.52 [-0.77, -0.26]	-	-	Not serious	Very serious[2]	Not serious	Serious[3]	Very low
***CAL (mm change from baseline) at 6 months - SRP versus usual care/no active intervention * (MD<0 favours SRP)**											
4	RCT	329	+/- 0.41	-0.66 [-0.80, -0.53]			Serious[1]	Not serious	Not serious	Not serious	Moderate
***CAL (mm change from baseline) 6 months SRP + mouth rinse versus usual care/no active intervention (MD<0 favours SRP + mouth rinse)**											
1	RCT	460	+/- 0.15	-0.25 [-0.36, -0.14]			Not serious	NA[4]	Not serious	Serious[3]	Moderate

* Reported using fixed effect model due to I^2<50% (as per NICE methods, Appendix B). NA = not applicable. SRP=subgingival scaling and root planning

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. I^2 > 66.7%
3. 95% confidence intervals cross one end of the defined MIDs
4. Only one study, inconsistency not applicable

Effects of periodontal treatment versus usual care/no active intervention on Probing pocket depth (PPD)

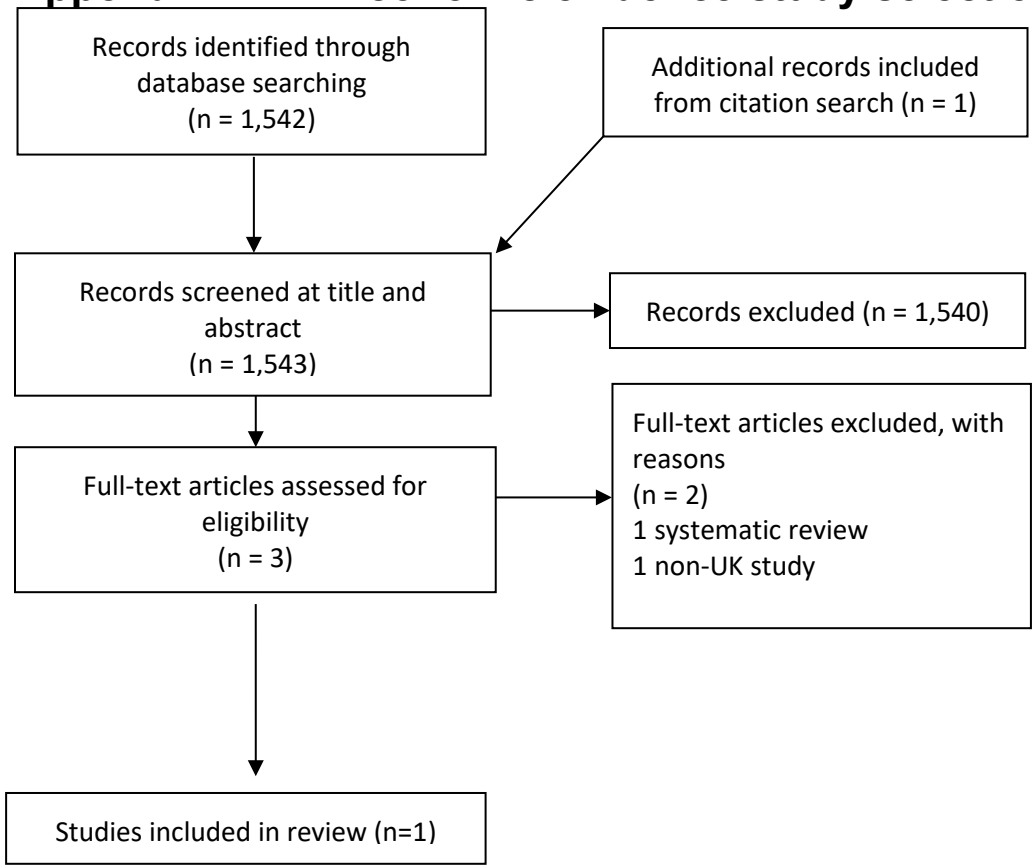
No. of studies	Study design	Sample size	MIDs	Effect size MD (95% CI)	Absolute risk: control (95% CI)	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
PPD (mm change from baseline) at 3-4 months: periodontal treatment versus usual care/no active intervention (MD<0 favours SPR)											
21	RCT	1775	+/- 0.31	-0.56 [-0.72, -0.40]	-	-	Serious[1]	Very serious[2]	Not serious	Serious[3]	Very low
PPD (mm change from baseline) at 3-4 months - SRP versus usual care/no active intervention (MD<0 favours SRP)											
12	RCT	691	+/- 0.28	-0.48 [-0.70, -0.26]	-	-	Serious[1]	Very serious[2]	Not serious	Serious[3]	Very low
PPD (mm change from baseline) at 3-4 months - SRP + systemic/locally delivered antimicrobials versus usual care/no intervention (MD<0 favours SRP+ systemic/locally delivered antimicrobials)											

9	RCT	532	+/- 0.30	-0.76 [-1.09, -0.43]	-	-	Serious[1]	Very serious[2]	Not serious	Serious[3]	Very low
***PPD (mm change from baseline) 3-4 months SRP + mouth rinse versus usual care/no active intervention (MD<0 favours SRP + mouth rinse)**											
3	RCT	532	+/- 0.35	-0.30 [-0.41, -0.20]	-	-	Not serious	Not serious	Not serious	Seirous[3]	Moderate
PPD (mm change from baseline) at 6 months: periodontal treatment versus usual care/no active intervention (MD<0 favours SPR)											
8	RCT	1181	+/- 0.32	-0.50 [-0.70, -0.29]	-	-	Serious[1]	Very serious[2]	Not serious	Serious[3]	Very low
***PPD (mm change from baseline) at 12 months: periodontal treatment versus usual care/no active intervention (MD<0 favours SPR)**											
1	RCT	264	+/- 0.57	-0.90 [-1.18, -0.62]			Serious[1]	NA[4]	Not serious	Not serious	Moderate

* Reported using fixed effect model due to I^2<50% (as per NICE methods, Appendix B). NA = not applicable. SRP=subgingival scaling and root planning

1. >33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias
2. I^2 > 66.7%
3. 95% confidence intervals cross one end of the defined MIDs
4. Only one study, inconsistency not applicable

Appendix H – Economic evidence study selection



Appendix I – Economic evidence tables

Solowiej-Wedderburn et al (2017)

Solowiej-Wedderburn et al (2017). Cost-effectiveness of non-surgical periodontal therapy for patients with type 2 diabetes in the UK.	
Study details	**Analysis** Cost-utility analysis **Approach to analysis:** Spreadsheet model estimating the costs and outcomes over a lifetime for patients with newly diagnosed T2DM and periodontitis. Impact of a decrease in HbA1c on costs and quality of life were estimated using the results from the DiabForecaster simulation model which is a simulation model that estimates the impact of reductions in HbA1c on lifetime costs of diabetes management and life expectancy adjusted for quality of life. **Perspective:** NHS provider prospective **Time horizon:** Lifetime **Discounting:** 3.5%
Interventions	**Intervention:** Non-surgical periodontal treatment **Comparator:** Lifetime maintenance
Population	**Population:** Patients with periodontitis newly diagnosed with T2DM **Characteristics:** The base case analysis was based on a 58 year old man with a baseline HbA1c level of 7-7.9%, results were presented for starting ages of 46 and 69, with three ranges of baseline HbA1c levels presented for each of the three age groups, these were 7-7.9 %, 8-8.9% and 9-9.9%.
Data sources	**Resource use:** Non-surgical periodontal therapy is assumed to be delivered as two 60-minute sessions performed by a dentist with experience of periodontal treatment (assuming the provider performer wage from PSSRU 2016), followed by maintenance which consists of a 30-minute hygienist sessions every 3 months and follow-up of periodontal therapy of one 60-minute session every 3 years. Regular dental care is assumed to cover routine scale and polish and only accounts for the costs of tooth loss repair. **Baseline/natural history:**. Natural history based on DiabForecaster model inputs **Effectiveness:** Outcome data for the absolute decrease in HbA1c is sourced from a Cochrane review (Simpson et al., 2015) as a conservative estimate of -0.29% at 3-4 months, from a range of -0.24% to -1.03% for 3 months follow up and from 0.02% to -1.18% from studies with 6 months follow up. **Costs:** Provider perspective was used which considered costs incurred by health care and dental care providers. Costs associated with periodontal treatment were calculated based on the estimated treatment duration and multiplying this by the wage of the expected level of dental practitioner, sourced from the PSSRU Curtis and Burns (2016) which accounts for the costs of all overheads as part of the hourly cost. Costs of tooth loss replacement was incorporated by using extraction times reported from Pennington et al. (2011) to calculate the labour cost and including laboratory costs for tooth replacements. A patient co-payment of 0.58 was deducted from the total costs to estimate the cost to the treatment provider. The costs based on labour time was used because the authors felt that the three UDAs attributable to a band 2 treatment estimated to be £75 based on a UDA value of £25 was unlikely to cover the true cost to the dental provider. The authors note that the cost to the NHS would be lower based on the current UDA system of reimbursement.

Solowiej-Wedderburn et al (2017). Cost-effectiveness of non-surgical periodontal therapy for patients with type 2 diabetes in the UK.	
	QoL: QALY gains associated with an absolute decline in HbA1C from DiabForecaster simulation model results are used for estimating the impact HbA1c reductions associated with periodontal treatment on quality of life.
Base-case results	**Incremental results for non-surgical periodontal treatment compared to usual care for the treatment of patients with newly diagnosed type 2 diabetes**

Age	HbA1c (%)	Incremental costs	Incremental QALYs	ICER (£ per QALY)
46	7-7.9%	£1,056	0.030	£35,023
	8-8.9%	£999	0.030	£33,131
	9-9.9%	£961	0.045	£21,425
58	7-7.9%	£840	0.030	£27,850
	8-8.9%	£783	0.030	£25,958
	9-9.9%	£745	0.045	£16,463
69	7-7.9%	£599	0.030	£19,858
	8-8.9%	£542	0.030	£17,965
	9-9.9%	£504	0.045	£11,135

Sensitivity analyses	**Deterministic:** One-way sensitivity analyses were performed by varying each parameter, either based on published confidence intervals, or using the published ranges when confidence intervals were unavailable. Scenarios were conducted for maintenance costs, and tooth loss by varying the treatment duration using a range of possible values from 40 to 240 minutes a year. Reduction in HbA1c level associated with treatment, the proportion of patients complying with treatment and the proportion of patients responding to treatment were found to be the biggest driver of the cost-effectiveness results. Many of these scenarios led to results not being cost-effective at the £30,000 threshold. **Probabilistic:** Due to the model structure, no probabilistic sensitivity analysis was conducted.
Comments	**Source of funding:** Unfunded **Applicability:** Partially applicable **Limitations:** Minor limitations

Solowiej-Wedderburn et al (2017). Cost-effectiveness of non-surgical periodontal therapy for patients with type 2 diabetes in the UK.		
Category	**Rating**	**Comments**
Applicability		

Solowiej-Wedderburn et al (2017). Cost-effectiveness of non-surgical periodontal therapy for patients with type 2 diabetes in the UK.		
Category	**Rating**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Yes newly diagnosed Type 2 patients
1.2 Are the interventions appropriate for the review question?	Yes	Scaling and root planing
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK based
1.4 Is the perspective for costs appropriate for the review question?	Yes	Provider prospective is used, uses the same costs as those used in the NHS and PSS
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	Oral health benefits were not included, however the authors have explained this is due to poor data availability and lack of sensitivity for quality of life measures.
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Assumes those sourced within the literature have been discounted appropriately
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	QALY gains associated with changes in HbA1c were derived from the literature
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	There is no need to use section 2 of the checklist if the study is considered 'not applicable'.
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime
2.3 Are all important and relevant outcomes included?	Partly	Partly, oral health benefits are not captured due to limited data availability
2.4 Are the estimates of baseline outcomes from the best available source?	Unclear	Baseline HbA1c ranges guided by reporting of economic models, however which models are not defined
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Partly	Partly, oral health costs were not included, cost of managing patients with extensive suppuration not included

Solowiej-Wedderburn et al (2017). Cost-effectiveness of non-surgical periodontal therapy for patients with type 2 diabetes in the UK.		
Category	**Rating**	**Comments**
2.7 Are the estimates of resource use from the best available source?	Partly	Treatment resource use based on assumptions because of limited data
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	A number of one-way sensitivity analyses were conducted through a number of scenarios, however probabilistic sensitivity analysis was not completed
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Appendix J – Health economic model

Full details of the health economic model are shown in the economic model report.

Appendix K – Excluded studies

Clinical

A list of studies excluded from this review at full-text stage and the ongoing studies:

Excluded studies (N=11)	Reasons for exclusion
Albrecht M, Banoczy J, Gyenes V, Ember G, Rigo O, Valkovics M, et al. Treatment of gingivitis and periodontal disease with insadol in diabetics. Fogorvosi Szemle 1988;81:65-71	No HbA1c outcome reported. Study was not translated to English, but advice sought from a Hungarian speaker on the content
* Botero JE, Yepes FL, Ochoa SP, Hincapie JP, Roldan N, Ospina CA, et al. Effects of periodontal non-surgical therapy plus azithromycin on glycemic control in patients with diabetes: a randomized clinical trial. Journal of Periodontal Research 2013;48(6):706-12. Hincapié JP, Castrillón CA, Yepes FL, Roldan N, Becerra MA, Moreno SM, et al. Microbiological effects of periodontal therapy plus azithromycin in patients with diabetes: results from a randomized clinical trial. Acta Odontológica Latinoamericana 2014;27(2):89-95.	Poorly reported. Further data needed (particularly accurate HbA1c means/SDs, data re: statin use) from author to complete assessment. Attempts to contacted authors unsuccessful. Categorised as 'awaiting classification' in 2015 version of review
* Chee HK, Lim LP, Tay F, Thai AC, Sum CF. Non-surgical periodontal therapy and serum lipid levels in patients with diabetes mellitus. Annals of the Royal Australasian College of Dental Surgeons 2006;18:46 Chee HK, Lim LP, Tay F, Thai AC, Sum CF. Non-surgical periodontal treatment and lipid levels in diabetic patients. Annals of the Royal Australasian College of Dental Surgeons 2008;19:183.	No indication whether patients had diagnosed periodontitis. Poorly reported. Insufficient data to complete assessment. Several attempts to contact authors for further details proved unsuccessful. Categorised as 'awaiting classification' in 2015 version of review
ChiCTR2000030393. Study for the effect of periodontal basic treatment on the microflora of patients with chronic periodontitis and diabetes mellitus. www.chictr.org.cn/showproj.aspx?proj=50096 (first received 1 March 2020).	Observational study
Elsadek MF, Ahmed BM, Alkhawtani DM, Zia Siddiqui A. A comparative clinical, microbiological and glycemic analysis of photodynamic therapy and Lactobacillus reuteri in the treatment of chronic periodontitis in type-2 diabetes mellitus patients. Photodiagnosis and Photodynamic Therapy 2020;29:101629.	No mention of randomisation
Goel K, Pradhan S, Bhattarai MD. Effects of nonsurgical periodontal therapy in patients with moderately controlled type 2 diabetes mellitus and chronic periodontitis in Nepalese population. Clinical Cosmetic and Investigative Dentistry 2017;9:73-80.	Not a relevant study design (quasi-randomised study)

Excluded studies (N=11)	Reasons for exclusion
Khader YS, Al Habashneh R, Al Malalheh M, Bataineh A. The eEect of full-mouth tooth extraction on glycemic control among patients with type 2 diabetes requiring extraction of all remaining teeth: a randomized clinical trial. Journal of Periodontal Research 2010;45(6):741-7.	Non-periodontal intervention: full-mouth tooth extraction for patients whose remaining teeth were indicated for extraction
Chandni R, Mammen J, Joseraj MG, Joseph R. Effect of nonsurgical periodontal therapy on insulin resistance in patients with type 2 diabetes mellitus and chronic periodontitis [abstract]. In: Conference: 75th Scientific Sessions of the American Diabetes Association Boston, MA United States. 2015. *Mammen J, Vadakkekuttical RJ, George JM, Kaziyarakath JA, Radhakrishnan CE. Effect of non-surgical periodontal therapy on insulin resistance in patients with type II diabetes mellitus and chronic periodontitis, as assessed by C-peptide and the Homeostasis Assessment Index. Journal of Investigative and Clinical Dentistry 2017;8(3).	Not a relevant study design (no mention of randomisation)
NCT01255254. The efffect of oral hygiene and full mouth scaling on metabolic control in patients with Type II diabetes. clinicaltrials.gov/show/NCT01255254 (2010).	Correspondence with trial investigator (May 2013) indicated trial was abandoned due to recruitment issues
Peña Sisto M, Calzado de Silva MC, Suárez Avalo W, Peña Sisto L, González Heredia E. Effectiveness of the periodontal treatment in the metabolic control of patients with diabetes mellitus [Efectividad del tratamiento periodontal en el control metabólico de pacientes con diabetes mellitus]. Medisan 2018;22(3):1029-3019.	Not a relevant study design (quasi-randomised study)
*Phetnin N, Vichayanrat T, Anunmana C. Effectiveness of the Diabetic and Oral Care Program for Senior in Older Patients with Diabetes in Muang District, Nakhon Ratchasima Province. In: RSU International Research Conference 2020. TCTR20200423005. Effectiveness of the Diabetic and Oral Care Program for Senior in Thai Older People with Type 2 Diabetes Mellitus: A randomized control trial. trialsearch.who.int/?TrialID=TCTR20200423005 (accessed 15 September 2021).	Not a relevant study design (quasi- randomised study)

Ongoing studies (N=4)
ACTRN12605000260628. Assessment of diabetes after periodontal treatment. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12605000260628 (first received 18 August 2005)
NCT01291875. Periodontal treatment and metabolic control in Type 2 diabetic patients. clinicaltrials.gov/ct2/show/NCT01291875 (first received 9 February 2011).
NCT01901926. Impact of non-surgical periodontal treatment on glycemic control in Type II diabetics. clinicaltrials.gov/ct2/show/NCT01901926 (first received 17 July 2013).
U1111-1124-3635. Influence of periodontal treatment in periodontitis and diabetes control. www.ensaiosclinicos.gov.br/rg/RBR-8dfrpt/ (2012).

* Major publication for the study; RCT - randomised controlled trial; SRP - scaling and root planing; SD - standard deviation

Health Economics

Excluded studies (N=2)	Reasons for exclusion
Choi, Sung Eun; Sima, Corneliu; Pandya, Ankur; Impact of Treating Oral Disease on Preventing Vascular Diseases: A Model-Based Cost-effectiveness Analysis of Periodontal Treatment Among Patients With Type 2 Diabetes.; Diabetes care; 2020; vol. 43 (no. 3); 563-571	Incorrect population, included some patients without diabetes and is a US based study, not representative of UK population.
Canadian Agency for Drugs and Technologies in, Health; Treatment of periodontal disease in patients with diabetes: a review of clinical and cost-effectiveness; 2010, Canadian Agency for Drugs and Technologies in Health (CADTH)	Systematic review, one study was identified from this paper which was screened out at the title and abstract stage.